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Full Title

The Mediterranean Diet and Cardiovascular Health: a critical review

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Short Title

Mediterranean Diet and CVD: a critical review

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Abbreviations

aMedDiet	alternative Mediterranean diet
CHD	coronary heart disease
CVD	cardiovascular disease
DASH	dietary approaches to stop hypertension diet
DGAC	dietary guidelines advisory committee
EVOO	extra-virgin olive oil
GAE	gallic acid equivalent
GOSPEL	Global Secondary Prevention Strategies to Limit Event Recurrence After Myocardial Infarction trial
MEDAS	Mediterranean diet adherence screener
MUFA	monounsaturated fat
MedDiet	Mediterranean diet
PREDIMED	PREvencion con DIeta MEDiterranea trial
RCT	randomized controlled trial
SFA	saturated fat
TPE	total polyphenol excretion
VCAM-1	vascular cell adhesion molecule 1

Abstract

The Mediterranean diet (MedDiet), abundant in minimally-processed plant-based foods, rich in monounsaturated fat from olive oil, but **lower** in saturated fat, meats and dairy products, seems an ideal nutritional model for cardiovascular health. Methodological aspects of Mediterranean intervention trials, limitations in the quality of some meta-analyses and other issues **may** have raised recent controversies. It remains unclear whether such limitations are important enough as to attenuate the postulated cardiovascular benefits of the MedDiet. **We aimed to** critically review **current** evidence on the role of the MedDiet in cardiovascular health. We systematically searched observational prospective cohorts and randomized controlled trials (RCTs) which explicitly reported to assess the effect of the MedDiet on hard cardiovascular end-points. We critically assessed all the original cohorts and RCTs included in the 5 most comprehensive meta-analyses published between 2014 and 2018 and additional prospective studies not included in these meta-analyses, totaling 45 reports of prospective studies (including 4 RCTs and 32 independent observational cohorts). We addressed the existing controversies on methodology and other issues. Some departures from individual randomization in **a subsample of the** landmark Spanish trial (PREDIMED) did not represent any clinically meaningful attenuation in the strength of its findings and the results of PREDIMED were robust in **a wide range** of sensitivity analyses. The criteria for causality were met and potential sources of controversies did not represent any reason to compromise the main findings of the available observational studies and RCTs. **The available evidence is large, strong and consistent.** Better conformity with the traditional MedDiet is associated with better cardiovascular health outcomes, including clinically meaningful reductions in rates of coronary heart disease, ischemic stroke and total cardiovascular disease.

Keywords: Mediterranean Diet, coronary heart disease, ischemic stroke, hemorrhagic stroke, cohort studies, meta-analysis

Diet has been traditionally considered as a main determinant of cardiovascular health. In fact, one of the 7 cardiovascular health metrics proposed in 2010 by the American Heart Association ("Life's simple 7") directly corresponds to a healthy diet.[1] But also, other 4 of the remaining 6 proposed health metrics (body mass index, blood pressure, total cholesterol and blood glucose) are closely determined by dietary habits. Moreover, an additional health metric, physical activity, represents just the other side of the energy balance equation and it is *indirectly* related to dietary energy intake. Therefore, a healthy diet is **essential** to meet most of the goals of Life's simple 7 and to ensure cardiovascular health.

In this context, the overall quality of the whole food pattern may be more important and more interpretable than analyses focused on single nutrients or foods. The study of overall food patterns represents the current state of the art in the investigation of the nutritional determinants of cardiovascular health.[2,3] This approach is advantageous because it limits confounding by individual dietary factors and it captures the synergistic effects of individual foods and nutrients. It may also provide a more powerful tool to assess the effect of dietary habits on cardiovascular health because the effect of a single dietary element is likely to be too small as to be detected in epidemiological studies or randomized controlled trials (RCTs). In contrast, it seems logical that the cumulative effect of many different aspects of diet is likely to be considerably larger.[4]

The Mediterranean diet (MedDiet) represents a salient overall dietary pattern in nutritional epidemiology that has been extensively studied, especially during the last two decades.

The MedDiet is defined as a traditional eating pattern found among populations living in the Mediterranean Basin during the 50s and 60s of the 20th century, but, unfortunately, not today.[5] The main characteristics of the MedDiet at those times were a low consumption of meat and meat products, with very low consumption of red meat (beef, pork and lamb were reserved only for special occasions), very low or null consumption of processed meats, butter, ice-creams or other whole-fat dairy products (only fermented dairy products, cheese and yogurt, were consumed in moderate amounts). **It** presented a relatively fat-rich profile because of the abundant consumption of olive oil, together with a high consumption of minimally processed, locally grown, vegetables, fruits, nuts, legumes, and cereals (mainly unrefined).[6] An important source of protein was a moderate consumption of fish and shellfish, that was variable depending on the proximity to the sea. The main sources of fat and alcohol among persons **in the** traditional MedDiet are primarily extra-virgin olive oil (EVOO) and red wine, respectively. The abundant use of olive oil, through salads, traditionally cooked vegetables, and legumes, together with the moderate consumption of red wine during meals **makes** this diet highly nutritious and palatable. Red wine and EVOO contain several bioactive polyphenols (hydroxytyrosol and tyrosol, oleocanthal, resveratrol) with postulated anti-inflammatory properties.[7] Postulated anti-atherogenic properties of olive oil were supposedly attributed to its high content of monounsaturated fat (oleic acid),[8] and some more recent investigations also suggest that bioactive polyphenols, only present in the EVOO, but not in the refined-common variety of olive oil, may contribute to these cardio-protective actions.[9] EVOO is the product from the first pressing of the ripe olive fruit and contains many antioxidants (polyphenols, tocopherols and phytosterols).[10] Lower-quality oils (refined or common olive oils) are believed to be devoid of most of these antioxidant, anti-inflammatory or pleiotropic capacities because they are obtained by physical and chemical procedures that keep the fat but lead to the loss of most bioactive elements.

In the Spanish landmark PREDIMED trial, with 7,447 high-risk participants initially free of cardiovascular disease, a 5-year intervention with a MedDiet significantly reduced the incidence of a composite major cardiovascular disease (CVD) end-point that included non-fatal stroke, non-fatal coronary heart disease (CHD) and all fatal CVD events. However, the results of that trial were recently retracted by the authors and simultaneously republished in the same journal.[11] They included many new analyses and comprehensively addressed **some small** departures from **individual randomization.** Notwithstanding, many questions remain as to whether the MedDiet can confer benefits for cardiovascular health in both Mediterranean and non-Mediterranean populations. It is also uncertain how variations in the components of the MedDiet indices used in different studies may influence this association. In addition, other potential sources of bias should be adequately addressed.

In the first sections of this article we will discuss some potential concerns about the beneficial cardiovascular effects of the MedDiet. In the following sections, we will address issues related to these concerns. The currently available evidence strongly supports the MedDiet as an ideal approach for cardiovascular health.

Concerns about the MedDiet

Potential limitations related to the concept and operational definitions of the MedDiet

Is the "MedDiet" a concept promoted mainly or partly for geographical-romantic-nostalgic reasons?

Many of the investigators who are currently strong supporters of the MedDiet have born, live or have an ancestry in Mediterranean countries.[6,12] This **might represent** a reason of concern because they may be biased when selecting the pieces of evidence that best fit in the picture of their pre-conceptions about what should be a healthy diet.[13] They are likely to include those aspects of their diet that they have loved since childhood and even they learnt from their grandparents or ancestors.[14] It is easy to think that there might be a sort of mixture of scientific and non-scientific reasons, some of them probably unconscious, in this group of investigators and these mixed motives may have contributed to the adoption of their strong positions and opinions on the cardiovascular benefits of the MedDiet. **As discussed below, this assertion is not supported by the fact that numerous studies conducted in non-Mediterranean populations have found similar benefits of Mediterranean type dietary patterns on CVD risk.**

Is the MedDiet a concept based on vested commercial interests of olive oil and nut companies?

The potential biases in biomedical investigation related to research funding by the pharmaceutical industry have been largely studied and documented. It is well known that there is a significant association between industry sponsorship and pro-industry

conclusions. But similar biases related to research funding by food industry have been only recently documented. Pro-industry bias in pharmaceutical research might have adverse health effects on millions of patients receiving medications, but pro-industry bias in nutrition research will have adverse health effects for absolutely everyone, with a substantially higher harm for public health. In addition, regulations are tighter for pharmaceutical research than for nutritional research.[15]

In the jungle of academic-industry interactions scientific truth —nothing more, nothing less— should be the primary aim that all should pursue.[16] This statement has been frequently repeated in the scientific environments surrounding investigators on nutrition and cardiovascular health. The primary interests of multinational food companies are to increase their profits, and consequently, to make easier the most profitable food choices. In contrast, the primary interest of public health is to make easier the healthiest choices. There is a clear clash of interests. Many published studies, particularly small trials with soft end-points and reviews or commentaries, on the benefits of the MedDiet for cardiovascular health have been funded by food industries or were written after their presentation in an industry-funded meeting. Although not to the same extent than for sugar-sweetened beverages,[17] this potential conflict of interest has been specifically criticized in relationship with the very concept of the MedDiet. Richard Smith, former editor of the BMJ, wrote “a combination of vested interests, including the International Olive Oil Council and a public relations company Oldways, which promoted the diet, has—together with the natural seductiveness of the Mediterranean region—made the diet popular”.[18] **These** criticisms, **however, do not hold water based on the fact that the vast majority of evidence on MedDiet has been funded publicly. We will discuss this issue in a later section.**

Should refined cereals be a part of the MedDiet?

The currently available epidemiological evidence consistently supports the recommendation to consume less refined grains and replace them by whole grains. This replacement will reduce the risks of type 2 diabetes and cardiovascular disease.[19-21] However, in the most frequently used operational definition of the MedDiet[22] all cereals are included as a single positive item. No difference is made between refined and whole grain cereals. The assumption that all grains, including refined grains, provide cardiovascular protection might be against the current scientific evidence. Fung et al.[23], modified the score developed by Trichopoulou and included only whole grain products in the alternative Mediterranean diet (aMeD) **score**. **Similarly**, Panagiotakos et al.[24] gave the greater adherence to the MedDiet to the highest consumption of whole grains (Table 1). This modification seems more consistent with current mainstream findings in nutrition science. The PREDIMED trial did not include the consumption of cereals in the Mediterranean diet adherence screener (MEDAS).[25] This difference **might** cast doubts on the reliability of **some MedDiet scores** to capture a dietary pattern with the largest potential for cardiovascular health.

Table 1. Mediterranean diet scores frequently used in cardiovascular research

	Mediterranean Diet score (Trichopoulou[22], 0 to 9 points)	Alternate Mediterranean Diet (aMED) Score (Fung[23], 0 to 9 points)	Mediterranean Diet score (Panagiotakos[24], 0 to 50 points)	Mediterranean Diet Adherence Screener (MEDAS-PREDIMED[25], 0 to 14 points)
Positively weighted components	Monounsaturated/Saturated * Vegetables * Fruits and nuts * Legumes * Fish * Cereals *	Monounsaturated/Saturated‡ Vegetables ‡ Fruits ‡ Nuts ‡ Legumes ‡ Fish ‡ Whole grains ‡	Olive oil in cooking ‖ Vegetables ‖ Fruits ‖ Legumes ‖ Fish ‖ Whole grains ‖	Olive oil as main culinary fat ≥4 tablespoon# /day olive oil ≥2 servings/day olive oil sauce with tomato, garlic, onion or leek (“sofrito”) ≥2 servings/day vegetables ≥3 servings/day fruits ≥3 servings/week nuts ≥3 servings/week legumes ≥3 servings/week fish Preference for poultry (chicken, turkey or rabbit) > red meats (beef, pork, hamburgers, or sausages)
Negatively weighted components	Meat/meat products † Dairy products †	Red and processed meat §	Red and processed meat ‖ Poultry ‖ Full fat dairy products ‖	<1/day red/processed meats <1/day butter/margarine/cream <1/day carbonated/sugar-sweetened beverages <2/week Commercial bakery, cakes, biscuits or pastries
Alcohol	5–25 g/day (women) 10–50 g/day (men)	5–15 g/day (women) 10–25 g/day (men)	>0 and <300 ml/day (5 points)	≥7 glasses** /week of wine

* One point if the consumption was at or above the sex-specific median, † One point if the consumption was below the sex-specific median, ‡ One point if the consumption was above the sex-specific median, § One point if the consumption was at or below the sex-specific median, || 0 to 5 points according to six categories for frequency of consumption, # 1 tablespoon = 13.5 g, **1 glass = 100 ml

Can alcohol still be part of the MedDiet?

A moderate intake of alcohol has usually been considered a positive item in most of the MedDiet indexes (Table 1). However, results from a recent study have pointed out alcohol consumption as one of the leading factors for global disease burden.[26] **There is a view – based on some studies with inherent limitations-** that alcohol, even when consumed moderately, increases the risk of many diseases.[27] Specifically, a dose-response relationship between alcohol and different types of cancer **is likely to exist**.[28] For this reason, some adapted MedDiet scores have excluded alcohol intake to assess the relationship between adherence to MedDiet and breast cancer.[29] Thus, one question is whether moderate alcohol consumption should no longer be used in the operational definition of the MedDiet. **As discussed below, moderate consumption of wine with meals is still considered one of components of MedDiet, although consumption of alcohol is not encouraged for individuals who do not drink.**

Do dairy products play any role in the MedDiet?

The role of dairy products in cardiovascular health is controversial. However, metabolic benefits have been reported for some dairy products, specially fermented dairy products in a non-linear relationship[30], and a meta-analysis found significant reductions in stroke incidence associated with dairy product consumption.[31] Nevertheless, all dairy products are *negatively* weighted in the MedDiet score proposed by Trichopoulou.[22] **However**, the aMed and the MEDAS excluded most dairy products giving them a null value. This is another source of discrepancy between the scores used in different studies which contributes to the consideration that the MedDiet is a broad term that varies across the literature.[32] In fact, Galbete et al[33] compiled 34 different published definitions of the MedDiet.

Are potatoes and eggs a part of the definition of the MedDiet?

In most of these 34 definitions[33] potatoes were excluded from the vegetable group when computing the MedDiet score. But potatoes were explicitly included together with vegetables in a small number of scores, such as those used by Tognon et al[34] and by Knoops et al[35]. In other 2 reports they were also positively weighted (as supposedly beneficial) because they were included together with cereals.[36,37]

Usually, egg consumption is not included in definitions of the MedDiet, but some studies did include eggs together with meats[38] or as a separate item giving to egg consumption a negative weight.[39]

In the landmark observational cohort study that first related the MedDiet with lower cardiovascular mortality[22], authors explicitly stated that potatoes and eggs should be kept apart from the scoring system for the MedDiet, and therefore they should receive a null consideration.

Should any diet rich in fruit and vegetables be classified as a "traditional Mediterranean diet"?

Surprisingly, some meta-analyses classified as "Mediterranean" any dietary pattern which met at least 2 of 7 criteria. The rationale for these criteria is more than debatable and this terminology is confusing because this would mean, for example, that any diet rich in fruit and vegetables could be called a "Mediterranean-style" diet.[40]

What are the main sources of fat and fat subtypes in the MedDiet?

In the most common definition of the MedDiet[22] the ratio monounsaturated:saturated fat (MUFA:SFA) is one of the 9 items used to build the score, but other scores have used instead the unsaturated:saturated fat ratio, including polyunsaturated fats to account for the fact that other sources of MUFA[41], different from olive oil, are usually important in non-Mediterranean regions and the usual finding of beneficial cardiovascular effects when saturated fat is replaced by polyunsaturated fat. In some other Mediterranean scores, instead of using the MUFA:SFA ratio, the authors selected only the consumption of olive oil for this item. Even if olive oil might not correspond to the most important source of fat for cardiovascular health, use of olive oil as main culinary fat is an essential characteristic of the MedDiet. The PREDIMED trial gave a special importance to EVOO as a source of bioactive polyphenols. These polyphenols are increasingly mentioned as **contributors to** the cardiovascular health benefits because of their anti-inflammatory properties.[42,43] Interestingly, the 14-item questionnaire used in the PREDIMED was one of the scores that captured the highest intake of polyphenol antioxidant content in a comparison of 21 MedDiet indexes.[44]

Are polyphenols consumed in sufficient amounts as to have a credible effect?

There are differences between Mediterranean and non-Mediterranean countries regarding the type of flavonoids and food sources.[45] But when a high polyphenol content of the MedDiet is invoked as **partly** responsible for the cardiovascular benefits of this food pattern, a relevant question is usually raised: what are the minimum amounts of bioactive polyphenols that can exert a sufficiently large pleiotropic effect as to yield meaningful clinical effects? One of the sub-studies of PREDIMED measured total polyphenol urinary excretion and the lower limit for the upper tertile of excretion was 32 mg GAE (gallic acid equivalent) per gram of creatinine.[46] How is it possible that these polyphenols which are present only in minuscule amounts may be able to account for an impressive reduction in cardiovascular clinical events? This quantitative question that was critical when postulating resveratrol as the main element responsible for the potential protective effect of red wine has not been sufficiently investigated with respect to the total amounts of polyphenols present in the typical foods of the MedDiet. **However, polyphenols are only a part of the synergy among many beneficial bioactive compounds in the MedDiet.**

Are valid the sample-specific cut-off points used for some MedDiet scores?

The usual approach to derive scores of adherence to the MedDiet is to use the sample-specific medians of consumption of each food group, and to assign one point to those who are at or above the sex-specific median of the sample for items that are in line with the concept of the traditional MedDiet. On the contrary, one point is given to those participants who are below the sex-specific median of consumption for items that are in opposition to the traditional MedDiet. In some other scores, the authors used tertiles (to give 2, 1 or 0 points) instead of using the dichotomization at the sample medians.[47]

A potential problem with these scoring systems is that the medians (or other quantiles) are dependent on the sample characteristics and can compromise between-study comparisons or its generalizability.

Why so many disparate scores?

A relevant question seems to be the disparate classification and the many different actual exposures that have been collectively classified under the same term "MedDiet". The most recent systematic review[33] assessed 70 original studies (including both cardiovascular and non-cardiovascular outcomes). Among them, 14 studies used the definition of Trichopoulou, and 18 other studies used definitions (nine different versions), that were basically similar to the Trichopoulou's definition.[22] The aMed proposed by Fung[23] (or several closely-related versions) was used by 14 studies. Other definitions and scores were less frequently used. This variability entrails a potential for misclassification.

Limitations in the available meta-analyses of observational studies

There are more systematic reviews than original studies

In 2016, an evaluation of the quality of systematic reviews relating the MedDiet with cardiovascular outcomes was published by Huedo-Medina et al[32]. They included 24 meta-analyses and systematic reviews in their evaluation. In 2015, Martínez-González et al included 37 meta-analyses or systematic reviews assessing the association between adherence to the MedDiet and cardio-metabolic outcomes.[48] Subsequently, in 2017 and 2018, five new meta-analyses or systematic reviews were published.[33,49-52] Most of the available systematic reviews included less than 25 original studies. Therefore, paradoxically, the literature seems to contain more reviews than original studies (Table 2).[32,33,48-85] A summary description is shown in Table 2 and the overlapping original studies[22,23,34,37-39,41,86-122] between systematic review are presented in Figure 1.

Table 2. Summary of the reviews and meta-analyses gathering evidence about Mediterranean diet and cardiovascular disease

Author, year	Systematic	Design (assessed designs)	Outcomes	Meta-analyzed articles	Results (meta-analysis)
de Lorgeril, 2001[53]	No	Narrative	CHD		
Panagiotakos, 2004[54]	Yes	Case-control and prospective studies	CHD		
Serra-Majem, 2006[55]	Yes	Trials	CVD		
Willett, 2006[56]	No	Personal perspectives			
de Lorgeril, 2008[57]	No	Narrative			
Roman, 2008[58]	Yes	Any design, participants older than 65	CVD		
Sofi, 2008[59]	Yes	Cohort studies	CVD mortality	22,35,95	0.91 (0.87-0.95)
Martínez-González, 2009[60]	No	Narrative	Chronic deseases		
Mente, 2009[61]					
Sofi, 2009[62]	No	Narrative	Health outcomes		
Sofi, 2010[63]	Yes	Cohort studies			
Tyrovolas, 2010[64]	Yes	Observational studies	CVD incidence or mortality	22,23,35,95,98,103	0.90 (0.87-0.93)
McKeown, 2010[65]	No	Narrative	CVD, CHD		
Foroughi, 2013[66]	Yes	Observational studies, trials, reviews and meta-analyses	Stroke		
Psaltopoulou, 2013[67]	Yes	Observational	Stroke	23,99,101,105	0.84 (0.74-0.95)
Rees, 2013[68]	Yes	Trials, primary prevention	CVD	Authors did not find any trial	-
de Lorgeril, 2013[69]	No	Narrative	CVD		

Table 2. Summary of the reviews and meta-analyses gathering evidence about Mediterranean diet and cardiovascular disease (cont.)

Author, year	Systematic	Design (assessed designs)	Outcomes	Meta-analyzed articles	Results (meta-analysis)
Grosso, 2014[70]	Yes	Epidemiological studies	CVD and risk factors		
Kontogianni, 2014[71]	Yes	Observational and trials	Stroke	89,107,109	0.68 (0.58-0.79)
Martínez-González, 2014[72]	Yes	Cohorts and trials	CVD	87,89 23,34,35,38,95,98,101,104,105,106,107,145	**RCTs:** 0.64 (0.53-0.79) **Observational:** 0.90 (0.86-0.94)
Ros, 2014[73]	No	Narrative	CVD		
Sofi, 2014[74]	Yes	Prospective studies	CVD incidence or mortality	23,34,35,36,37,95,99,100,101,104,105,107,145,169	0.90 (0.87-0.92)
Trichopoulou, 2014[75]	No	Narrative			
Whayne, 2014[76]	No	Narrative	Ischemic Heart disease		
Sleiman, 2015[77]	Yes	Cross-sectional, prospective and controlled clinical trials	CVD, CVD mortality, PAD		
Widmer, 2015[78]	No	Narrative	CVD		
D'Alessandro, 2015[79]	No	Narrative	CVD		
Shen, 2015[80]	No	Narrative	CVD, AF, CVD mortality		
Martínez-González, 2015[48]	No	Narrative	CVD, CVD mortality		
Huedo-Medina, 2016[32]	Yes	Systematic reviews and meta-analyses	CVD outcomes		

Table 2. Summary of the reviews and meta-analyses gathering evidence about Mediterranean diet and cardiovascular disease (cont.)

Author, year	Systematic	Design (assessed designs)	Outcomes	Meta-analyzed articles	Results (meta-analysis)
Liyanage, 2016[81]	Yes	Randomized controlled trials	CVD mortality Coronary events Stroke HF	86,88,89,168 86,88,89 88,89 86,88	0.90 (0.72-1.11) 0.65 (0.50-0.85) 0.66 (0.48-0.92) 0..25 (0.05-1.17)
Martínez-González, 2016[82]					
Bloomfield, 2016[83]	Yes	Controlled trials	CVD	89	
Dinu, 2017[52]	Yes	Meta-analyses of observational studies and randomized trials	CVD and health outcomes		
Rosato, 2017[49]	Yes	Observational studies	CHD, MI Unspecified stroke i-stroke h-stroke Unspecified CVD	34,98,101,104,105,111,116, 117,145,170,173,99,105, 107,109,117,172,23,99, 101,115,116 23,99,115,116 35,37,100,101,105,113, 114,117,120,121,145	0.70 (0.62-0.80) 0.73 (0.59-0.91) 0.82 (0.73-0.92) 1.01 (0.74-1.37) 0.81 (0.74-0.88)
Martínez-González, 2017[50]	Yes	Clinical trials or prospective cohort studies	CVD incidence or mortality	22,23,34,35,38,86,89,95, 98,100,101,104,105,107, 116,118,119,120,122,145, 171	0.89 (0.86-0.91)

Table 2. Summary of the reviews and meta-analyses gathering evidence about Mediterranean diet and cardiovascular disease (cont.)

Author, year	Systematic	Design (assessed designs)	Outcomes	Meta-analyzed articles	Results (meta-analysis)
Grosso, 2017[51]	Yes	Prospective studies and RCT	CVD incidence	23,38,39,96,98,99,101,103, 104,105,106,107,110	0.73 (0.66-0.80)
			CVD mortality	23,34,35,38,95,100,102,104, 105,106,107,111,112	0.71 (0.65-0.78)
			CHD incidence	23,98,114,145	0.72 (0.60-0.86)
			MI incidence	38,101,105	0.67 (0.54-0.83)
			Stroke incidence	23,38,99,101,105	0.76 (0.60-0.96)
			MI (RCT)	88,89,97	0.60 (0.44-0.82)
			Stroke (RCT)	89,97	0.64 (0.47-0.86)
			CVD mortality (RCT)	87,88,89,97	0.59 (0.38-0.93)
			Composite (RCT)	87,88,89,97	0.55 (0.39-0.76)
Galbete, 2018[33]	Yes	Systematic reviews and meta-analyses	CVD and chronic diseases		
Martinez-Lacoba, 2018[84]	Yes	Reviews and meta-analyses	CVD and other health outcomes		
Salas-Salvadó, 2018[85]	No	Narrative	CVD		

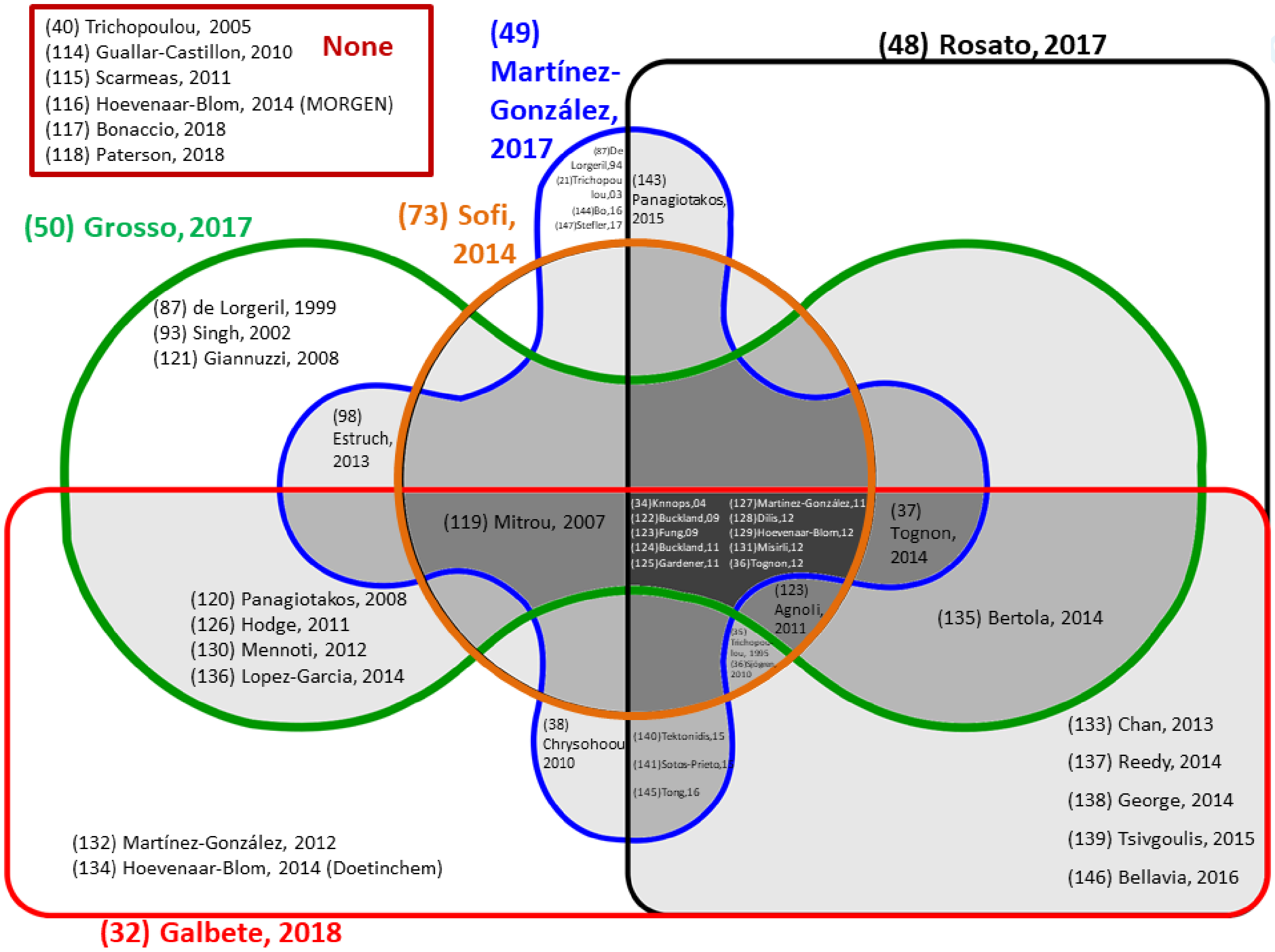

Figure 1. Overlapping studies between systematic reviews

Some of the available meta-analyses were rated as of low-quality

The quality assessment conducted by Huedo-Medina et al[32] reported that on average, systematic reviews on MedDiet and cardiovascular health achieved a low-quality score and 60% of the 24 reviews presented limitations because they did not report the search details or used inappropriate statistical methods. Only 42% used appropriate statistical methods to combine the findings.[32] **This weakness does not pertain to the original studies, but to the meta-analytic methods.**

Sources of heterogeneity in meta-analyses

Rather than establishing an artificial summary estimate of the effect of the MedDiet on cardiovascular health across a set of several disparate studies, the primary aim of a meta-analysis should have been to identify and estimate the differences among study-specific effects (i.e., an analytical goal).[123] This is especially important in the field of MedDiet and cardiovascular health because of the need to deal with studies using different definitions of exposure, different outcomes, different methodology and different geographical or demographical origins. The major goal should be to assess whether these characteristics determine a different result. In **one** meta-analysis[72], 5 out of the 16 estimates were the main source of heterogeneity because they only assessed fatal outcomes. When these 5 estimates were removed, the heterogeneity disappeared and the effect became slightly stronger. More recently, Rosato et al[49] assessed sources of heterogeneity and found an overall relative risk (RR) for cardiovascular disease of 0.61 (95% CI 0.44–0.86) for two studies conducted in Mediterranean regions and 0.84 (95% CI 0.77–0.92) for the eight original studies conducted outside the Mediterranean area (p for heterogeneity = 0.11). Other candidate variables did not show any significance in the heterogeneity test. Galbete et al[33] reported that studies using the Trichopoulou's MedDiet score[22] showed a stronger inverse association (RR 0.87, 95% CI 0.83, 0.91 for high versus low adherence) compared to studies using the aMed score (RR 0.92, 95% CI 0.89, 0.94), with **only** marginal heterogeneity (p=0.06).

Publication Bias

Statistically significant studies going in the expected direction are more likely to be published.[124] This fact is the source of publication bias that represents a major threat for the validity of systematic reviews. Huedo-Medina et al criticized that only one fourth of the systematic reviews that they evaluated assessed publication bias.[32] Rosato et al reported that the Begg's and Egger's tests conducted to assess publication bias respectively gave p values of 0.087 and 0.034 for CHD, 0.13 and 0.008 for unspecified stroke, and 0.44 and 0.27 for unspecified CVD, showing a potential for publication bias for CHD and unspecified stroke.[49] This **might represent** a concern**. However, most of these p values were not significant.**

Limitations of the available RCTs

Strengths and limitations of the Lyon trial: too good to be true?

The French Lyon Diet-Heart study was a landmark trial in the study of diet and cardiovascular health.[86] It was a secondary prevention trial aimed at reducing the risk of cardiovascular deaths and recurrent myocardial infarction by diet modification in 605 patients, survivors of a previous myocardial infarction and recruited between 1988 and 1992. Patients were randomized to a Mediterranean-type diet (302 patients) or to a control group (303 patients). In the active intervention group, patients were encouraged to increase their consumption of fruit (no day without fruit), vegetables, bread and fish. They were also advised to reduce the consumption of red meat (beef, pork and lamb should be replaced by poultry), and to replace butter and cream by a special margarine, much richer in alpha-linolenic acid than olive oil (4.8 % v. 0.6 %), but, with 48% oleic acid, low content of saturated fatty acids and, slightly higher content of linoleic acid (16.4 % vs. 8.6 %) than olive oil. Control subjects were allocated the usual care by their physicians, who recommended a diet similar to the low-fat Step 1 diet of the American Heart Association. The results of the Lyon Diet Heart Study were impressive, **but the intervention did not exactly correspond to the traditional MedDiet**. The trial showed a dramatic reduction in major coronary events and deaths, that was maintained over a 4-year follow-up period.[87] In an interim analysis at 27 months of follow-up there was a 73% reduction in coronary events and a 70% reduction in total mortality and the study was stopped early.[125]

Other methodological limitations of the Lyon trial have been highlighted.[60,126] **As, apparently, there was no pre-specified stopping rule, it is likely that early stopping of the trial would have led** to an overestimation of the effect.[127] Baseline diet was only assessed in the experimental group but not in the control group and, consequently it was impossible to assess the dietary changes that occurred in the control group. Information on diet at the end of the trial was reported for only 27% of the control group and only 48% of the experimental group. Very importantly, no sufficient consideration was given in the Lyon trial to the pivotal role of olive oil in the traditional MedDiet. The fat composition among evaluated participants of the experimental group in the Lyon trial was 30.5% of energy intake as total fat (12.9% MUFA). This value for MUFA intake is below the 15-20% MUFA content from olive oil usually present in the traditional MedDiet. The Lyon trial included only subjects with a previous coronary event (**it was a secondary prevention trial**). **Primary and secondary prevention trials are different because mortality** or relapses of CHD are not only related to CHD incidence but also to the quality and timeliness of medical care.[128]

The scarce reliability of the Indo-Mediterranean trial

Lancet published in 2002 the results of the Indo-Mediterranean trial[88] reporting a dramatic reduction in the incidence of cardiovascular outcomes in 499 patients randomly allocated to a diet rich in whole grains, fruits, vegetables, walnuts, and almonds as compared to 501 controls allocated to the consumption of a local diet similar to the low-fat Step I National Cholesterol Education Program diet. But subsequently, in 2005, Lancet issued an expression of concern due to the failure to locate original research records[129]. **Though this study is still**

sometimes included in both narrative and systematic reviews, it has been largely discredited, and it should be considered at least as a severely flawed investigation.

Deviations from the individual randomization protocol in the PREDIMED trial

The Spanish PREDIMED trial included 7447 participants at high cardiovascular risk allocated to one of three diets: a Mediterranean diet supplemented with EVOO, a Mediterranean diet supplemented with mixed nuts, or a control diet (advice to reduce all subtypes of dietary fat). The trial was planned for 6 years, but it stopped early after intervention for 4.8 years, as recommended by the Data and Safety Monitoring Board following stopping rules established *a priori* in the protocol.[11,48,130,131] The incidence of cardiovascular disease (myocardial infarction, stroke or cardiovascular death, totaling 288 events) in the Mediterranean diet groups was lowered by approximately 30% when compared to the control diet.

PREDIMED is a landmark study and it remains to date as the largest dietary intervention trial to assess the effects of the Mediterranean diet on cardiovascular disease prevention. **However, a review published in June 2017 identified the PREDIMED trial as having distributions that were significantly different from those expected from randomization.[132] This** report prompted the Investigators of PREDIMED to take the initiative to contact the editors of The New England Journal of Medicine. After July, 2017, the investigators of PREDIMED identified 2 departures from the reporting or application of the protocol:

a) the allocation by clusters (by small clinics), instead of individual allocation of some participants at 1 of 11 study sites (site D), affecting 467 participants (6.2% of total PREDIMED participants) in 11 clinics (2 allocated to Mediterranean diet + virgin olive oil, 5 allocated to Mediterranean diet + nuts and 4 allocated to control). In another site (site I), with 1094 participants recruited from 37 small clinics, the research team of that site conducted the intervention in participants from 11 clinics for only one arm of the trial in each clinic (on a total of 247 participants, 22.6% in this site). They also reported that an apparent inconsistent use of randomization tables was done at another site (site B). **However, baseline characteristics were well balanced in sites I and B.**

b) enrollment of household members (partners of a previous participant) without randomization; members of the household of randomized participants were invited to participate and allocated to the same intervention group as their relatives. The second enrolled partners of a previous participant represented 5.7% of PREDIMED participants, with a slightly lower proportion in the control group (4.82%) than in the Mediterranean diet group + extra virgin olive oil (6.72%) or the Mediterranean diet group + nuts (5.54%). This was done to avoid assigning members of the same household to different diets. Assigning all participants in a household to the same diet was viewed as the best approach to achieve dietary changes in the household. This procedure was inadvertently omitted in the reporting of the protocol and the original publication.

Baseline imbalances were **minor and consisted only in** a slightly higher percentage of women in the control group (5.7% higher in control than in the Mediterranean diet+nuts group and 1% higher in control than in the Mediterranean diet+extra-virgin olive oil group) and a 5.3% higher percentage of patients with high levels of low-density-lipoprotein cholesterol in the Mediterranean diet + extra virgin olive oil than in the control group. **Interestingly, both would be in any case operating against the hypothesis of the trial and therefore cannot provide any alternative non-causal explanation of the PREDIMED findings.** Several criticisms were raised after these departures from the protocol were disclosed.[133]

The investigators of PREDIMED decided to retract their original paper[89], and simultaneously republished a new version in the same journal[11] where these issues were fully addressed. The republication included the results of many new sensitivity and ancillary analyses that showed no changes with respect to the original results of PREDIMED[11].

Strengths of the MedDiet

All the previous considerations represent **potential** caveats and drawbacks threatening the validity of the MedDiet paradigm for cardiovascular health. There are also many strengths in the currently available evidence to support the validity of the proposal defending the MedDiet model as the ideal approach for cardiovascular health.

The MedDiet possesses a millenary tradition of use without any evidence of harm.[56] Current definitions of the MedDiet are in line with traditional food patterns followed in Mediterranean areas during the 50s and 60s of the past century, where life expectancies after 45 years were among the highest of the world.[134]

The pioneer epidemiologic study supporting the MedDiet for cardiovascular health was not conducted by anybody living in the Mediterranean or with a Mediterranean ancestry. These first pieces of evidence came from the Seven Countries Study, an ecologic, international, investigation of diet and cardiovascular-disease in 16 groups totaling nearly 13,000 men in Seven Countries (Greece, Italy, Japan, Finland, the former Yugoslavia, the Netherlands and the United States). This study was started in 1958 by an American investigator, Ancel Keys[135] (Figure 2). He was the one who developed and promoted for the first time the concept of the cardio-protective **MedDiet**. Therefore, it is not likely that geographical-nostalgic-romantic motivations related to the diet learnt by some investigators in their childhood from their grandparents might be at the root of this concept. Keys was a physiologist and epidemiologist at the University of Minnesota who “discovered” the cardiovascular health benefits of the MedDiet in the early 1950s, when he visited Mediterranean countries as a scientist concerned on the rapidly growing trend of coronary mortality in the US.[136] Keys did his first research on the MedDiet by studying *in situ* the dietary patterns of men in Italy, Spain, and Crete and their association with cardiovascular health, with special emphasis on the effects of dietary fat and fatty acids on serum cholesterol levels and cardiovascular disease risk. His findings were particularly prominent regarding the importance of fat subtypes –and not of *total* fat intake–, and the relevance of the monounsaturated to saturated fat ratio. The MedDiet relatively rich in fat (even to levels of 40% of calories from fat) but with an optimal MUFA:SFA ratio appeared as an ideal model for cardiovascular health. All these facts were in accordance with the long-lasting experience of use of this dietary pattern in relatively poor sectors of the world with high rates of smoking and, nevertheless, with a very low CHD mortality

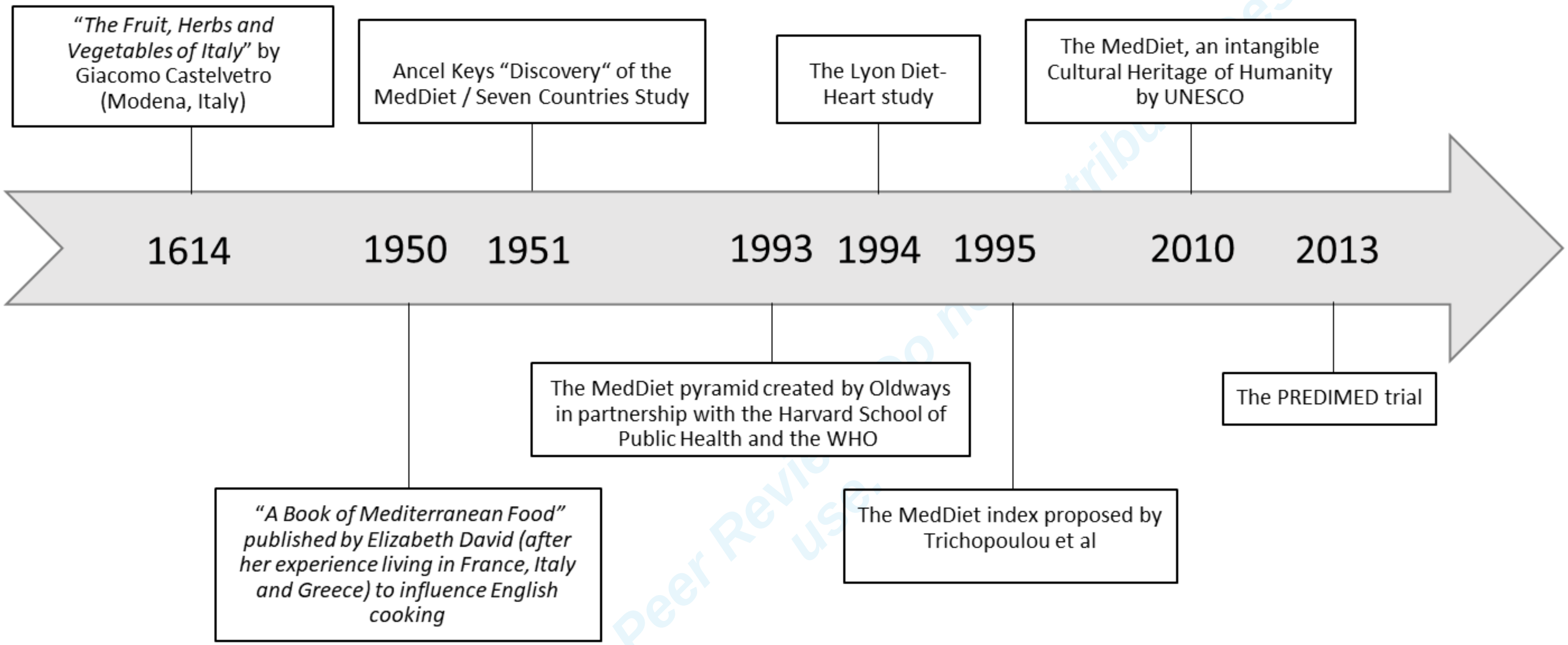

Figure 2. Historical and scientific milestones of the MedDiet and its cardiovascular benefits

The paradigm of dietary patterns has many advantages

In contrast with the classical analytical approach of only assessing exposures to single nutrients or isolated food items, the study of overall dietary patterns has become the current prevalent framework in nutrition research. This approach has been fully adopted and endorsed by the 2015 Dietary Guidelines Advisory Committee (2015-DGAC)[137]. The food pattern approach is advantageous for many reasons: a) because food items and nutrients could have synergistic or antagonistic effects when they are consumed in combination; b) overall food patterns represent the current practices found in the assessed population (people do not eat isolated nutrients) and, therefore, they better capture the actual exposure of interest; c) they provide useful sociological information of great interest in itself for public health; d) the use of dietary patterns as the relevant exposure in nutrition reduces the potential for confounding by other dietary exposures; e) and, very importantly, the focus on the overall food pattern seems clearly superior to the reductionist and overly optimistic assumption of attributing all the effect to a single nutrient or food. It would seem very unlikely that a single nutrient or food could exert a sufficiently strong effect as to substantially change the rates of cardiovascular outcomes. In contrast, the additive effect of small changes in many foods and nutrients seems to exert a more biologically plausible and clinically meaningful effect. In fact, during the last 2 decades, numerous well-conducted prospective epidemiological studies have confirmed strong relationships between a priori defined high-quality dietary patterns and a lower risk of chronic disease, including cardiovascular clinical outcomes. As one of the members of the 2015-DGAC recently highlighted, hypothesis-oriented patterns based on available scientific evidence for chronic disease are an attractive alternative, because the use of an *a priori* scoring system offers a consistent metric that can be applied across multiple studies and the consistency in methods then allows comparisons of results across populations.[137] In this context, as Figure 3 shows, the MedDiet pyramid[138] includes many different foods with specific recommendations for their consumption on every main meal, daily, weekly or less frequently. Consequently, the MedDiet fits very appropriately in the paradigm of overall dietary patterns and it represents one of the best-known models for this paradigm. Moreover, the MedDiet was explicitly endorsed by the 2015-DGAC after reviewing all the available scientific evidence.[139]

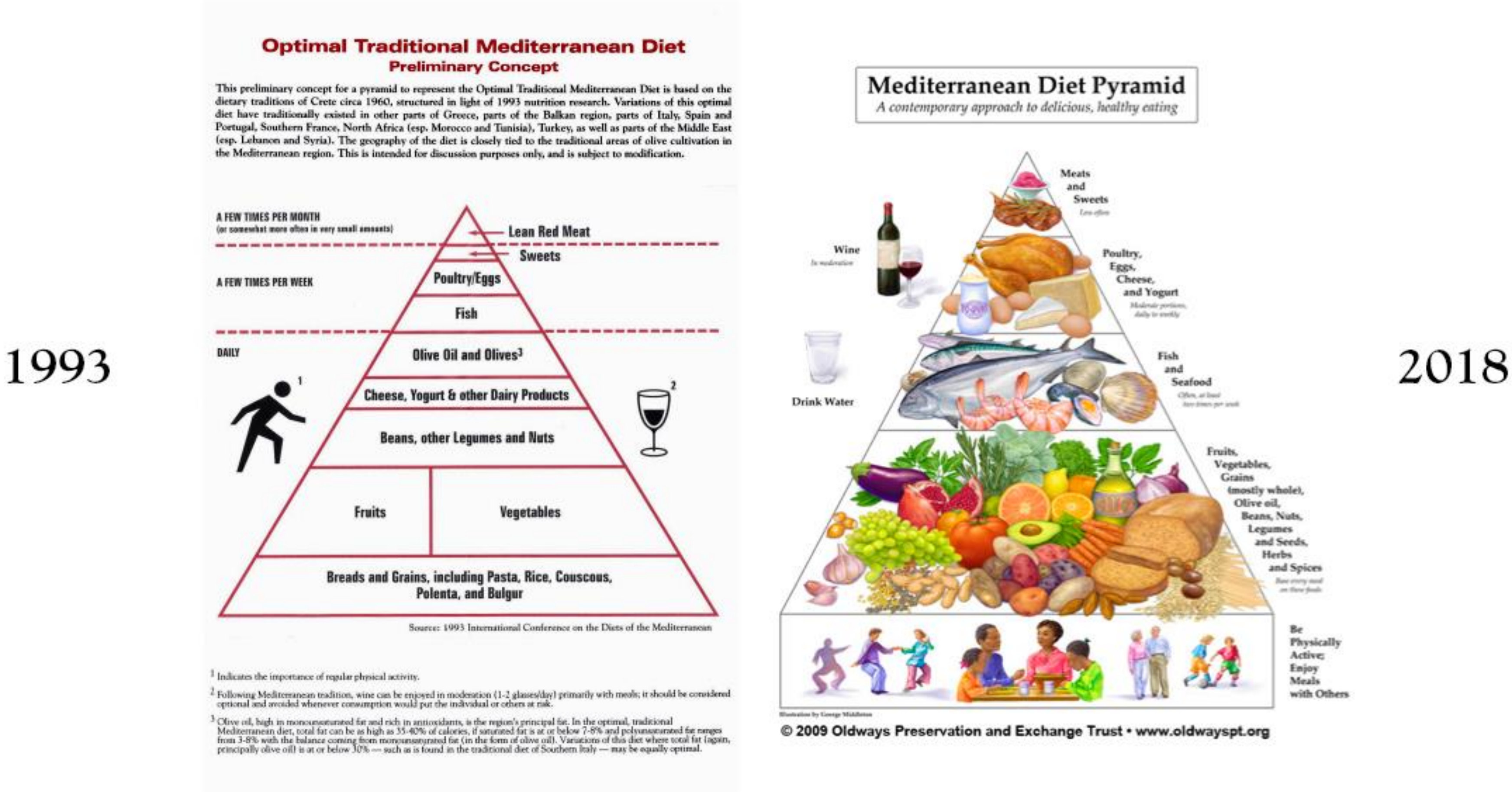

Figure 3. First and last version of the MedDiet pyramid developed by Oldways

The variety of definitions had little impact on the cardiovascular health effects

It would be desirable to adopt a universal definition of MedDiet for the sake of comparability among different studies in the future. The use of different definitions does not help to assess the consistency among studies nor to translate the scientific research into practical recommendations for the general population.[140] **Notwithstanding, we standardized the comparisons to represent the association for a 22.2% increment in the used score, equivalent to a 2-point increment in the 0 to 9 score proposed by Trichopoulou.[22] However, it should be acknowledged that the groupings used in the studies shown in Figure 4 do not represent always the same comparison, due to the previously mentioned diversity in the content of the different indexes. This should be taken into account when interpreting the results summarized in Figure 4.**

The use of sample quantiles as cut-off points to compute the MedDiet scores might be seen as a limitation because they depend on sample characteristics. However, this approach can present also advantages because using quantile-defined categories instead of *a priori* defined cut-off points is in better agreement with characteristics of food-frequency questionnaires and other dietary assessment tools which are better suited to rank individuals than to accurately measure absolute intakes.[50] Therefore, the wider use of a score based on medians (or its variants using tertiles) should not be viewed as any major problem.

Moreover, when Rosato et al[49] restricted their meta-analysis to the studies using only the initial definition proposed in 2003 by Trichopoulou.[22] When they compared highest versus lowest **categories**, they obtained a RR=0.82 (95% CI: 0.70-0.97) for cardiovascular disease. Interestingly, similar results were found for studies using other scores different from the score proposed by Trichopulou, with a RR=0.80 (95% CI: 0.73-0.87) with no evidence of heterogeneity between both set of studies (p=0.52).[49] Analogous similarities without evidence of heterogeneity were found for CHD (p[heterogeneity]=0.63) and stroke (p[heterogeneity]=0.85). Therefore, there is no evidence to support that the differences in the definitions of the MedDiet may have affected the available results on cardiovascular health.

Light-to-moderate alcohol consumption is one item used in most of the MedDiet scores reflecting a common tradition in Mediterranean countries. This moderate consumption (1 or 2 drinks/day) has been consistently associated with a lower risk of cardiovascular diseases.[141] Moreover, a Mediterranean alcohol-drinking pattern is characterized by a moderate consumption of alcohol, with preference of fermented drinks instead of spirits, and especially red wine consumed during meals.[142] This level of alcohol consumption in the context of a MedDiet probably contributes to the synergistic effect of other components of the MedDiet with similar cardioprotective mechanisms such as **increasing** HDL cholesterol, decreasing platelet aggregation, promoting antioxidant effects and reducing inflammation.[143,144]

Very importantly, the use of varied and disparate operational definitions and scores to capture the construct of the MedDiet will represent a potential for non-differential misclassification in individual original studies and a source of heterogeneity in meta-analyses. Both factors most likely will tend to attenuate the associations towards the null value. This attenuation of effects may concur with other aspects of the definitions that may mainly represent a tendency to underestimate the effects. For example, the exclusion of all dairy products in the Trichopoulou's score may lead to losing the potential cardio-metabolic benefits of yogurt consumption and may attenuate the estimates of RR. Similarly, the inclusion of potatoes in the group of vegetables or the inclusion of refined grains in the group of cereals would also produce an attenuating effect, as it was specifically shown in the SUN cohort, where the group of cereals and, specifically white bread, showed an association with higher risk of CVD.[145] As all these issues related to different criteria for the selection of food items in the operational definitions of MedDiet will potentially tend to attenuate the protective effects, it seems very unlikely that the consistent inverse association for the MedDiet with cardiovascular clinical events reported by many studies can be alternatively explained by the use of disparate criteria for computing the operational definitions and scores.

The causality criteria are met

The 9 classical criteria for supporting causality proposed half a century ago by Bradford Hill[146] are met for the **effect of** the MedDiet **on** cardiovascular health. Bradford Hill stated that "none of my nine viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as a sine qua non. What they can do, with greater or less strength, is to help us make up our minds on the fundamental question- is there any other way of explaining the set of facts before us, is there any other answer equally, or more, likely than cause and effect?".[146] However, the criterion of temporal sequence should be viewed as a *sine qua non* element. The application of these 9 principles to the association between better conformity to the MedDiet and a causal effect to reduce the risk of cardiovascular events is as follows.

a) *Temporal sequence*: the design of the studies included in this review are prospective cohorts and randomized controlled trial that provide a strong evidence for an adequate temporal sequence, because in all of them the exposure (MeDiet) clearly preceded the end-point (CVD).
b) *Strength of the association*: a MeDiet reduced the incidence of major CVD events by 30% (or even higher) after using either an intention-to-treat approach or a per protocol analysis in the PREDIMED trial.[11] Findings are in line with prior predicted benefits calculated from a large body of observational evidence.[33,49,50]
c) *Dose-response gradient*: greater adherence to the MedDiet showed an increased protection in a linear trend fashion. Each additional 2-point increment in baseline adherence to the 0 to 9 MedDiet score was associated with a monotonic 11% reduction in CVD.[50]
d) *Consistency*: The 5 most comprehensive and recent meta-analyses published between 2014 and 2018 systematically evaluated this principle of consistency and concluded in favor of a strong cardiovascular protection by the MedDiet.[33,49-52,74] Also 6 additional prospective studies not included in any of these meta-analyses supported this notion.[41,90-94] In total, 45[11,22,23,35-39,41,86,89-122, 147] reports of prospective studies were available, including 5 RCTs and 32 independent observational cohorts (some cohorts made several publications) (Figure 4 and Supplementary Table 1). The immense majority of these studies repeatedly found that a MeDiet was beneficial for cardiovascular health under quite a wide variety of circumstances, ruling out chance or confounding as an explanation for this association.

Figure 4. Adherence to the MedDiet and cardiovascular disease in prospective studies (cohorts and trials)

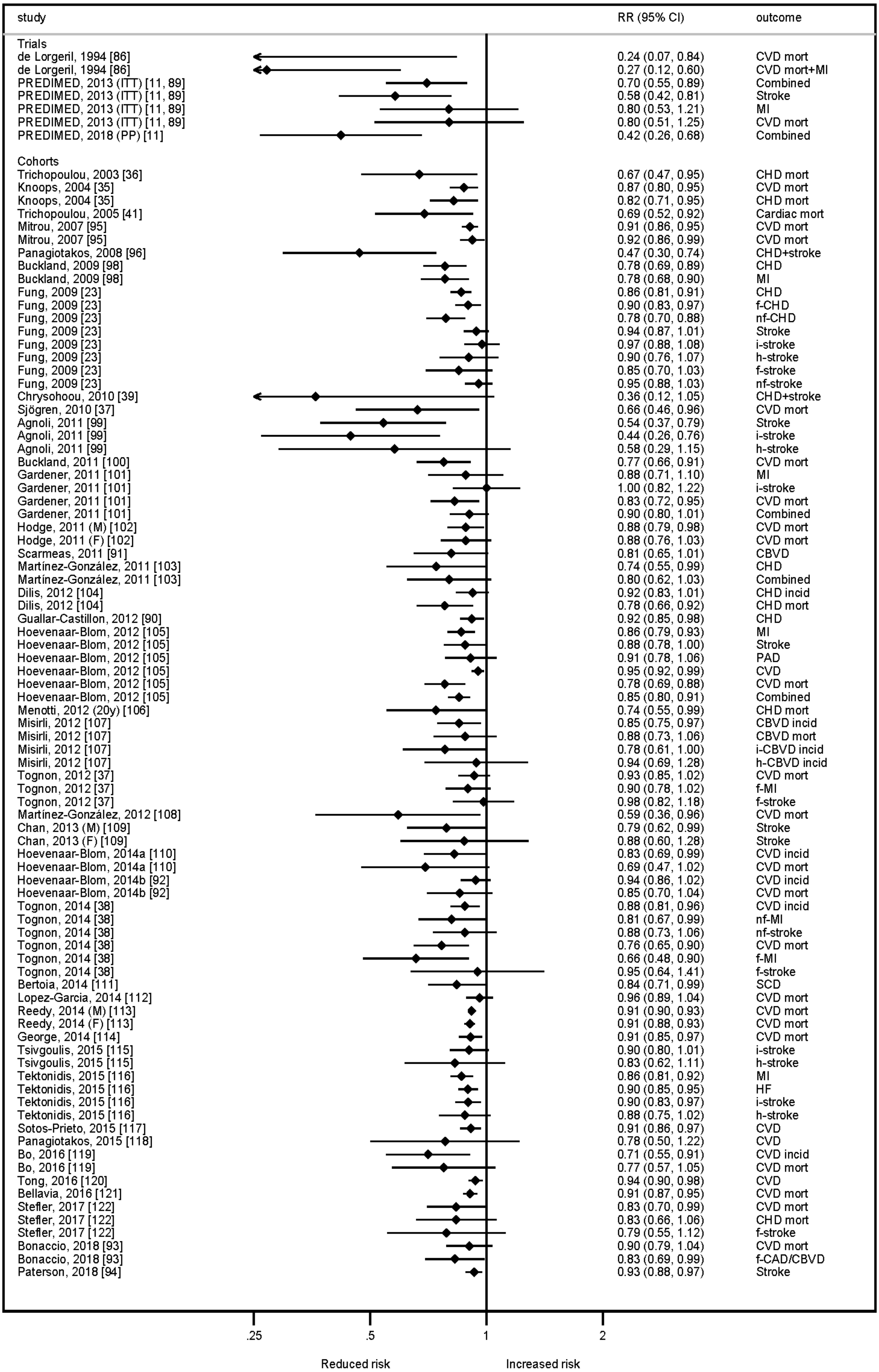

Figure 4 footnote:

ITT: intention-to-treat
PP: per-protocol
CVD: cardiovascular disease
CHD: coronary heart disease
MI: myocardial infarction
CBVD: cerebrovascular disease
HF: heart failure
mort: mortality
f-: faltal
nf: non-fatal
i-stroke i-CBVD: ischemic stroke
h-stroke h-CBVD: hemorrhagic stroke

Furthermore, both measured and unmeasured potential confounding were rigorously discarded as alternative explanations in additional specific analyses conducted in the republished report of PREDIMED (please check the Supplementary Appendix table S25 of that report[11]). In several meta-analyses the removal of one study as a time did not nullify the inverse association between MedDiet and cardiovascular events.

e) *Biological plausibility*: The MedDiet is associated with marked and consistent reductions in cardiovascular risk factors[148] and in levels of vascular inflammatory biomarkers.[7] The high fruit and vegetable intake contributes to its high antioxidant content and other pleiotropic benefits provided by the polyphenols and other bioactive molecules present in fruits, vegetables, EVOO, nuts, whole grains and wine, in the context of a MeDiet. Additionally, it is known that food items and nutrients may have synergistic effects when they are consumed in combination.

f) *Specificity*: **this criterion is probably one of the weakest among the list proposed by Hill, since many exposures, including the MedDiet, are well known to be associated with multiple outcomes. However, in** agreement with the anti-atherogenic properties of the foods typical of the MedDiet, closer adherence to the MeDiet appears to protect specifically against ischemic manifestations of CVD (myocardial infarction, ischemic stroke or peripheral artery disease[149]) but its effects were found null against hemorrhagic stroke with a RR= 1.01 (95% CI 0.74–1.37).[49] In the PREDIMED trial, the protective effect was present against the composite CVD outcome (composed mainly of ischemic clinical manifestations), but it was absent for total mortality, an end-point that was not specific, because it included any cause of death, regardless that it may be related to nutrition or not.

g) *Coherence*: the association between MedDiet adherence and better cardiovascular health fits within the known facts of the natural history and biology of CVD, as demonstrated by the Lyon trial for secondary prevention.[87] Beneficial effects on surrogate markers of CV risk adds coherence to the epidemiologic evidence that supports a protective effect of the MeDiet.

h) *Experimental evidence*: the availability of several randomized trials using not only intermediate marker, but hard clinical end points is a considerably strength of the MedDiet, that is not available for any other dietary pattern. In addition, **a good number of** mechanistic trials conducted in subsets of participants by the PREDIMED investigators (see www.predimed.es/publications.html) provide substantial **analytical** evidence supporting the biological bases for the effect of a MeDiet in lowering the risk of CVD events.

i) *Analogy*: other high-quality dietary patterns, such as the Dietary Approaches to Stop Hypertension (DASH) diet or the Alternative Healthy Eating Index, have also been associated with reduced incidence of CVD events. However**, lack of analogy should not be considered as a criterion against causality. In fact, first-level evidence for the cardioprotective effect of the MedDiet**, as collected and analyzed in PREDIMED and other trials, is not available for any other dietary pattern.

The high nutritional quality of the MedDiet adds biological plausibility to these findings

Nutrition profiling and nutritional quality are topics of considerable current interest.[150] In this context, an additional element that adds biological plausibility to the findings of cohort studies and RCTs is a body of evidence supporting the high nutritional quality of the MedDiet (i.e. it is a nutrient-dense option) over alternative actual dietary patterns which tend to be energy-rich but nutrient-poor.

Maillot et al modeled nutritionally adequate diets to simultaneously met the requirements for a whole set of nutrient goals (proteins, fiber, essential fatty acids, 10 vitamins, 9 minerals, sodium, saturated fatty acids, free sugars) while deviating the least from the observed diet in terms of food content. They found a strong consistency in the dietary changes needed to fulfill the constraints, and the greatest increases were seen for unsalted nuts, whole grains, legumes, fruit, fish/shellfish, and vegetables. They reported a strong consistency in the needed changes in dietary habits needed to meet the constraints with the greatest increases observed for unsalted nuts, unrefined grains, legumes, fruit, fish/shellfish, and vegetables. They concluded that regardless of the different scenarios that they assumed, those foods which are typical of the MedDiet are needed to reach overall nutrient adequacy.[151]

In the Mediterranean "Seguimiento Universidad de Navarra" (SUN) cohort, a closer adherence to the MedDiet was reported to be strongly associated with a lower risk of failing to meet the goals for nutrient adequacy.[152,153] As adherence to the MedDiet increased, the probability of not fulfilling the micronutrient goals sharply decreased.[153] This finding was replicated in other studies.[154] In another study, the SUN cohort investigators evaluated the intakes of Zn, I, Se, Fe, Ca, K, P, Mg, Cr and vitamins B1, B2, B3, B6, B12, C, A, D, E and folic acid. The probability of intake adequacy was evaluated using the estimated average requirement cut-off point approach and the probabilistic approach. Logistic regression analysis was used to assess the nutritional adequacy according to adherence to the MedDiet, evaluated the intakes of Zn, I, Se, Fe, Ca, K, P, Mg, Cr and vitamins B1, B2, B3, B6, B12, C, A, D, E and folic acid. The results were similar showing a strong inverse association between adherence to the MedDiet and overall nutritional adequacy.[153] These results were replicated also in the PREDIMED cohort.[155] Therefore, it seems very likely that the overall better nutritional quality of the Mediterranean dietary pattern may be able to bring about a substantial reduction in the risk of atherosclerotic-ischemic events, which are known to be related to biochemical disorders caused by suboptimal intakes of several micronutrients.[156,157]

Concordance between cohorts and trials

The findings of large observational cohort studies with good control for confounding are found to be replicated by the results of the two major trials (Lyon and PREDIMED). Such a strong consistency between large and well conducted observational prospective cohorts and experimental studies is not available for any other dietary pattern. In addition to these two trials, there is another trial, the Global Secondary Prevention Strategies to Limit Event Recurrence After Myocardial Infarction (GOSPEL) study. GOSPEL was a multicenter, randomized secondary prevention trial in survivors of a myocardial infarction who were on cardiac rehabilitation, that compared a long-term, reinforced, multifactorial educational and behavioral intervention with usual care.[97] The intervention program where 1620 patients were allocated included the adoption of “a healthy MedDiet” together with smoking cessation, promotion of physical activity and addressing conventional cardiovascular risk factors. The control group (n=1621) received usual care. At baseline, the scores of adherence to the MedDiet were equal in both groups. At 6 months, the score increased by 18% in the intervention group and by 14% in the usual care group, with modest but statistically significant differences between both. This difference in dietary habits between the 2 groups was maintained throughout the 3-y average duration of the study. The primary endpoint included many softer events (cardiovascular mortality, nonfatal MI, nonfatal stroke, and hospitalization for angina pectoris, heart failure, or urgent revascularization procedure) than the PREDIMED trial. The intensive intervention **non-significantly** decreased the *absolute* risk **by 2.1% (from 18.2% to 16.1%)** of this combined primary cardiovascular end-point (in total, 556 events). **The *relative* reduction was 12%** (RR=0.88; 95% CI, 0.74-1.04; p=0.12) compared with usual care. **However,** it significantly decreased cardiovascular mortality plus nonfatal myocardial infarction and stroke (in total 129 events) RR=0.67 (95% CI, 0.47-0.95; p=0.02) with respect to usual care **(relative risk reduction: 33%)**. However, the specific effect of the modest dietary contrast achieved between the intervention and control groups cannot be **separated** from the overall intervention program that included many other aspects. In any case, given the small magnitude of the dietary contrast and the probably non-specific nature of the primary end-point of the GOSPEL trial, the results for the combination of myocardial infarction, stroke and cardiovascular death are more specific and they go in agreement with their expected direction.

Robustness of the findings of the PREDIMED trial in a wide variety of sensitivity and ancillary analyses

The greatest challenge in the PREDIMED trial was to obtain an effective change in the overall dietary pattern of 7,447 participants. A validated 14-item score was used to appraise the achieved changes in the overall food pattern.[25] The intervention was based on quarterly individual interviews and quarterly group sessions (with less than 20 participants per group) run by trained dietitians, provision of information on typical Mediterranean foods and dishes, shopping lists, weekly menus, cook recipes and gifts of extra-virgin olive oil and mixed nuts. Figure 5 shows the contrast between the baseline 14-item score (all participants) and this score after 1-year of intervention in the 2 groups allocated to MedDiets. The intervention was successful in attaining changes in many aspects of the overall food pattern and this is the main strength of PREDIMED.

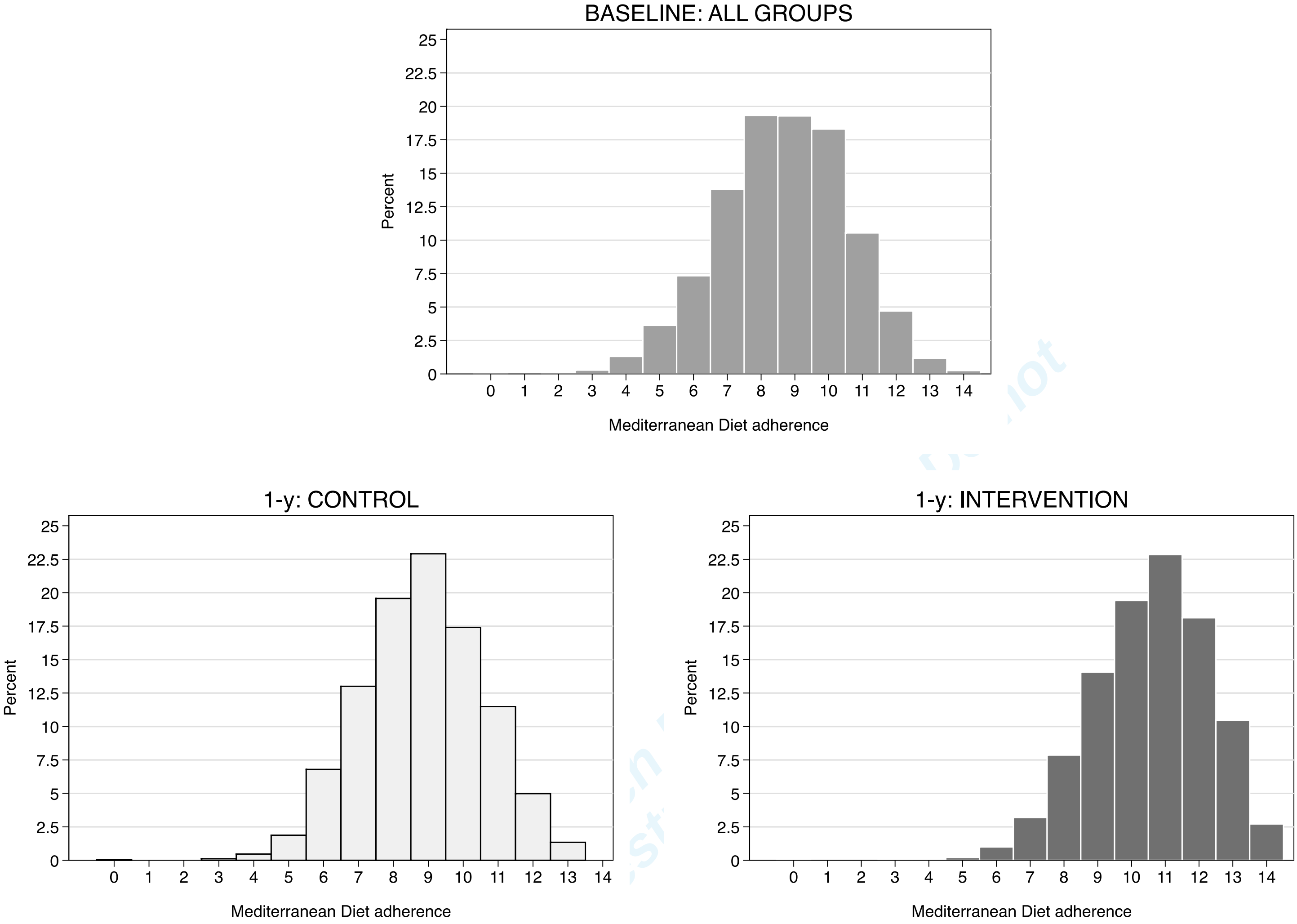

Figure 5. Adherence to the MedDiet in participants from the PREDIMED trial at baseline and after 1-year follow-up.

The methodological issues in the PREDIMED trial **consisted in departures from the individual randomization protocol recently reported in detail elsewhere[11]. Briefly, 425 participants, members of the same household of a previous participant were directly allocated during all trial duration to the same group as their previously randomized relative. In addition, 441 individual participants and 26 participant members of the same household from 1 of the 11 recruiting centers were allocated by clusters (clinics) instead of using individual randomization. These issues were addressed by additionally adjusting for propensity scores that used 30 variables to estimate the probability that a participant would be allocated to each of the 3 intervention groups and with the use of robust variance estimators to account for intra-cluster correlations[11]. T**he results and conclusions remained intact after accounting for these small and partial departures from individual randomization in a subset of the trial. **As a sensitivity analysis, a new per-protocol (adherence-adjusted) analysis was conducted and it found a hazard ratio for the primary cardiovascular end-point of 0.42 (95% CI, 0.24 to 0.63) for the MedDiet as compared with the control diet. Further sensitivity analyses excluding participants not individually randomized provided** a very convincing picture, and kept the same message: the intervention caused a 30 percent reduction in the composite cardiovascular end-point of myocardial infarction, stroke or cardiovascular death **(the point estimates of the hazard ratios in all these intention-to-treat sensitivity analyses ranged from 0.64 to 0.72, and their upper 95% confidence limits from 0.88 to 0.97).**

There might be some concerns because of the possibility of unmeasured confounding. In this regard, the observed hazard ratio of 0.70 could be explained away by an unmeasured/unknown confounder that was associated with both the intervention group and the outcome by a risk ratio of 2.21, but weaker confounding could not do so (E-value=2.21 for the point estimate, and 1.5 for the upper limit of the confidence interval).[158] In addition, it is important to not forget that when subjects with potential issues regarding departures from individual randomization were excluded, the protective effect was not attenuated, in fact it slightly increased.

Biological plausibility for the effects of polyphenol-rich foods in the MedDiet

A substudy of PREDIMED including 1139 subjects measured total urinary polyphenol excretion at baseline and after 1-year intervention and categorized participants according to thirds of their changes in urinary total polyphenol excretion (TPE). Participants in the highest tertile of changes in urinary TPE showed significantly lower plasma levels of inflammatory biomarkers including vascular cell adhesion molecule 1 (VCAM-1), intercellular adhesion molecule 1, interleukin 6, tumor necrosis factor alpha and monocyte chemotactic protein 1 as compared to those in the lowest tertile. A significant inverse correlation existed between urinary TPE and the plasma concentration of VCAM-1. Systolic and diastolic blood pressure decreased and plasma high-density lipoprotein cholesterol increased in parallel with increasing urinary TPE.[46] This finding suggests a dose-dependent anti-inflammatory effect of polyphenols within the amounts that they were consumed in participants allocated to receive quarterly education and advice on the MedDiet during one year. Moreover, in the PREDIMED trial, polyphenol intake, as derived from food-frequency questionnaires, was inversely associated with the incidence of cardiovascular events[159], blood pressure[160] and total mortality.[161]

The polyphenol-rich MedDiet has also been found to influence the expression of key genes involved in vascular inflammation, foam cell formation and thrombosis. **In addition, specific polyphenols should not be viewed in isolation, but as one of many co-factors in synergistic action with other beneficial elements included in the overall MedDiet pattern. For example, a** substudy of PREDIMED demonstrated that the dietary intervention was able to actively modulate the expression of pro-atherothrombotic genes.[162]

In plasma metabolomic studies, the MedDiet was able to attenuate the harmful cardiovascular effects of branched-chain amino-acids[163], ceramides[164] and adverse metabolites in the tryptophan-kynurine pathway.[165] Many other mechanistic studies support that the amounts of polyphenols usually present in the traditional MedDiet are enough as to bring about substantial changes in metabolic pathways which play a pivotal role in cardiovascular health.[166]

<u>Further experimental evidence beyond the PREDIMED and Lyon trials</u>

Dinu et al, in their umbrella meta-analysis of the health effects of the MedDiet[52] assessed 16 different meta-analyses of RCTs on the effects of the MedDiet on different outcomes. They reported that 26 evaluations of cardiovascular outcomes were included in these meta-analyses. All point estimates from these meta-analyses were in the direction towards a benefit of the MedDiet for cardiovascular health, and most of these meta-analytical estimates from RCTs showed statistically significant results. Dinu et al. repeated the same methodology than Huedo-Medina et al have used earlier[32] for the evaluation of the quality of meta-analyses and applied the AMSTAR-MedSD tool used by Huedo-Medina. Dinu et al[52] in their updated evaluation obtained better results since they concluded that "all the investigated meta-analyses achieved a medium-to-high quality score, so suggesting that current meta-analyses evaluating the effects of the MedDiet on health status partially or almost fully comply with methodologic quality standards".

The question of potential publication bias was explicitly addressed by Rosato et al.[49] They found suggestion of small-study effects, but when they stratified the results according to number of cases of CHD, they found a RR=0.71 (95% CI 0.64–0.79) and a RR=0.60 (95% CI 0.48–0.76), respectively, for studies including more than 600 cases compared with smaller studies. Similarly, for stroke, the RRs were 0.82 (95% CI 0.72–0.94) and 0.52 (95% CI 0.26–1.03) for studies including more than 300 cases compared with smaller studies. This finding of inverse association both in large and small studies does not indicates that publication bias may provide an alternative, non-causal, explanation of these findings.

The 95% prediction intervals in meta-analyses go beyond confidence intervals because they also account for between-study heterogeneity and provide a credible range to be 95% confident that the effect reported by a new imaginary study examining the same association will lie within that range.[167] Galbete et al[33] examined the 95% prediction interval for the association of the MedDiet with chronic disease risk. They reported that 95% prediction intervals excluded the null value for the associations with CVD incidence, or mortality, CHD and stroke. Therefore, there is reassuring evidence for these associations.

We acknowledge that both the Lyon trial and PREDIMED were conducted in Mediterranean areas, where the expected compliance with the MedDiet is likely to be higher. However, many of the studies shown in Figure 4 were conducted outside the Mediterranean basin and they found excellent results for this dietary pattern. Therefore, though there is a need to replicate the findings of PREDIMED in other Western areas, the MedDiet seems to have also a high potential for transferability[50].

The major sources of information had no conflict of interest with the food industry

In the PREDIMED trial, which remains as the most significant contribution to the scientific literature on a traditional MedDiet, food companies only donated the food items, but the trial was funded by an independent public agency (Instituto de Salud Carlos III, i.e., the "Spanish NIH") without any commercial interest whatsoever. The umbrella meta-analysis by Galbete et al[33] was funded by the German Federal Ministry of Education and Research. The authors of the main recent meta-analyses,[49-52,74] reported no conflicts of interest with the food industry. The studies included in these meta-analyses that contributed with a higher amount of person-years (Nurses Health Study[23], EPIC study[22,120] and the National Institutes of Health (NIH)-AARP (formerly known as the American Association of Retired Persons),[95] were publicly funded.

Conclusions

We have shown here that there is a large, strong, plausible and consistent body of available prospective evidence to support the benefits of the Meddiet on cardiovascular health. Moreover, in the era of assessing overall food patterns, no other dietary pattern has undergone such a comprehensive, repeated and international assessment of its cardiovascular effects. The MedDiet has successfully passed all the needed tests and it approaches the gold standard for cardiovascular health.

The MedDiet can be adapted to many different geographical settings by tailoring it to individual characteristics such as food and cultural preferences and health conditions. Promotion of the MedDiet requires changes in the food environment, the food systems and public health policies to improve overall diet quality of individuals, communities, and populations.

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Disclosures
None.

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