A Comprehensive Meta-analysis on Evidence of Mediterranean Diet and Cardiovascular Disease: Are Individual Components Equal?

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A comprehensive meta-analysis on evidence of Mediterranean diet and cardiovascular disease: are individual components equal?

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Abstract
Many studies have reported that higher adherence to Mediterranean diet may decrease cardiovascular disease (CVD) incidence and mortality. We performed a meta-analysis to explore the association in prospective studies and randomized control trials (RCTs) between Mediterranean diet adherence and CVD incidence and mortality. The PubMed database was searched up to June 2014. A total of 17 studies were extracted and 11 qualified for the quantitative analysis. Individuals in the highest quantile of adherence to the diet had lower incidence (Relative Risk [RR]: 0.76, 95% confidence intervals [CI]: 0.68, 0.83) and mortality (RR: 0.76, 95% CI: 0.68, 0.83) from CVD compared to those least adherent. A significant reduction of risk was found also for coronary heart disease (RR: 0.72, 95% CI: 0.60, 0.86), myocardial infarction (RR: 0.67; 95% CI: 0.54, 0.83), and stroke (RR: 0.76; 95% CI: 0.60, 0.96) incidence. Pooled analyses of individual components of the diet revealed that the protective effects of the diet appear to be most attributable to olive oil, fruits, vegetables, and legumes. An average reduced risk of 40% for the aforementioned outcomes has been retrieved when pooling results of RCTs. A Mediterranean dietary pattern is associated with lower risks of CVD incidence and mortality, including CHD and MI. The relative effects of specific food groups should be further investigated.

Keywords
Prevention; randomized controlled trials; prospective cohort studies; olive oil; vegetables; fruit; legumes.

Introduction

Cardiovascular disease (CVD) is a major public health issue worldwide and the leading cause of morbidity and mortality in the western world (Capewell and Buchan 2012). The rising prevalence of cardio-metabolic conditions, such as obesity, hypertension, and diabetes is considered a prominent cause of this increasing trend (Capewell and Buchan 2012). Dietary and lifestyle factors are among the most important determinants of these metabolic risk factors (Capewell and Buchan 2012). Based on epidemiological and experimental studies, it has been suggested that certain types of diet rich in whole grain cereals, fruit and vegetables, and low in animal fats may have beneficial cardio-protective effects (Buscemi et al., 2013; Grosso et al., 2014a; Grosso et al., 2014b; Yang et al., 2014). Among them, the geographical difference in CVD incidence and mortality observed in the '60s in favor of Southern European population led to the hypothesis that a Mediterranean dietary pattern was protecting against CVD, lately supported by the strongest evidence relating its beneficial effects on coronary heart disease (CHD) risk (Mente et al., 2009). Some of the most common features of Mediterranean diet are represented by i) consumption of a large quantity of plant-derived foods (fruit, vegetables, and legumes), cereals (especially whole-grains) and fish; ii) low

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intake of meat and dairy products; iii) daily intake of olive oil and nuts, and iv) moderate intake of wine (especially red wine) during meals (Estruch and Salas-Salvado 2013). According to such characteristics, this plant-rich diet may provide benefits through the high content of antioxidants and fiber, with fish, nuts and olive oil that ensure a high intake of polyunsaturated fatty acids (PUFA) and monounsaturated fatty acids (MUFA), associated with a low intake of saturated and trans-fatty acids from meat and sweets (Estruch and Salas-Salvado 2013). Besides the several indexes and scores that have been developed to assess adherence to the Mediterranean dietary pattern (Bach et al., 2006), the main issue on what really differentiate such diet from other pattern found to be similarly protective against CHD (such as "prudent" diets, equally rich in anti-oxidant phytochemicals and similar lipid profiles) is still an open debate (Mente et al., 2009). Approaches aimed to individualize whether the protective effects depend on single foods or nutrients seem to conclude that the efficacy of Mediterranean diet should be considered as relying on the whole diet including each of its components. Nevertheless, there is no single definition for this traditional dietary pattern because the variety of foods specifically consumed among and within countries makes the Mediterranean diet extremely heterogeneous and strongly influenced by food availability and cultural heritage differences by geographical regions.

A number of studies reported that individuals more adherent to this dietary pattern have a significantly decreased risk in CVD incidence and mortality (Sofi et al., 2013). Furthermore, adherence to Mediterranean diet has been associated with better survival after an established diagnosis of CVD (Kastorini et al., 2010). Previous quantitative meta-analyses of prospective cohort studies pooling fatal and non-fatal CVD events together reported a decreased risk of 10% for a 2-point increase in Mediterranean diet adherence score, but analyses for specific outcomes, such as the risk of CHD, myocardial infarction (MI), and stroke, are lacking. Moreover, the actual meta-analyses refer only to studies using a specific dietary index and relied only on observational studies (Sofi et al., 2013). Overall, it would be of interest to evaluate findings from both observational and experimental studies with specific CVD outcomes by considering the adherence to the Mediterranean diet irrespectively of the score used, rather focusing on the highest level of adherence possible, in line with the corroborated idea that benefits of this dietary pattern depend on each of its main features. Nevertheless, the impact of its single components in the context of Mediterranean diet has never been evaluated in pooled analyses and could be taken into account to provide insights of their effective role in protecting against CVD.

The aim of this study was to systematically review and compare results from prospective investigations and randomized controlled trials (RCTs) exploring the effectiveness of Mediterranean diet in reducing CVD incidence and mortality. This is the first meta-analysis designed to evaluate the effects of high adherence to the diet on specific outcomes, such as CHD, MI, and stroke, with no restriction on the adherence score used in any component study. We also explored whether individual components of Mediterranean diet, being evaluated in its context, were significantly related with any CVD related outcome.

Methods

Search strategy and study selection

Literature databases including PubMed, SCOPUS, and EMBASE were searched from January 2000 through June 2014. Relevant keywords relating to Mediterranean diet ("Mediterranean diet") were searched in combination with keywords relating to cardiovascular events ("cardiovascular disease" or "cardiovascular event" or "myocardial infarction" or "coronary heart disease" or "coronary artery disease" or "ischemic heart disease" or "angina" or "stroke" or "cerebrovascular disease"), and in combination with keywords relevant to the study methods ("incidence" or "cohort" or "follow-up" or "trial" or "hazard ratio" or "odds ratio" or "relative risk" or "rate ratio"). Reference lists of retrieved articles were manually searched by two researchers (GG and SM). The literature search was limited to English. If more than one article was published using the same cohort, the most recent article with the longest follow-up period was considered. Studies included in this systematic review met all of the following inclusion criteria: i) evaluated the risk or association between Mediterranean diet adherence, CVD incidence and/or mortality (including CHD, MI, and stroke) with a prospective or RCT design; ii) used an *a priori* method to evaluate adherence to the diet; iii) clearly defined the intervention diet as "Mediterranean" and described its characteristics (only RCTs). The two investigators independently assessed articles for compliance with the inclusion and exclusion criteria and resolved disagreements through consensus.

In total, 230 studies that evaluated the effect of Mediterranean diet on the outcomes of interest were identified. The full process of identification and selection of studies is shown in Figure 1. The relevance of studies was assessed with a hierarchical approach on the basis of title, abstract, and the full manuscript. Of the 47 studies considered relevant as prospective, 29 were excluded for the following reasons: 15 studies had different design; 7 studies evaluated non CVD outcomes; 3 studies defined the Mediterranean dietary pattern through principal component analysis (PCA); 2 studies had reported longer follow-up in updated reports; 1 study reported insufficient statistics; 1 study was conducted on a subgroup of an entire cohort already included. Of the 13 studies considered relevant as RCTs, 9 were excluded for the following reasons: 3 had different design; 2 did not sufficiently specify the intervention as "Mediterranean"; 2 were duplicate publications; 1 had reported longer follow-up in updated reports; 1 study reported insufficient statistics. Overall, 20 prospective studies (Knoops et al., 2004; Mitrou et al., 2007; Panagiotakos et al., 2008; Buckland et al., 2009; Fung et al., 2009; Chrysohoou et al., 2010; Agnoli et al., 2011; Buckland et al., 2011; Gardener et al., 2011; Hodge et al., 2011; Martinez-Gonzalez et al., 2011; Dilis et al., 2012; Hoevenaar-Blom et al., 2012; Menotti et al., 2012; Misirli et al., 2012; Tognon et al., 2012; Hoevenaar-Blom et al., 2013; Tognon et al., 2013; Bertoia et al., 2014; Lopez-Garcia et al., 2014) and 4 RCTs (de Lorgeril et al., 1999; Singh et al., 2002; Giannuzzi et al., 2008; Estruch et al., 2013) were included in this systematic review and meta-analysis.

Data extraction

The following information was extracted from each study: i) name of the first author; ii) year of publication; iii) study cohort or name; iv) country; v) number of participants; vi) gender of participants; vii) age range or mean age of the study population at baseline; viii) follow-up period; ix)

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endpoints and cases; x) diet adherence score used; xi) RRs or HRs with 95% CIs for high adherence categories of exposure; and xii) covariates used in adjustments. Regarding RCTs, description of intervention and controls was also evaluated.

The quality of observational studies was assessed according to the Newcastle-Ottawa quality assessment Scale (Wells et al., 1999), consisting of three parameters of quality: selection (four points), comparability (two points), and outcome (three points), with a score of seven or more points reflecting high quality. Study quality of RCTs was measured according the Jadad criteria (Jadad et al., 1996).

Exposure and outcome measures

Adherence to a Mediterranean diet was defined through scores that estimated dietary pattern conformity of the studied population with traditional Mediterranean dietary pattern. Overall, people more adherent to the Mediterranean diet were considered those included in the highest quantile of the score used in each study. In studies where point scale system was utilized instead of quantiles, we transformed HR by calculating differences between upper half score individuals versus lower half score individuals.

CVD events comprised cases of myocardial infarction/acute coronary syndromes (MI), stroke, and/or CHD, when present. CVD mortality was defined as fatal events related with cardiovascular system according to definitions provided in each study.

Statistical analysis

RRs or HRs with 95% CIs for all categories of exposure were extracted for the analysis and random-effects models were used to calculate pooled RRs with 95% CIs for highest compared with lowest category of exposure (i.e., highest vs. lowest quantile of adherence to Mediterranean diet). Heterogeneity was assessed by using the Q test and I^2 statistic. The significance for the Q test was defined as $P < 0.10$. The I^2 statistic represents the amount of total variation that could be attributed to heterogeneity. I^2 values ≤25%, ≤50%, ≤75% and >75% indicated no, little, moderate, and significant heterogeneity, respectively. Meta-regression analyses for number of participants, number of cases, year of publication, geographical location, and duration of follow-up were performed to identify source of heterogeneity. A sensitivity analysis was conducted by excluding one study at a time was performed to assess the stability of results. Subgroup analyses were conducted by geographical region (Mediterranean and non-Mediterranean countries), duration of follow-up (≤10 and >10 years), sample size (≤10,000 and >10,000 participants), and method of Mediterranean diet adherence assessment (modified Mediterranean diet score [mMed score] and others). Publication bias was assessed by visual observation of funnel plot. All analyses were performed with Review Manager (RevMan) version 5.2 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration).

Results

Prospective studies on Mediterranean diet

The major characteristics of the 20 studies included in this systematic review are presented in Table 1 (Knoops et al., 2004; Mitrou et al., 2007; Panagiotakos et al., 2008; Buckland et al., 2009; Fung et al., 2009; Chrysohoou et al., 2010; Agnoli et al., 2011; Buckland et al., 2011; Gardener et al., 2011; Hodge et al., 2011; Martinez-Gonzalez et al., 2011; Dilis et al., 2012; Hoevenaar-Blom et al., 2012; Menotti et al., 2012; Misirli et al., 2012; Tognon et al., 2012; Hoevenaar-Blom et al., 2013; Tognon et al., 2013; Bertoia et al., 2014; Lopez-Garcia et al., 2014). In total, there were 888,257 participants with 22,987 cumulative incident cases of CVD (including deaths). Most studies comprised individuals of age ranging from 20 to 70 years old, while 3 studies (Knoops et al., 2004; Dilis et al., 2012; Misirli et al., 2012) were conducted solely on elderly participants (>70 years old). Two studies evaluated the prevalence of CVD at follow-up visit, hence reporting ORs (Panagiotakos et al., 2008; Chrysohoou et al., 2010). Three studies explored Mediterranean diet adherence in patients at high CVD risk, two of them including individuals with previous CVD incidents (Chrysohoou et al., 2010; Lopez-Garcia et al., 2014) and one was conducted on diabetic individuals (Hodge et al., 2011). All studies included covariates that are considered to have significant influence on cardiovascular outcomes such as age, gender (when not analyzed separately), BMI, education, physical activity, and smoking status. The comprehensive groups of covariates used for adjustments are described in Table 1.

Thirteen studies (Panagiotakos et al., 2008; Buckland et al., 2009; Fung et al., 2009; Chrysohoou et al., 2010; Agnoli et al., 2011; Gardener et al., 2011; Martinez-Gonzalez et al., 2011; Dilis et al., 2012; Hoevenaar-Blom et al., 2012; Menotti et al., 2012; Misirli et al., 2012; Hoevenaar-Blom et al., 2013; Tognon et al., 2013) accounting for 13,434 CVD events [6 studies (Chrysohoou et al., 2010; Agnoli et al., 2011; Martinez-Gonzalez et al., 2011; Dilis et al., 2012; Misirli et al., 2012; Hoevenaar-Blom et al., 2013) included composite incidence and mortality cases] were pooled together to estimate the risk of CVD incidence as a function of Mediterranean diet adherence. High Mediterranean diet adherence was inversely associated with decreased risk of CVD incidence (RR: 0.73, 95% CI: 0.66, 0.80) compared to lowest adherence (Figure 2), with no significant evidence of heterogeneity (I^2 = 36%). Sensitivity analysis was conducted by removing one study at a time and no significant changes in result were found. No significant evidence of heterogeneity was found at meta-regression analysis. After considering separately those studies accounting for composite incidence and mortality outcome (Chrysohoou et al., 2010; Agnoli et al., 2011; Martinez-Gonzalez et al., 2011; Dilis et al., 2012; Misirli et al., 2012; Hoevenaar-Blom et al., 2013), risk of CVD slightly decreased (RR: 0.66, 95% CI: 0.55, 0.80) due to the effect of one study (Panagiotakos et al., 2008) responsible also for heterogeneity (I^2 = 72%), which after its exclusion dropped to 36% and the reported risk estimate remain unchanged.

Thirteen studies (Knoops et al., 2004; Mitrou et al., 2007; Fung et al., 2009; Buckland et al., 2011; Hodge et al., 2011; Dilis et al., 2012; Hoevenaar-Blom et al., 2012; Menotti et al., 2012; Misirli et al., 2012; Tognon et al., 2012; Tognon et al., 2013; Bertoia et al., 2014; Lopez-Garcia et al., 2014) accounting for 9563 cases of death from CVD were pooled together to estimate the risk of CVD mortality as a function of Mediterranean diet adherence. High adherence to the Mediterranean diet was inversely associated with risk of CVD mortality (RR: 0.75; 95% CI: 0.68, 0.83) compared to that of the lowest adherence (Figure 2), with significant

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evidence of heterogeneity (I^2 = 75%). Evidence of heterogeneity may be attributed to two studies (Tognon et al., 2012; Tognon et al., 2013) for which HRs were estimated by 1-point score increase for two categories of exposure. However, after exclusion of such studies at sensitivity analysis, risk estimate remained mostly unchanged (RR: 0.73; 95% CI: 0.68, 0.79). No further evidence of heterogeneity was found at meta-regression analysis.

A pooled analysis was performed to evaluate as a composite outcome the risk of incidence and/or death from CVD (Figure 2), resulting in a cumulative RR of 0.71 (95% CI: 0.65, 0.78), with significant evidence of heterogeneity (I^2 = 78%) and slight asymmetry at funnel plot (Supplemental Figure 1). Sensitivity analysis by excluding the studies responsible for asymmetry at funnel plot (Panagiotakos et al., 2008; Chrysohoou et al., 2010; Martinez-Gonzalez et al., 2011) did not change the results (RR: 0.74; 95% CI: 0.68, 0.80). The analysis was repeated excluding those studies conducted on patients at high risk, which resulted in unchanged risk estimate (RR 0.71, 95% CI 0.63, 0.77). Table 2 shows results of subgroup analyses by geographical area, sample size, length of follow-up, and type of Mediterranean adherence score, with no substantial differences between groups.

Regarding specific CVD outcomes, 4 studies examined CHD incidence (Buckland et al., 2009; Fung et al., 2009; Martinez-Gonzalez et al., 2011; Dilis et al., 2012), 3 studies on MI incidence (Gardener et al., 2011; Hoevenaar-Blom et al., 2012; Tognon et al., 2013) and 5 studies on stroke incidence (Fung et al., 2009; Gardener et al., 2011; Hoevenaar-Blom et al., 2012) (Agnoli et al., 2011; Tognon et al., 2013). High adherence to Mediterranean diet was inversely associated with risk of CHD (RR: 0.72, 95% CI: 0.60, 0.86), MI (RR: 0.67; 95% CI: 0.54, 0.83), and stroke (RR: 0.76; 95% CI: 0.60, 0.96), with little evidence of heterogeneity only for stroke outcome (I^2 = 52%) (Figure 3). However, no significant source of heterogeneity was found at meta-regression and sensitivity analysis.

Food group components of the Mediterranean diet and CVD outcomes

Scoring systems used in studies assessing the Mediterranean diet adherence are listed in Table 1. Some differences among food groups used in the studies existed, especially in relation to the food category of (i) vegetables, grouped with potatoes in those studies using the mMed score (Knoops et al., 2004; Dilis et al., 2012; Hoevenaar-Blom et al., 2012; Misirli et al., 2012; Tognon et al., 2012; Hoevenaar-Blom et al., 2013; Tognon et al., 2013); (ii) meat and meat products, grouped with poultry in studies using the relative Mediterranean diet score (rMed score) (Buckland et al., 2009; Buckland et al., 2011); and (iii) nuts and seeds, grouped with fruits in some studies (Mitrou et al., 2007; Buckland et al., 2009; Buckland et al., 2011; Martinez-Gonzalez et al., 2011), with legumes in another study (Knoops et al., 2004), and considered a group by themselves in some others (Fung et al., 2009; Hoevenaar-Blom et al., 2012), irrespectively of the score used.

For individuals considered as highly adherent to the Mediterranean dietary pattern (highest quantile of the score), average daily consumption of specific food groups are summarized in Table 3. Quantitative amounts of individual food groups were highly variable across studies. Generally, higher intakes of fruit, vegetables, and fish were described in Mediterranean cohorts (Buckland et al., 2009; Buckland et al., 2011; Martinez-Gonzalez et al., 2011; Misirli et al., 2012) whereas meat and dairy products were consumed in higher quantities in non-Mediterranean countries (Tognon et al., 2012; Tognon et al., 2013). Pooled risk analysis for single Mediterranean diet food components showed in Figure 4 revealed a significant reduction of CVD risk for adequate olive oil consumption (RR: 0.83; 95% CI: 0.77, 0. 89; I^2 = 0%), vegetable intake (RR: 0.87; 95% CI: 0.77, 0.98; I^2 = 54%), fruit (RR: 0.88; 95% CI: 0.81, 0.96; I^2 = 33%), and legumes (RR: 0.91; 95% CI: 0.83, 0.98; I^2 = 33%), and increased risk for dairy products (RR: 1.10; 95% CI: 1.02, 1.19; I^2 = 49%). Non-significant trend toward decreased risk were also found for fish (RR: 0.96; 95% CI: 0.91, 1.01; I^2 = 36%), cereals consumption (RR: 0.95; 95% CI: 0.90, 1.00; I^2 = 0%), and alcohol intake (RR: 0.97; 95% CI: 0.88, 1.07; I^2 = 70%), and increased for meat products consumption (RR: 1.02; 95% CI: 0.96, 1.08; I^2 = 0%). Sensitivity analysis reduced heterogeneity to 0% for all food components except alcohol with substantially unchanged results; however, neither alcohol, meat products, nor fish intake reached significance.

RCTs on Mediterranean diet

The main characteristics of the 4 included RCTs are summarized in Table 4 (de Lorgeril et al., 1999; Singh et al., 2002; Giannuzzi et al., 2008; Estruch et al., 2013). A total of 12,293 individuals at high CVD risk (7418 interventions/4874 controls) and 590 composite cases of CVD (including CVD mortality, MI and stroke incidence) were included in the analysis. Interventions among studies differed based on investigators' emphasis on the Mediterranean diet; major focus was given to margarine enriched diet in de Lorgeril et al. (2004), fruit and vegetables in Singh et al. (2002), general advices according to the mMed score in Giannuzzi et al. (2008), and olive oil and nuts in Estruch et al. (2013). Subjects in control groups were given similar dietary advice among studies (Table 3).

Overall, all outcomes evaluated agreed with an average 40% decreased risk of CVD incidence (for MI, RR: 0.60; 95% CI: 0.44, 0.82; I^2 = 26%; for stroke, RR: 0.64; 95% CI: 0.47, 0.86; I^2 = 0%;) and mortality (RR: 0.59; 95% CI: 0.38, 0.93; I^2 = 46%) in the intervention group compared with controls. However, differences between studies in the efficacy of intervention were evident when considering specific outcomes, such as CVD mortality (Singh et al., 2002; de Lorgeril and Salen 2004) and MI incidence (Singh et al., 2002; Giannuzzi et al., 2008), which were significant in studies published earlier in time, or stroke incidence, which was significant only in the PREDIMED study (Estruch et al., 2013). However, when evaluating the composite outcome (provided by all studies), a pooled estimated risk of 0.55 (95% CI: 0.39, 0.76) was found with moderate heterogeneity among studies (I^2 = 68%) and no evidence of publication bias at funnel plot. Meta-regression analysis revealed that a significant effect in the final result could be attributed to the year of publication due to a gradient toward lower risk for older studies (data not shown).

Discussion

To the best of our knowledge, this is the first study to systematically assess, through meta-analysis, the role of Mediterranean diet on CVD incidence and mortality in prospective studies and RCTs, including a specific analysis

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on CHD, MI, and stroke, with no restriction of method in assessing diet adherence. Besides the corroborated idea that adherence to a Mediterranean dietary pattern is protective against CVD, we aimed to quantify this association for individuals highly adherent (identified as those grouped in the highest quantile in each prospective study) and compare it with the risk estimated by experimental studies. The current meta-analysis supports the hypothesis that highly adherent individuals had lower CVD morbidity and mortality with a decreased risk of about 30% in prospective studies and of about 40-45% in RCTs conducted on patients with high CVD risk. Such differences in risk reduction observed in intervention studies compared with observational may be due to that the latter were mostly conducted on general populations [with the exception of three studies (Chrysohoou et al., 2010; Hodge et al., 2011; Lopez-Garcia et al., 2014)], whereas RCTs enrolled individuals at high CVD risk, thus maximizing the interventional effects.

When examining specific types of CVD, we found mostly stable estimated risks for CHD, MI, and stroke among different study designs, despite slight heterogeneity was found among prospective studies on stroke incidence. The fact that ischemic stroke could be etiologically heterogeneous may have contributed to the lack of association observed in some studies, whereas results on MI were more uniform as pathological mechanisms of MI are more homogeneous. Likewise, similar issues have been faced when considering RCTs, with a certain grade of discordance regarding potential protection of the Mediterranean diet toward both MI and stroke incidence. Considering the limited number of studies with available information on specific outcomes, further research is needed to clarify whether high Mediterranean diet adherence provides protection against specific cardio- and/or cerebrovascular diseases.

Despite current scientific findings and understandings of the observed cardio-protective effects of Mediterranean-style diet, the full mechanisms and pathways are not completely understood. The protective effects of this dietary pattern may depend on its action towards CVD risk factors, such as abdominal obesity, lipids levels, glucose metabolism, and blood pressure levels (Grosso et al., 2014c; Grosso et al., 2014d). Among direct action on cardiovascular system, observational and experimental studies reported that adherence to the Mediterranean diet has been associated not only with a reduction in endothelial function but also with improvement in inflammatory status (Schwingshackl and Hoffmann 2014). Furthermore, adhering to a Mediterranean dietary pattern may also provide better cardiac autonomic function, independently of genetic or lifestyle factors other than diet (Dai et al., 2010). Similar benefits have been found also in patients with a previous episode of CVD, in whom Mediterranean diet adherence provided preservation of left ventricular systolic function (Chrysohoou et al., 2010). General components of the diet that seems to play a major role in cardiovascular health are: (i) fiber, especially from fruit and vegetables; (ii) whole grains and legumes (Satija and Hu 2012); (iii) an favorable fatty acids ratio, with special regard to omega-3 PUFA (Christensen et al., 2005; Park et al., 2009), in particular α-linolenic acid (ALA) from vegetal origin (de Lorgeril and Salen 2004); and (iv) docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) from fish (Mozaffarian and Wu 2012; Marventano et al., 2015). Other nutrients with anti-inflammatory properties, such as vitamins and phenolic compounds from fruit and vegetables, may lead to better functionality and ameliorate inflammation and oxidative stress in case of infarction, limit infarct size and improve ventricular remodeling process (Nadtochiy and Redman 2011), which are all major determinants of post-infarction survival and prognosis (Zamora-Ros et al., 2013; Tresserra-Rimbau et al., 2014).

Adherence to the Mediterranean diet has been evaluated by using scoring systems in previous studies. While different systems all included main features of this dietary pattern, slight differences are seen on classification of food groups, for example, nuts and fish as independent components, and definition of amount to be considered highly adherent, such as frequency of consumption versus portion size. This non-conformity in the interpretation of Mediterranean diet has to be considered when comparing results across studies, especially when conducted in different countries with significantly different dietary habits. A recent meta-analysis (Sofi et al., 2013) proposed a Mediterranean diet adherence score system by using literature-based cut-off points. In comparison, our calculation of food amount consumed by individuals highly adherent to the diet did not differ substantially for components such as fruit, vegetables, alcohol and cereals. However, in our analysis consumption of fish (roughly more than 30 g/d) and legumes (20 g/d) among individuals highly adherent to Mediterranean diet was less than suggested by previously published analysis (more than 100 g/d and 70 g/d, respectively), while their CVD-protective effect was significant for legumes and near significant for fish intake. While no significant risk was associated with dairy products in previous review (Soedamah-Muthu et al., 2011), our analysis resulted in increased CVD risk associated with dairy consumption.

The role of olive oil (Martínez-González et al., 2014), fruit and vegetables (Wang et al., 2014), and legumes and nuts (Afshin et al., 2014; Grosso et al, 2015) on CVD outcomes have been extensively reported. While the effects of specific food categories may be attenuated due to synergic effect of the overall diet, the significant inverse associations with CVD outcomes suggest the individual role of specific Mediterranean diet components in determining disease risk outcomes. Therefore, when evaluating point increase in adherence of the Mediterranean diet, the evaluation should be accompanied by analysis of individual component effects. While adherence to the Mediterranean diet was considered as a whole in the GOSPEL study (Giannuzzi et al., 2008), the characterization of this dietary pattern has been proposed to rely on some specific key factors in other RCTs examined in this meta-analysis. For instance, a diet rich in ALA in the Lyon Diet Heart Study (de Lorgeril et al., 1999); consumption of fruit, vegetables, and nuts in the Indo-Mediterranean Diet Heart Study (Singh et al., 2002); and consumption of extra-virgin olive oil and nuts in the PREDIMED study (Estruch and Salas-Salvado 2013). The identification of the key components is important since differences in the definition of a Mediterranean-type diet among studies are generally relevant. In the Lyon Diet Heart Study, patients did not accept olive oil as the only source of fat and ALA was supplied by a rapeseed (canola) oil-based margarine consumption (de Lorgeril et al., 1999). As well, in the Indo-Mediterranean Diet Heart Study, olive oil was never mentioned and was not considered part of the diet. In contrast, one arm of the PREDIMED study focused on extra-virgin olive oil consumption (Estruch et al., 2013). Moreover, nut consumption was emphasized in the Indo-Mediterranean Diet Heart Study and the PREDIMED study while less considered in other RCTs. Differences between prospective

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and experimental studies emerged when we examined specific components of the diet. For example, olive oil had far more effective results in reducing CVD risk than other Mediterranean diet components in prospective studies, but not particularly in RCTs with the exception of the PREDIMED study (Estruch and Salas-Salvado 2013). Moreover, it is not clear whether the main sources of ALA should be margarine or nuts. Pooled analysis of prospective studies further suggested that the phytochemicals and antioxidants content of fruits and vegetables could alone play a major role in the observed benefits of the Mediterranean diet. Although the benefits of the overall dietary pattern can be considered as exerted from a holistic point of view due to a likely synergic effect of all its components, future RCTs should also assess the role of specific components, as according to our results the classic approach to randomly consider any of this diet characteristics as equivalent in decreasing the risk of CVD may not be entirely appropriate.

Certain limitations of this study should be mentioned. To begin with, food categories included in the Mediterranean dietary pattern are not homogeneous among scores and methods used to assess the diet may vary across different studies. For instance, only two studies (Fung et al., 2009; Hoevenaar-Blom et al., 2012) included nut consumption separately whereas in other studies (Knoops et al., 2004; Mitrou et al., 2007; Buckland et al., 2009; Buckland et al., 2011; Martinez-Gonzalez et al., 2011) nuts were included with fruit and legumes consumption. Some other studies did not included legumes (Buckland et al., 2011; Tognon et al., 2012; Tognon et al., 2013) and one study used frequency of weekly consumption by portion rather than daily amount by weight (Fung et al., 2009). Although the basic diet characteristics were present in all of the included epidemiological studies, the differences in diet adherence assessment, mostly due to lack of specific food group components, may underestimate the effects on CVD protection. Another limitation is the non-conformity of exposure categories included in the meta-analysis (the use of different methodologies to group individuals according to exposure categories). However, despite these variations in exposure assessment, this approach is widely used in literature and we observed similar results across studies and no evidence of significant heterogeneity.

The findings of the present meta-analysis confirm that high adherence to the Mediterranean dietary pattern is associated with lower risk of CVD incidence and mortality, but the effects on specific cardiovascular outcomes between prospective studies and RCTs varies. Results from RCTs are limited due to scarce number of studies and warrants further investigations to better quantify the effectiveness of Mediterranean diet adherence especially in high-risk groups (secondary prevention). Among the single components of the diet, olive oil, vegetable, fruit, and legumes seem to provide the strongest cardio-protective properties and should be considered as crucial in the definition of future RCTs to effectively evaluate their effects.

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Table 1. Main characteristics of prospective studies exploring the relation between Mediterranean diet adherence and cardiovascular disease (CVD) incidence and mortality.

Author, year	Country (cohort)	No of subjects	Gender	Age range	Follow-up	Type of score	Outcome	No of cases	Adjustments	Categories of exposure	Study
Knoops et al, 2004	HALE (SENECA and FINE)	2339	M and F	70-90	10 y	mMed score	CHD mortality	122	Dietary and lifestyle factors, age, gender, number of years of education, body mass index, and study	2 groups (median)	8
							CVD mortality	371			
Mitrou et al, 2007	NIH-AARP	380,296	M and F	50-71	10 y	tMed score	CVD mortality	3451	Age, race, total energy, BMI, education, marital status, physical activity, menopausal hormone therapy in women only, and smoking variables (integrating smoking status, years since quitting for former smokers, smoking dose for both former and current smokers).	Tertiles	6
Panagiotakos et al, 2008	Greece (ATTICA)	3042	M and F	45 (mean)	5 y	aMed score	CVD incidence	170	Age, gender, physical activity, smoking status, waist-to-hip ratio, years of school, diabetes, hypercholesterolemia, triglycerides >150 mg/dl, hypertension, family history of CHD, C-reactive protein	2 groups (median)	8
Buckland et al, 2009	Spain (EPIC-Spain)	41,078	M and F	29-69	10.4 y	rMed score	CHD event	609	Center, age, education, physical activity, BMI, smoking status, diabetes, hypertension, hyperlipidemia status, and total energy intake.	Tertiles	8
Fung et al, 2009	US (Nurses' Health Study)	74,886	F	38-63	20 y	aMed score	CHD event	1597	Age, smoking, BMI, menopausal status and postmenopausal hormone use, energy intake, multivitamin intake, alcohol intake, family history, physical activity, and aspirin use.	Quintiles	6
							CHD mortality	794			
							Stroke event	1480			
							Stroke mortality	283			
Chrysohoou et al, 2010	Greece	1000	M and F with previous CAD	65	2 y	MedDietScore	CVD incidence (fatal + non-fatal)	237	Age, gender, physical activity, smoking status, BMI, hypercholesterolemia, diabetes mellitus, history of CVD, family history of CVD.	Terzile	5
Buckland et al, 2011	Spain (EPIC-Spain)	40,622	M and F	29-69	13.4 y	rMed score	CVD mortality	399	Center, age, gender, BMI, waist circumference, education level, physical activity, smoking status and intensity and total energy intake.	Tertiles	8
Gardener et al, 2011	US (Northern Manhattan Study)	2568	M and F	68.6 (mean age)	9 y	MeDi score	Stroke event	171	Age, gender, race-ethnicity, completion of high school education, moderate-to-heavy physical activity, total energy intake, cigarette smoking, hypertension, diabetes, hypercholesterolemia, and history of cardiac disease.	Quintiles	8
							MI event	133			
							Composite (ischemic stroke, MI, or vascular death)	314			

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Martinez-Gonzales et al, 2011	Spain (SUN cohort study)	13,609	M and F	38 (mean age)	4.9 y	aMed score	Composite (CVD death, CHD, MI, revascularization procedures or fatal or non-fatal stroke)	100	Age, gender, family history of coronary heart disease, total energy intake, physical activity, smoking, BMI, diabetes at baseline, use of aspirin, history of hypertension and history of hypercholesterolemia.	Quartiles	8
							CHD event	68			
Hodge et al, 2011	Australia Melbourne Collaborative Cohort	2150	M and F with diabetes	27-75	12.3	mMed score	CVD mortality	464	None	Terzile	8
Agnoli et al, 2011	Italy (EPICOR)	40,681	M and F	35-74	7.9	IMed index	Stroke event	178	Gender, smoking status, education, nonalcoholic energy intake, and BMI; stratified for center and age.	Tertiles	8
Misirli et al, 2012	Greece (EPIC-Greece)	23,601	M and F	20-86	10.6 y	mMed score	CBVS event	395	Age, education, smoking status, BMI, physical activity, hypertension, diabetes, and total energy intake.	Tertiles	8
							CBVS mortality	196			
Dilis et al, 2012	Greece (EPIC-Greece)	23,929	M and F	20-86	10.6 y	mMed score	CHD event	636	Age, gender, BMI, height, physical activity, years of schooling, total energy intake, smoking status, and arterial blood pressure	Tertiles	8
							CHD mortality	240			
Hoevenaar-Blom et al, 2012	Germany (EPIC-NL)	40,011	M and F	20-70	11.8 y	mMed score	CVD event	4881	Age, gender, cohort, smoking, physical activity, energy intake and educational level.	Quartiles	8
							CVD mortality	487			
							MI event	1070			
							Stroke event	448			
Menotti et al, 2012	Italy (Seven Countries Study)	1139	M	40-59	40 y	MAI	CHD mortality	162	Age, cigarettes, systolic blood, pressure, serum cholesterol, physical activity, and BMI.	2 groups (median)	8
Tognon et al, 2012	Subartic region	77,151	M and F	30-70	9 y	mMed score	CVD mortality	680	Age, obesity, smoking status, education, and physical activity	2 groups (median)	6
Tognon et al, 2013	Sweden (MONICA)	1849	M and F	30-59	14 y	mMed score	CVD event (fatal + non-fatal)	755	Gender, BMI, education, physical activity, cigarette smoking, blood pressure, TAG and total cholesterol:HDL-cholesterol ratio.	2 groups (median)	7
							CVD mortality	223			
							MI event (fatal + non-fatal)	161			
							Stroke event (fatal + non-fatal)	167			
Hoevenaar-Blom et al, 2013	Germany (Doetinchem Cohort Study)	7769	M and F	20-65	10 y	mMed score	CVD event	168	Age, gender, smoking, sports, energy intake, and educational level.	Tertiles	8
							CVD mortality	38			
Bertoia et al, 2014	US (Women's Health Initiative study)	93,122	F (post-menopausal)	50-79	10.5 y	mMed score	CVD mortality (cardiac death)		Age, energy, race, income, smoking status, physical activity, pulse in 60 s, waist-to-hip ratio, BMI, coronary artery disease, heart failure, diabetes, and hypertension.	Quintiles	8

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Lopez-Garcia et al, 2014	US (Health Professionals Follow-Up Study)	6137	M with CVD	40-75	7.7 y	aMed score	CVD mortality	873	Age, smoking status, BMI, leisure-time physical activity, parental history of myocardial infarction before age 65 y, menopausal status and use of hormone therapy in women, multivitamin use, and medication use.	Quintiles	7
	US (Nurses' Health Study)	11,278	F with CVD	30-55	5.8 y	aMed score	CVD mortality	902	Age, smoking status, BMI, leisure-time physical activity, parental history of myocardial infarction before age 65 y, menopausal status and use of hormone therapy in women, multivitamin use, and medication use.	Quintiles	

aMed, Alternate Mediterranean diet score; IMed index, Italian Mediterranean index; mMed, Modified Mediterranean diet score; MAI, Mediterranean Adequacy Index; MeDi, Mediterranean-style diet score; rMed, Relative Mediterranean diet score; tMed, Traditional Mediterranean diet score.

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Table 2. Subgroup analyses for composite CVD incidence and mortality.

	Number of studies	RR (95% CI)	Heterogeneity (I^2)
Geographical area			
Mediterranean	9	0.55 (0.44, 0.71)	72%
Non-Mediterranean	11	0.77 (0.70, 0.83)	74%
Sample size			
≤10,000	10	0.72 (0.62, 0.83)	83%
>10,000	10	0.71 (0.65, 0.77)	42%
Duration of follow-up			
≤10 years	12	0.74 (0.67, 0.81)	79%
>10 years	8	0.66 (0.55, 0.79)	68%
Type of adherence score			
mMed Diet	9	0.77 (0.69, 0.85)	75%
Others	11	0.65 (0.57, 0.75)	70%

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Table 3. Cut-off points of individual components of Mediterranean diet in participants in the highest category of exposure (highest adherence). Values should be intended as lower cut-off for foods considered beneficial according to the Mediterranean diet (i.e., fruit, vegetable, olive oil, alcohol, fish, legumes, cereals, nuts), and upper cut-off for those considered detrimental (i.e., meat and dairy products).

	Fruit	Vegetable	Olive oil	Alcohol	Fish	Legumes	Cereals	Meat	Dairy products	Nuts
						g/day				
Knoops et al, 2004	228	306	-	-	26	7[a]	248	130	313	-
Buckland et al, 2009	366[a]	270	24	within range	62	54	204	131	340	-
Fung et al, 2009	480	440	-	7	50	42	160	80	-	15
Buckland et al, 2011	380[a]	282	25	within range	64	-	214	137	352	-
Gardener et al, 2011	131	67	-	0	10	9	61	33	92	-
Martinez-Gonzales et al, 2011	250[a]	450		35	86	21	85	174	162	
Misirli et al, 2012	350	520	50		23	8	150	100	196	-
Dilis et al, 2012	209	231	23	19	17	7	70	54	147	-
Hoevenaar-Blom et al, 2012	155	113	-	8	8	13	194	110	371	6
Tognon et al, 2012	60	120	-	2	10	-	35	53	210	-
Tognon et al, 2013	109	192	-	16	25	--	180	182	297	-
mean cut-off	247	281	30	12	35	20	146	108	248	11

[a] Include nuts

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Table 4. Main characteristics of clinical randomized trials exploring the efficacy of Mediterranean diet on cardiovascular disease-related outcomes.

Author, year	Country	Number of participants (intervention/ control)	Inclusion criteria	Exclusion criteria	Age, mean (intervention/ controls)	Follow-up	Dietary intervention	Non-dietary intervention	Control	Outcome	Cases (intervention/ controls)	Drop-outs	Adjustments
de Lorgeril et al, 1999	France	605 (302/303)	Previous MI	Heart failure (stage III or IV of the New York Heart association functional class), hypertension (systolic > 180 mm Hg, diastolic > 110 mmHg), and inability to complete an exercise test due to recurrent angina, ventricular arrhythmias, or atrioventricular block); any conditions thought to limit survival or ability to participate in a long-term trial.	53.5/53.5	4 y	Mediterranean-type diet: more bread, vegetables, fruit, and fish; less red meat (to be replaced with poultry); butter and cream to be replaced with margarine.	None	Prudent diet	CVD mortality	6/19	19/15	Age, gender, smoking, serum lesterol, systolic blood pressure, and infarct location.
										MI incidence	8/25		
										Stroke incidence	0/4		
										Composite	14/44		
Singh et al, 2002	India	1000 (499/501)	One or more of the major risk factors for CAD, (hypertension, hypercholesterolaemia, or diabetes mellitus, or angina pectoris or a previous myocardial infarction in absence or presence of other risk factors.	Not declared	49/48	2 y	Indo-Mediterranean diet: less than 30% of energy from total fat, less than 10% from saturated fat, and less than 300 mg of cholesterol consumed per day; consuming at least 400–500 g of fruits, vegetables, and nuts per day, (i.e., 250–300 g of fruit, 125–150 g of vegetables, and 25–50 g of walnuts or almonds); 400–500 g of whole grains, legumes,	Walk briskly for a minimum of 3–4 km, or to jog intermittently for a minimum of 10–15 minutes per day; Smoking and alcohol consumption were discouraged, and we encouraged mental relaxation through yoga meditation techniques and breathing exercises in	Prudent diet: less than 30% of energy from total fat, less than 10% from saturated fat, and less than 300 mg of cholesterol consumed per day.	CVD mortality	6/16	9/11	Age, gender, body-mass index, cholesterol and blood pressure.

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							rice, maize, and wheat) daily; mustard seed or soy bean oil, in three to four servings per day	both groups.					
										MI mortality	12/17		
										MI incidence	21/23		
										Composite	39/76		
Giannuzzi et al. 2008	Italy	3241 (1620/1621)	Previous MI	Age older than 75 years, an unfavorable short-term outlook (eg, overt congestive heart failure, cancer), any systemic disease limiting exercise, and inability to participate in the trial for any logistic reason.	57.8/58	3 y	Mediterranean diet according to the "modified Mediterraneand diet score"	Monthly from month 1 to month 6, then every 6 months for 3 years 0 minutes of supervised aerobic exercise, plus lifestyle and risk factor coun- seling lasting at least 1 hour and reinforcement of preventive interventions lasting approximately 30 minutes.	General health advices	CVD mortality	18/24	62/57	None
										MI incidence	23/44		
										Stroke incidence	11/13		
										Composite	52/77		
Estruch et al. 2013	Spain	7447 (2543/2454/2450)	no cardiovascular disease at enrollment, who had either type 2 diabetes mellitus or at least three of the following major risk factors: smoking, hypertension, elevated low-	Previous CVD; any other conditions that may impair the ability to be adherent to the intervention program; istituzionalized patients; illiteracy.	67.0/66.7/67.3	5 y	Mediterranean diet: olive oil >4 spoons/day; tree nuts and peanuts >3 servings/week; fruit, vegetables, fish, legumes, sofrito >2 servings/week; white meat instead of red meat; wine with meals >7 servings/week.	None	Low-fat diet: low-fat dairy products, bread, potatoes, pasta, rice, fruits, vegetables, and fish; discouraged vegetable oils (including olive oil),	CVD mortality	26/31/30	91/155/277	Gender, age, family history of premature coronary heart disease, smoking status, BMI, waist-to-height ratio, hypertension at baseline, dyslipidemia at baseline, and

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	density lipoprotein cholesterol levels, low high-density lipoprotein cholesterol levels, overweight or obesity, or a family history of premature coronary heart disease.	nuts.			diabetes at baseline.
			MI incidence	37/31/38	
			Stroke incidence	49/32/58	
			Composite	96/83/109	

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Figure 1. Flowchart of publications included in this systematic review and meta-analysis.

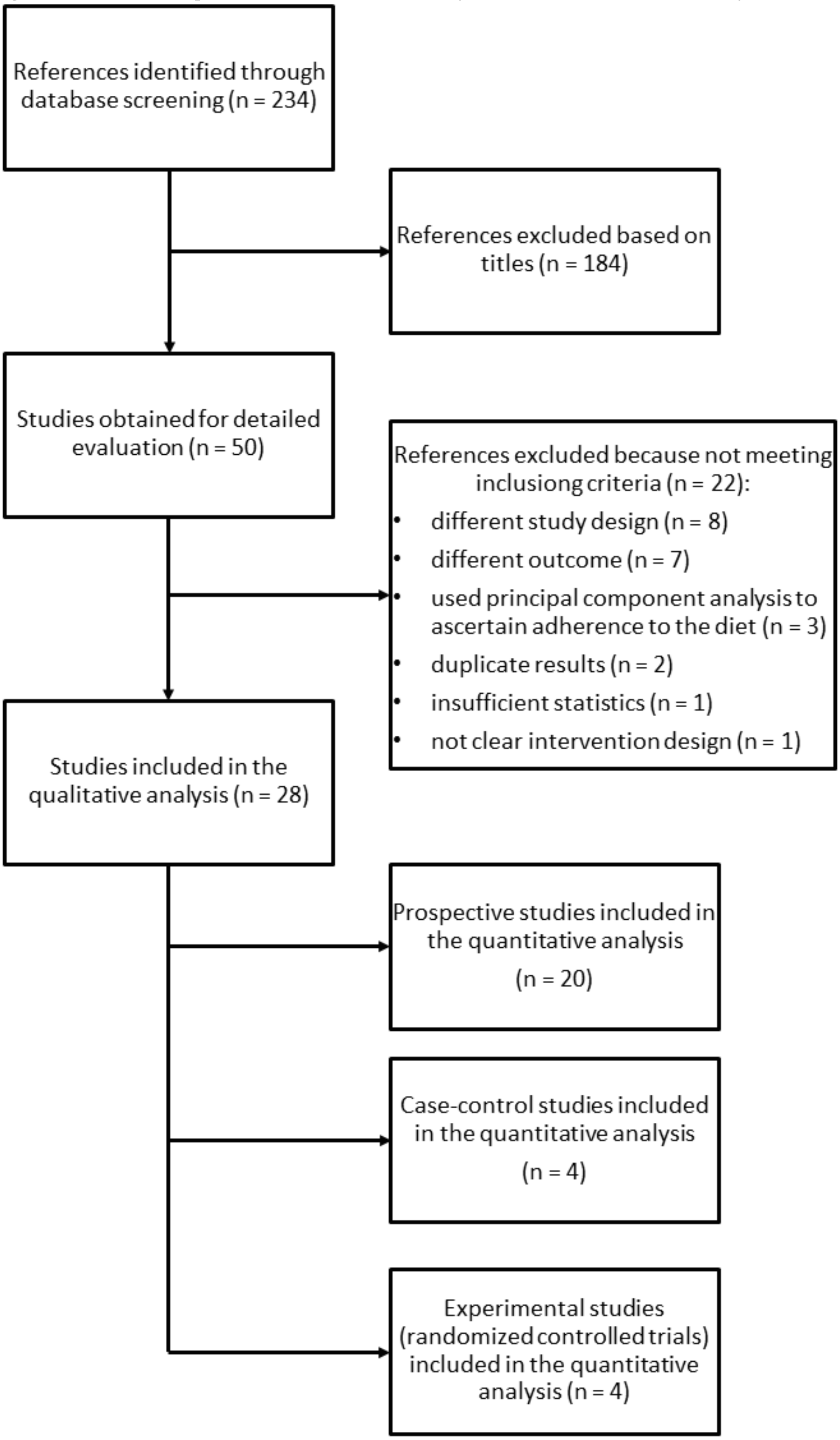

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Figure 2. Meta-analysis of prospective studies evaluating Mediterranean diet adherence and cardiovascular disease (CVD) risk by using relative risk (RR) and 95% confidence intervals (CI) comparing highest diet adherence with the lowest category. Size of symbol is proportional to inverse of variance of RR; horizontal line represents 95% CI.

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
CVD incidence				
Panagiotakos et al, 2008	-2.2073	0.4023	0.0%	0.11 [0.05, 0.24]
Buckland et al, 2009	-0.5108	0.1246	9.9%	0.60 [0.47, 0.77]
Fung et al, 2009	-0.2485	0.0626	18.6%	0.78 [0.69, 0.88]
Martinez-Gonzales et al, 2011	-0.8916	0.42	1.3%	0.41 [0.18, 0.93]
Menotti et al, 2012	-0.4463	0.2029	4.9%	0.64 [0.43, 0.95]
Tognon et al, 2013	-0.3285	0.1192	10.5%	0.72 [0.57, 0.91]
Agnoli et al, 2011	-0.755	0.2291	4.0%	0.47 [0.30, 0.74]
Chrysohoou et al, 2010	-0.844	0.4167	1.4%	0.43 [0.19, 0.97]
Gardener et al, 2011 (IS)	0.0296	0.2673	3.1%	1.03 [0.61, 1.74]
Gardener et al, 2011 (MI)	-0.4308	0.2739	2.9%	0.65 [0.38, 1.11]
Misirli et al, 2012	-0.3285	0.1468	8.0%	0.72 [0.54, 0.96]
Dilis et al, 2012	-0.1985	0.1107	11.4%	0.82 [0.66, 1.02]
Hoevenaar-Blomet al, 2012	-0.1744	0.0578	19.4%	0.84 [0.75, 0.94]
Hoevenaar-Blomet al, 2013	-0.4308	0.2108	4.6%	0.65 [0.43, 0.98]
Total (95% CI)			**100.0%**	**0.73 [0.66, 0.80]**
CVD mortality				
Knoops et al, 2004	-0.3425	0.1032	7.1%	0.71 [0.58, 0.87]
Mitrou et al, 2007 (M)	-0.2485	0.0626	8.9%	0.78 [0.69, 0.88]
Mitrou et al, 2007 (F)	-0.2107	0.0893	7.7%	0.81 [0.68, 0.96]
Fung et al, 2009	-0.4943	0.1223	6.3%	0.61 [0.48, 0.78]
Buckland et al, 2011	-0.4155	0.152	5.2%	0.66 [0.49, 0.89]
Hodge et al, 2011 (F)	-0.2485	0.16	5.0%	0.78 [0.57, 1.07]
Hodge et al, 2011 (M)	-0.2485	0.109	6.9%	0.78 [0.63, 0.97]
Hoevenaar-Blomet al, 2012	-0.821	0.1954	3.9%	0.44 [0.30, 0.65]
Menotti et al, 2012	-0.4463	0.2029	3.8%	0.64 [0.43, 0.95]
Tognon et al, 2012 (F)	-0.1054	0.0475	9.4%	0.90 [0.82, 0.99]
Tognon et al, 2012 (M)	-0.0101	0.0319	9.9%	0.99 [0.93, 1.05]
Dilis et al, 2012	-0.2485	0.0852	7.9%	0.78 [0.66, 0.92]
Misirli et al, 2012	-0.2744	0.2136	3.5%	0.76 [0.50, 1.16]
Tognon et al, 2013	-0.5621	0.1936	4.0%	0.57 [0.39, 0.83]
Bertoia et al, 2014	-0.4005	0.1919	4.0%	0.67 [0.46, 0.98]
Lopez-Garcia et al, 2014	-0.1625	0.1214	6.4%	0.85 [0.67, 1.08]
Total (95% CI)			**100.0%**	**0.75 [0.68, 0.83]**
Composite				
Total (95% CI)			**100.0%**	**0.71 [0.65, 0.78]**

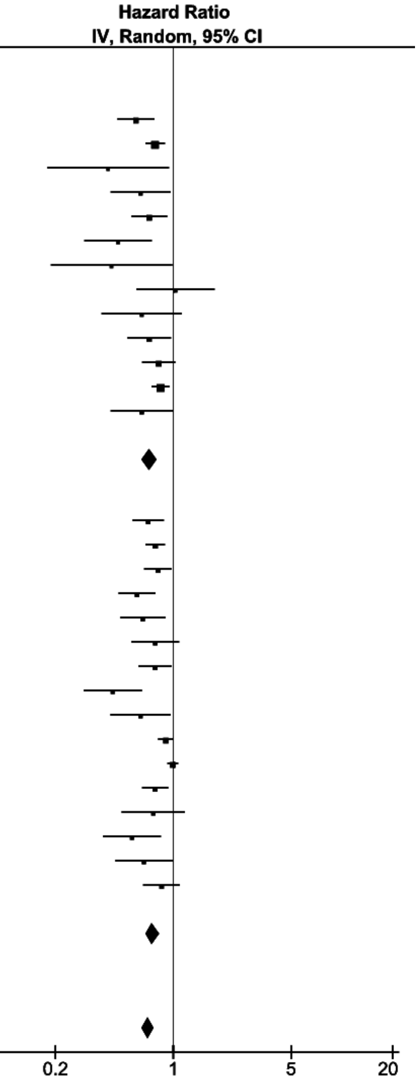

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Figure 3. Meta-analysis of prospective studies evaluating Mediterranean diet adherence and coronary heart disease (CHD), myocardial infarction (MI), and stroke risk by using relative risk (RR) and 95% confidence intervals (CI) comparing highest diet adherence with the lowest category. Size of symbol is proportional to inverse of variance of RR; horizontal line represents 95% CI.

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
CHD incidence				
Buckland et al, 2009	-0.5108	0.1246	28.1%	0.60 [0.47, 0.77]
Dilis et al, 2012	-0.1985	0.1107	31.7%	0.82 [0.66, 1.02]
Fung et al, 2009	-0.2485	0.093	36.9%	0.78 [0.65, 0.94]
Martinez-Gonzales et al, 2011	-0.8675	0.4924	3.2%	0.42 [0.16, 1.10]
Total (95% CI)			**100.0%**	**0.72 [0.60, 0.86]**
MI incidence				
Gardener et al, 2011	-0.4308	0.2739	15.9%	0.65 [0.38, 1.11]
Hoevenaar-Blomet al, 2012	-0.3567	0.1419	59.3%	0.70 [0.53, 0.92]
Tognon et al, 2013	-0.462	0.2192	24.8%	0.63 [0.41, 0.97]
Total (95% CI)			**100.0%**	**0.67 [0.54, 0.83]**
Stroke incidence				
Fung et al, 2009	-0.1054	0.093	32.5%	0.90 [0.75, 1.08]
Gardener et al, 2011	0.0296	0.2673	13.6%	1.03 [0.61, 1.74]
Agnoli et al, 2011	-0.755	0.2291	16.5%	0.47 [0.30, 0.74]
Hoevenaar-Blomet al, 2012	-0.3567	0.2032	18.9%	0.70 [0.47, 1.04]
Tognon et al, 2013	-0.2877	0.2069	18.5%	0.75 [0.50, 1.13]
Total (95% CI)			**100.0%**	**0.76 [0.60, 0.96]**

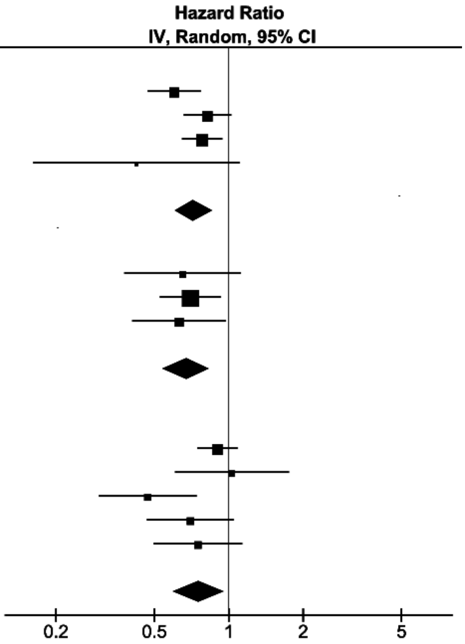

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Figure 4. Pooled risk ratios of individual Mediterranean diet components and composite CVD outcomes.

Med diet Component	Risk Ratio IV, Random, 95% CI
Alcohol	0.97 [0.88, 1.07]
Cereals	0.95 [0.90, 1.00]
Dairy products	1.10 [1.02, 1.19]
Fish	0.96 [0.91, 1.01]
Fruit	0.88 [0.81, 0.96]
Legumes	0.90 [0.83, 0.98]
Meat	1.02 [0.96, 1.08]
Olive oil	0.83 [0.77, 0.89]
Vegetable	0.87 [0.77, 0.98]

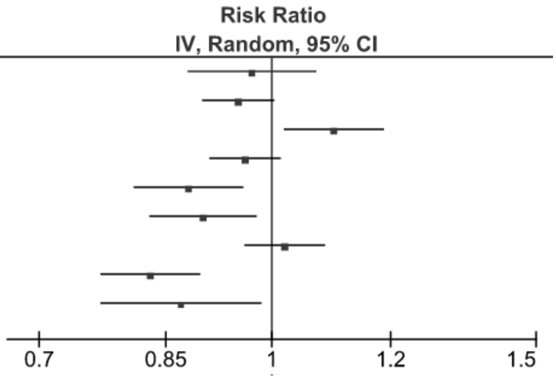

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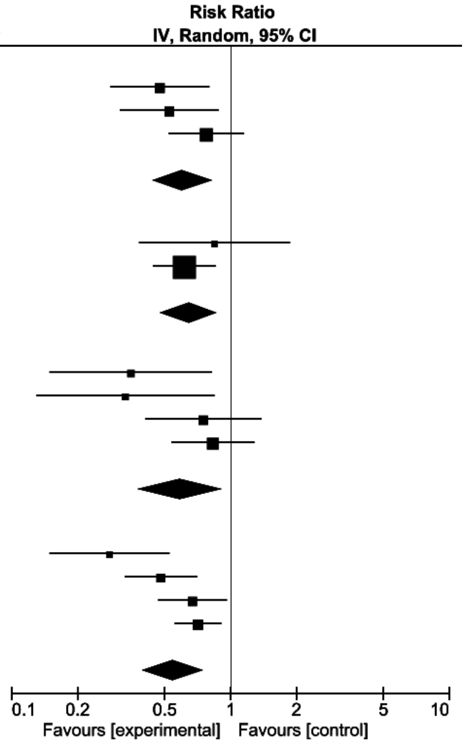
Figure 5. Meta-analysis of randomized controlled trials evaluating Mediterranean diet adherence and various cardiovascular outcomes by using relative risk (RR) and 95% confidence intervals (CI). Size of symbol is proportional to inverse of variance of RR; horizontal line represents 95% CI.

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI	Year
MI incidence					
Singh et al, 2002	-0.755	0.2643	28.6%	0.47 [0.28, 0.79]	2002
Giannuzzi et al, 2008	-0.6539	0.2639	28.7%	0.52 [0.31, 0.87]	2008
Estruch et al, 2013	-0.2614	0.2003	42.7%	0.77 [0.52, 1.14]	2013
Total (95% CI)			**100.0%**	**0.60 [0.44, 0.82]**	
Stroke incidence					
Giannuzzi et al, 2008	-0.1744	0.4047	14.5%	0.84 [0.38, 1.86]	2008
Estruch et al, 2013	-0.4943	0.1667	85.5%	0.61 [0.44, 0.85]	2013
Total (95% CI)			**100.0%**	**0.64 [0.47, 0.86]**	
CVD mortality					
de Lorgeril et al, 1999	-1.0498	0.4323	18.8%	0.35 [0.15, 0.82]	1999
Singh et al, 2002	-1.1087	0.4753	16.5%	0.33 [0.13, 0.84]	2002
Giannuzzi et al, 2008	-0.2877	0.3081	27.8%	0.75 [0.41, 1.37]	2008
Estruch et al, 2013	-0.1863	0.2193	36.9%	0.83 [0.54, 1.28]	2013
Total (95% CI)			**100.0%**	**0.59 [0.38, 0.93]**	
Composite					
de Lorgeril et al, 1999	-1.273	0.3185	16.0%	0.28 [0.15, 0.52]	1999
Singh et al, 2002	-0.734	0.1912	25.5%	0.48 [0.33, 0.70]	2002
Giannuzzi et al, 2008	-0.4005	0.1809	26.5%	0.67 [0.47, 0.96]	2008
Estruch et al, 2013	-0.3425	0.1211	32.0%	0.71 [0.56, 0.90]	2013
Total (95% CI)			**100.0%**	**0.55 [0.39, 0.76]**	



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Supplemental Figure 1. Funnel plot of studies evaluating incidence of and mortality from cardiovascular disease.