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**Deep dive to the secrets of the PREDIMED trial**

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## **ABSTRACT**

### **Purpose of review**

To briefly summarize the contribution of the PREDIMED (PREvención con Dieta MEDiterránea) trial on cardiovascular evidence and examine in depth its groundbreaking trajectory.

PREDIMED was conducted during 2003-2010 and represented the largest primary prevention trial ever testing the effects of changes in a complete food pattern (namely, the Mediterranean diet) on cardiovascular disease (CVD). Major contributions relied on the relevant changes in the food pattern attained by the behavioral intervention and their dramatic effect in reducing hard clinical end-points. Given some potential concerns, which eventually were shown to be unfounded, this review is timely and relevant.

### **Recent findings**

PREDIMED has continued contributing to the existing literature with extensive, robust, and abundant new evidence on the benefits of the Mediterranean diet, particularly on cardiovascular health, including recent studies using high-throughput metabolomic techniques. After robustly addressing some controversies, the conclusions of the original trial remained unaltered.

### **Summary**

The Mediterranean diet represents the best nutritional strategy to reduce CVD. Recent findings from the PREDIMED have identified a metabolic signature of the Mediterranean diet that can objectively determine dietary adherence and predict CVD risk. The signature opens up a new era for nutritional epidemiology and personalized nutrition.

### **Keywords**

PREDIMED Study, Mediterranean diet, cardiovascular disease, randomized controlled trial.

## ***introduction***

The Mediterranean diet (MedDiet) resembles traditional meals consumed in regions of the Mediterranean basin characterized by an abundant use of olive oil, high consumption of fruits, vegetables, legumes, whole grains, nuts, and seeds, moderate consumption of seafood and fermented dairy products, and limited intake of red meat, processed meat products, whole dairy products and sweets (1). This dietary pattern has been recommended for the prevention of cardiovascular disease (CVD) in different guidelines such as the European Society of Cardiology (2) or the Scientific Report for the Dietary Guidelines for Americans (3). Moreover, the MedDiet was declared an intangible cultural heritage of Humanity by UNESCO (4) and its popularity has increased to non-Mediterranean countries, being for example proposed as the best diet in America by popular media.

The cardiovascular benefits of the MedDiet are supported by dozens of large and well conducted prospective observational studies and a number of systematic reviews (1,5-9). However, the number of large randomized trials with long-term follow-up and hard end-points such as myocardial infarction or stroke is very scarce. The PREDIMED (PREvención con Dieta MEDiterránea) trial is an internationally recognized landmark study, and it remains to date as the largest dietary intervention trial ever conducted to assess the effects of an overall food pattern on primary CVD prevention. Our aim in this article is to explain why the PREDIMED trial can be considered the most methodologically robust study so far to support the MedDiet as one of the best dietary patterns for the prevention of CVD.

## ***PREDIMED Study: design, methods, and results***

The PREDIMED primary prevention trial ([www.predimed.es](http://www.predimed.es)) was conducted in Spain between 2013 and 2010. A total of 7,447 participants, men and women at high cardiovascular risk, were allocated one of the following three diets: a Mediterranean diet supplemented with extra-virgin olive oil, a Mediterranean diet supplemented with mixed nuts, or a control diet

(advice to reduce all subtypes of dietary fat) (10). The trial was planned for six years, but it had to be stopped after a median of 4.8 years of intervention for early evidence of benefit, as recommended by the Data and Safety Monitoring Board, following stopping rules established a priori in the protocol (11-12).

The results of the PREDIMED trial showed a relative reduction of approximately 30% in the incidence of the primary CVD end-point (a composite of myocardial infarction, stroke, and cardiovascular death) in each of the two Mediterranean diet groups as compared to the control group.

### ***Deep Secrets of PREDIMED***

The characteristics of PREDIMED made it a unique study. PREDIMED was quite challenging as it required a complex design and logistics, a long follow-up period, and a strict adherence to the prescribed diet. While in drug RCTs participants only have to “take a pill” (either the drug treatment or the placebo), nutritional RCTs require a more complex action, namely a comprehensive action to obtain dietary behavior change. PREDIMED was pioneer in trying to modify the complete food pattern and not only the intake of some macro- or micronutrient. Precisely, one of the secrets of the success of the PREDIMED relies on the dietary changes attained by the behavioral intervention in the 2 active groups. After one year of intervention, participants in these 2 groups significantly modified their adherence to the Mediterranean dietary pattern. A common misperception is that the only modifications introduced by the intervention pertained to changes in the consumption of olive oil and tree nuts. On the contrary, actual changes were fairly more comprehensive. The behavioral intervention can be more clearly understood when comparing (within the two active intervention groups) the distribution of the 14-point PREDIMED dietary adherence score (13) at baseline and after 1-year follow-up (Figure 1). As observed in Figure 1, the distribution of the

Mediterranean adherence score in the active intervention groups was notably displaced to the right. This is easier said than done, but how was it possible to get a behavioral change from thousands of participants of advanced age?

The PREDIMED trial was composed of a multidisciplinary and well-coordinated team of dietitians, nurses, technicians, basic researchers, epidemiologists, and clinicians. Regular and consistent communication between team members was essential for the success of the trial. Registered certified dietitians, who had previously received tailored intervention training them for months, were ultimately responsible for delivering the intervention. The intervention consisted in quarterly individual and group sessions (no more than 20 participants) and recommendations for dietary changes to improve adherence to the Mediterranean diet (14-15). For any successful behavioral change, high motivation is required to pursue the desired goals. PREDIMED accounted for highly enthusiastic and motivated dietitians that strove to transmit recommendations and motivation for dietary changes. However, recommendations are not binding, and they cannot be equated to enforceable orders. One of the PREDIMED trial's secrets relied on the ability to listen to participants and make recommendations based on the participant's intimate perceptions, concerns and internal motivations related to their baseline clinical situation. Similar to the concept of medication adherence, where adherence is defined as the degree to which the person's behavior corresponds with the agreed recommendations from a health care provider (16), the PREDIMED dietitians applied the approach of "negotiated" goal setting with participants. This statement implies a shift away from the paternalistic relationship between dietitians and participants towards a more patient-centered approach and to shared decision-making (17). In the quarterly personal interviews, dietitians adapted their messages to the specific personal conditions of the participant, because all participants selected for the trial had either type 2 diabetes or at least 3 major cardiovascular risk factors (10). In other words, personalized recommendations tailored to individuals' clinical conditions, preferences, and beliefs were repeatedly delivered in face-to-

face interviews.

After an initial adherence assessment to the Mediterranean diet with the 14-point Mediterranean diet questionnaire (13), the dietitians used this immediate feedback to identify specific areas of improvement, and then negotiated the goals to be attained during the next 3 months. The core statement of this negotiation relied on five key steps: a) keep doing what you are doing right; b) identify one or at most two issues of the questionnaire that you need to improve (forget about to modify everything at the same time); c) start by achieving the easier and most straightforward goals for you; d) imply, as much as possible, the rest of your family or the persons of your household in this change; e) repeat, every three months, the 14-point MeDiet questionnaire to evaluate where you are at and set up a new goal if accomplished previous ones.

The behavioral intervention included repetitive advice, clear and concise information on Mediterranean foods and abundant written material (including recipes, shopping lists and weekly menu plans adapted to each season) together with continuous support from dietitians, and multiple alternatives to overcome hurdles faced by participants to improve their diets. Dietitians provided dietary advice by delivering a variety of recipes, weekly and seasonal menus, shopping lists, and delivering free allotments of extra-virgin olive oil (1 l/wk for the participant and his/her family) and mixed nuts (sufficient to consume 30 g/d). Moreover, when participants found some Mediterranean dishes “monotonous” or faced difficulties incorporating certain foods, several creative and ingenious ideas were offered. For example, some participants found it challenging to eat three pieces of raw fruit per day. Alternatives to incorporate more fruit into their diets consisted of preparing natural juices, stewed fruits, baked fruits or fruit salads; combining chunks of fruit with yogurt, chocolate, or other desserts; or using fruit garnish for homemade dishes in the background of fish, poultry or rice.



### ***Unfounded concerns on randomization methods and their potential consequences***

After the publication of the main results on the primary end-point in the *New England Journal of Medicine (NEJM)* (18), a sizable beneficial effect was also reported for other secondary hard clinical outcomes, including type 2 diabetes (19), peripheral arterial disease (20), atrial fibrillation (21), hypertension (22,23), and breast cancer (24). A non-significant result was found for a reduced risk of heart failure (25). These research conclusions consolidated the evidence of the Mediterranean diet's benefits on health outcomes (Table 1).

At that time, the PREDIMED trial was surrounded by a calm and peaceful atmosphere. With more than 3,000 citations in the five years after its publication, the study became one of the most influential randomized trials ever published. Dark clouds, however, were gathering over the PREDIMED evidence. In June 2017, Dr. Carlisle, a British consultant anesthesiologist, applied a statistical method, namely the Carlisle-Stouffer-Fisher method –known to have many limitations (26)– to baseline characteristics of participants in more than 5,000 published RCTs. The rationale for this method was to assess whether the distribution of continuous baseline variables (categorical characteristics were excluded) actually matched their expected distribution. Carlisle identified an ample subset of trials with departures from the expected distribution, including the PREDIMED trial and other major trials also published in *The New England Journal of Medicine* (27).

Immediately after the publication of this report, the PREDIMED Investigators took the initiative to contact the editors of *The New England Journal of Medicine*, sent them the data set with the relevant variables and expressed their commitment to review in full transparency all aspects of the study design, methods and statistical analyses that the editors may request from them. After multiple and exhaustive scrutiny, two small departures from the reporting or application of the protocol were identified.

The first departure was related to the random allocation of participants. A total of 467

participants (6.2% of total PREDIMED participants) were allocated by clusters — i.e., by small clinical sites — instead of individual allocation, affecting only 1 of the 11 recruiting centers (site D). The second departure was related to enrollment without randomization of second members of the same household where a previous participant was already randomized (the second members were partners of a previously recruited participant). Household members of previous participants were allocated to the same intervention group to avoid having different diets in the same family. Assigning all household members to the same diet was considered the best approach to successfully achieve dietary changes within a family. This procedure was inadvertently omitted in the reporting of the protocol and the original publication. This second deviation affected only 5.7% of PREDIMED participants, with similar proportions in the control group (4.8%), the Mediterranean diet group + extra virgin olive oil (6.7%) and the Mediterranean diet group + nuts (5.5%). More detailed information about these deviations can be found elsewhere (28-30).

### ***Withdrawal and republication of the PREDIMED results***

Because of these small divergences, the investigators of the PREDIMED trial decided to request the removal of their original publication (29) and simultaneously re-published a new version in June 2018 in the same *Journal* (30). In this new version, the PREDIMED Investigators fully disclosed all issues related to the allocation of these two small subsets of participants and addressed both of them by conducting multiple and robust new sensitivity and ancillary analyses. The republication of PREDIMED (30) also disclosed additional potential concerns on allocation divergences in another recruitment center (site I) where the site research team conducted the intervention in participants from some small clinics for only one arm of the trial in each clinic (on a total of 247 participants) but this was done for logistic reasons and the distribution of participants matched the expected balance. PREDIMED investigators also

reported an apparent inconsistent use of randomization tables in site B, but without any practical consequence for ensuring a balanced distribution at baseline of participant characteristics. All these issues created only very small imbalances (with a magnitude <5% for absolute differences) in the comparison of baseline variables among the three dietary groups and without any clinical or practical implication. The only imbalances that exceeded 5% (absolute differences) consisted in a slightly higher percentage of women in the control group (5.7% higher in control than in the Mediterranean diet+nuts group) and a 5.3% higher percentage of participants with high levels of low-density-lipoprotein cholesterol in the Mediterranean diet + extra virgin olive oil than in the control group. However, both issues will operate in any case *against* the hypothesis of the trial and in no way could account for the observed beneficial effects of the intervention. Therefore, the original results remained intact.

***So then... what changed and what did not change in the PREDIMED?***

To address the issues raised on the allocation procedures, the PREDIMED team incorporated two modifications in the main statistical analyses. On one hand, analyses were rerun after correcting the standard errors for potential intra-cluster correlations within households or clinics and applied propensity-score methods to correct the minor imbalances in baseline characteristics. On the other hand, they decided to conduct sensitivity analyses after excluding 1,588 participants — those whose trial-group assignments were known or suspected to have departed from proper individual randomization protocol— resulting in an analytical sample size of 5,859 participants. These exclusions were performed to ensure that all participants analyzed had received proper individual randomized allocation and thus avoided any further questioning about the allocation process.

To the surprise of many — but by no means of PREDIMED Investigators — the protection afforded by the Mediterranean diet was even greater after excluding the 1,588 participants

with doubtful individual randomization (instead of 30% relative risk reduction, it was 36% in the Mediterranean diet+nuts group and 34% in the Mediterranean diet+extra-virgin olive oil group).

More importantly, no significant change –from the clinical point of view– in the results was observed with the republished study when the correction for intra-cluster correlations and the propensity score methodology were applied (30). The republished trial included a long appendix with 99 pages addressing with full details and transparency all these potential concerns, with robust demonstrations of the permanent validity and rigor of the trial. After reanalyzing the data with the appropriate statistical analyses, the reduction in the incidence of the primary CVD end-point in the Mediterranean groups was almost identical in the republished study than in the original article, with hazard ratios changing from 0.70 (95% confidence interval [CI]: 0.53-0.92) to 0.69 (95% CI: 0.53-0.91) in the Mediterranean diet+extra-virgin olive oil group and changing from 0.70 (95% CI: 0.53-0.94) to 0.72 (95% CI: 0.54-0.95) in the Mediterranean diet+nuts, as compared to the control group. Changes only slightly affected the second decimal place of estimates. When both groups were merged together and compared to the control group, the hazard ratio was 0.70 (95% CI: 0.55-0.89) exactly the same in the original analysis and in the new analysis. Therefore, the authors' conclusions remained unchanged; an intervention with the traditional Mediterranean diet conferred a relative 30% reduction in the risk of major CVD events.

The retraction and republication of PREDIMED shall not clutter the big picture. There is reliable and extensive evidence from other randomized trials and prospective cohorts (1,5-9,31-36) supporting the multiple benefits of the Mediterranean dietary pattern for the prevention of CVD. In other words, nutritional epidemiology is not based on the findings on one single study but the results of consistent and extensive research over many years.

## Life after criticism?

After the disclosure of departures from the PREDIMED protocol, several unfounded criticisms were raised on the findings of PREDIMED (37-39). Simultaneously, some authors such as Mascha et al. (26) detected many flaws in the statistical method applied in 2017 to raise criticisms on PREDIMED, and questioned this statistical method. Moreover, these authors pointed out numerous weaknesses in this approach and recommended using simultaneous and more sophisticated statistical methods before unfoundedly calling out authors on scientific misconduct. In addition, some unfounded criticisms on PREDIMED were included in some published opinions which lacked any sound statistical analysis and contained gross flaws as correctly pointed out by Giovannucci (40,41).

But far from receiving additional critics, the Investigators of the PREDIMED welcomed and appreciated recognitions by numerous societies, research groups, and credits from the most distinguished nutritional epidemiologists. Examples of these recognitions were given, for example, by the American College of Cardiology, which congratulated the PREDIMED Investigators for the re-analyses and highlighted the randomized trial's importance and power. The *New England Journal of Medicine*, through the former editor-in-chief Dr. JM Drazen, underlined the exemplary predisposition of the PREDIMED Investigators on handling these issues and emphasized that the republication did not alter any conclusions. In Dr. Drazen words, “[PREDIMED] conclusions should raise public trust in science, not erode it”. *Medscape*, supported the words by Dr. Drazen and additionally pointed out how “the PREDIMED authors investigated the problem, wrote clearly about it, and did vigorous statistical analysis to account for the irregular randomization” (2018 Mandrola's 10 top Cardiology news) (42).

After 2018, the PREDIMED trial has continued contributing to increase the evidence on the benefits of the Mediterranean eating pattern on health outcomes. Among the 318 manuscripts published between 2006 until May 2020, around 70 have been accepted in top peer-reviewed

journals after reporting protocol's deviations. No journal has snubbed any manuscript due to the controversies on methodology raised in 2017. The groundbreaking trajectory of PREDIMED has reached another hallmark point with the recent publication of *The Mediterranean diet, plasma metabolome, and cardiovascular disease risk* (43,44). For the first time, a metabolic signature that measured adherence to an overall high-quality dietary pattern was identified. In addition, this signature was shown to be replicated and to exert reproducible effects in independent cohorts in the US. These findings represent a turning point in nutritional epidemiology, given the signature's objectivity to measure substrates, intermediates, and metabolism products and reduce the dependency on self-reported information collected by food frequency questionnaires susceptible to measurement errors. Moreover, the metabolic signature's ability to account for synergies and interactions among different foods and nutrients, genetic variability, and microbiota potentially confers its utility for future approaches based on personalized nutrition. Individual interventions considering genetic predisposition or specific phenotypes rather than population-based interventions may be the first step for a new nutritional era. Understanding biological mechanisms through which diet may impact health will give the final push for changing "prescription pills" for "prescription foods". This shift should be accompanied by additional shifts from the industry and policy-makers towards healthier foods, integrating nutrition into health care, and greater responsibility for addressing the food system's challenges. This change is an essential requirement for healthier individuals, families, and communities.

### ***Legacy of the PREDIMED trial***

Adherence to the Mediterranean diet was measured in PREDIMED with a validated 14-point Mediterranean diet questionnaire (13) that provided immediate feedback and it was also used to improve compliance in the intervention by means of negotiated goal setting. This

questionnaire has been used in multiple independent studies and it has been translated and validated in several other countries where it is now frequently used (45-50).

## **CONCLUSION**

Not only PREDIMED, but multiple studies have demonstrated over many years a large, strong, and consistent evidence of the benefits of the Mediterranean diet on a wide range of health outcomes, particularly cardiovascular outcomes. Although some might be reluctant to accept the factual evidence of the effects of the Mediterranean diet, no other food pattern counts on such a huge accrual of evidence supporting cardiovascular benefits. Admittedly, most available evidence, though prospective and well conducted, is observational in design, but observational studies are ethical and feasible, whereas the logistics, ethical issues and feasibility aspects will make almost impossible to conduct in the near future many large RCTs similar to PREDIMED. The good news is that both observational and experimental evidence supports that the Mediterranean dietary pattern represents the best "preventive medicine" for CVD. Moreover, the newly identified metabolic signature objectively underscores the Mediterranean diet's beneficial properties for the prevention of CVD at a molecular level.

## **KEY POINTS**

- PREDIMED is the first RCT to demonstrate the protective effects of the dietary Mediterranean pattern on hard cardiovascular events
- The successful results of PREDIMED are primarily explained by changes in Mediterranean adherence attained by participants on the intervention arms of the trial
- Despite small departures from the protocol of individual randomization, the conclusions of the PREDIMED trial remained intact

- A newly identified Mediterranean metabolic signature represents a promising tool towards personalized nutrition

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**Conflicts of interest:** None



## References

1. \*\*Martínez-González MA, Gea A, Ruiz-Canela M. The Mediterranean Diet and Cardiovascular Health. *Circ Res*. 2019;124:779-798.
2. Perk J, De Backer G, Gohlke H, et al. European Association for Cardiovascular Prevention & Rehabilitation (EACPR); ESC Committee for Practice Guidelines (CPG). European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). *Eur Heart J* 2012;33:1635-701.
3. US Government. Scientific Report of the Dietary Guidelines for Americans 2020-2025. Available on <https://www.dietaryguidelines.gov/2020-advisory-committee-report> (accessed on Nov 21, 2020).
4. Bach-Faig A, Berry EM, Lairon D, Reguant J, Trichopoulou A, Dernini S, Medina FX, Battino M, Belahsen R, Miranda G, Serra-Majem L; Mediterranean Diet Foundation Expert Group. Mediterranean diet pyramid today. Science and cultural updates. *Public Health Nutr*. 2011;14:2274-84.
5. Saulle R, Lia L, De Giusti M, La Torre G. A systematic overview of the scientific literature on the association between Mediterranean Diet and the Stroke prevention. *Clin Ter*. 2019;170:e396-e408.
6. Rosato V, Temple NJ, La Vecchia C, Castellan G, Tavani A, Guercio V. Mediterranean diet and cardiovascular disease: a systematic review and meta-analysis of observational studies. *Eur J Nutr*. 2019;58:173-191.
7. Becerra-Tomás N, Blanco Mejía S, Viguiouk E, Khan T, Kendall CWC, Kahleova H, Rahelić D, Sievenpiper JL, Salas-Salvadó J. Mediterranean diet, cardiovascular disease and mortality in diabetes: A systematic review and meta-analysis of prospective cohort studies and randomized clinical trials. *Crit Rev Food Sci Nutr*. 2020;60:1207-1227.
8. \*\*Galbete C, Schwingshackl L, Schwedhelm C, Boeing H, Schulze MB. Evaluating Mediterranean diet and risk of chronic disease in cohort studies: an umbrella review of meta-analyses. *Eur J Epidemiol*. 2018;33:909-931.
9. \*Serra-Majem L, Román-Viñas B, Sanchez-Villegas A, Guasch-Ferré M, Corella D, La Vecchia C. Benefits of the Mediterranean diet: Epidemiological and molecular aspects. *Mol Aspects Med*. 2019;67:1-55.
10. Martínez-González MA, Corella D, Salas-Salvadó J, Ros E, Covas MI, Fiol M, Wärnberg J, Arós F, Ruíz-Gutiérrez V, Lamuela-Raventós RM, Lapetra J, Muñoz MÁ, Martínez JA, Sáez G, Serra-Majem L, Pintó X, Mitjavila MT, Tur JA, Portillo MP, Estruch R; PREDIMED Study Investigators. Cohort profile: design and methods of the PREDIMED study. *Int J Epidemiol*. 2012;41:377-85.
11. Guasch-Ferré M, Salas-Salvadó J, Ros E, Estruch R, Corella D, Fitó M, Martínez-González MA. The PREDIMED trial, Mediterranean diet and health outcomes: How strong is the evidence? *Nutr Metab Cardiovasc Dis* 2017;27:624–32.
12. \*\*Martínez-González MA, Salas-Salvadó J, Estruch R, Corella D, Fitó M, Ros E. Benefits of the Mediterranean Diet: Insights From the PREDIMED Study. *Prog Cardiovasc Dis* 2015;58:50–60.
13. Schröder H, Fitó M, Estruch R, et al. A Short Screener Is Valid for Assessing Mediterranean Diet Adherence among Older Spanish Men and Women. *J Nutr* 2011;141:1140–5.
14. Zazpe I, Sanchez-Tainta A, Estruch R, Lamuela-Raventós RM, Schröder H, Salas-Salvado J, Corella D, Fiol M, Gomez-Gracia E, Aros F, Ros E, Ruíz-Gutierrez V, Iglesias P, Conde-Herrera M, Martinez-Gonzalez MA. A large randomized individual and group intervention conducted by registered dietitians increased adherence to Mediterranean-type diets: the PREDIMED study. *J Am Diet Assoc*. 2008;108:1134-44.

15. Downer MK, Gea A, Stampfer M, Sánchez-Tainta A, Corella D, Salas-Salvadó J, Ros E, Estruch R, Fitó M, Gómez-Gracia E, Arós F, Fiol M, De-la-Corte FJ, Serra-Majem L, Pinto X, Basora J, Sorlí JV, Vinyoles E, Zazpe I, Martínez-González MÁ. Predictors of short- and long-term adherence with a Mediterranean-type diet intervention: the PREDIMED randomized trial. *Int J Behav Nutr Phys Act.* 2016;13:67.
16. Sabaté E. Adherence to long-term therapies: evidence for action. Switzerland: World Health Organization; 2003.
17. Moleman M, Regeer BJ, Schuitmaker-Warnaar TJ. Shared decision-making and the nuances of clinical work: Concepts, barriers and opportunities for a dynamic model. *J Eval Clin Pract.* 2020 Nov 8. doi: 10.1111/jep.13507. Epub ahead of print.
18. Estruch R, Ros E, Salas-Salvadó J, et al. Primary prevention of cardiovascular disease with a Mediterranean diet. *N Engl J Med* 2013;368:1279–90.
19. Salas-Salvadó J, Bulló M, Estruch R, et al. Prevention of diabetes with Mediterranean diets: A subgroup analysis of a randomized trial. *Ann Intern Med* 2014;160:1–10.
20. Ruiz-Canela M, Estruch R, Corella D, et al. Association of Mediterranean diet with peripheral artery disease: The PREDIMED randomized trial. *JAMA* 2014;311(4):415–7.
21. Martínez-González MÁ, Toledo E, Arós F, et al. Extravirgin olive oil consumption reduces risk of atrial fibrillation: The PREDIMED (Prevención con Dieta Mediterránea) trial. *Circulation* 2014;130:18–26.
22. Toledo E, Hu FB, Estruch R, Buil-Cosiales P, Corella D, Salas-Salvadó J, Covas MI, Arós F, Gómez-Gracia E, Fiol M, Lapetra J, Serra-Majem L, Pinto X, Lamuela-Raventós RM, Saez G, Bulló M, Ruiz-Gutiérrez V, Ros E, Sorli JV, Martinez-Gonzalez MA. Effect of the Mediterranean diet on blood pressure in the PREDIMED trial: results from a randomized controlled trial. *BMC Med.* 2013;11:207.
23. Damasceno NR, Sala-Vila A, Cofán M, Pérez-Heras AM, Fitó M, Ruiz-Gutiérrez V, Martínez-González MÁ, Corella D, Arós F, Estruch R, Ros E. Mediterranean diet supplemented with nuts reduces waist circumference and shifts lipoprotein subfractions to a less atherogenic pattern in subjects at high cardiovascular risk. *Atherosclerosis.* 2013;230:347-53.
24. Toledo E, Salas-Salvado J, Donat-Vargas C, et al. Mediterranean diet and invasive breast cancer risk among women at high cardiovascular risk in the PREDIMED trial a randomized clinical trial. *JAMA* 2015;175:1752–60.
25. Papadaki A, Martínez-González MÁ, Alonso-Gómez A, Rekondo J, Salas-Salvadó J, Corella D, Ros E, Fitó M, Estruch R, Lapetra J, García-Rodríguez A, Fiol M, Serra-Majem L, Pintó X, Ruiz-Canela M, Bulló M, Serra-Mir M, Sorlí JV, Arós F. Mediterranean diet and risk of heart failure: results from the PREDIMED randomized controlled trial. *Eur J Heart Fail.* 2017;19:1179-1185.
26. Mascha EJ, Vetter TR, Pittet JF. An Appraisal of the Carlisle-Stouffer-Fisher Method for Assessing Study Data Integrity and Fraud. *Anesth Analg.* 2017;125:1381-1385.
27. Carlisle JB. Data fabrication and other reasons for non-random sampling in 5087 randomised, controlled trials in anaesthetic and general medical journals. *Anaesthesia* 2017;72:944–52.
28. PREDIMED. Questions & Answers. Re-Publication of the PREDIMED Trial. 2019. Available online: [www.predimed.es/q--a-2018-news.html](http://www.predimed.es/q--a-2018-news.html) (accessed on Nov 21, 2020).
29. Estruch R, Ros E, Salas-Salvadó J, et al. Retraction and Republication: Primary Prevention of Cardiovascular Disease with a Mediterranean Diet. *N Engl J Med* 2013;368:1279 90. *N Engl J Med* 2018;378:2441–2.
30. \*\*Estruch R, Ros E, Salas-Salvadó J, et al. Primary Prevention of Cardiovascular Disease with a Mediterranean Diet Supplemented with Extra-Virgin Olive Oil or Nuts. *N Engl J Med* 2018;378:e34.
31. de Lorgeril M, Salen P, Martin J-L, et al. Mediterranean Diet, Traditional Risk Factors, and the Rate of Cardiovascular Complications After Myocardial Infarction. *Circulation* 1999;99:779–85.

32. de Lorgeril M, Renaud S, Salen P, et al. Mediterranean alpha-linolenic acid-rich diet in secondary prevention of coronary heart disease. *Lancet* 1994;343:1454–9.
33. Buckland G, Travier N, Barricarte A, Ardanaz E, Moreno-Iribas C, Sánchez MJ, et al. Olive oil intake and CHD in the European Prospective Investigation into Cancer and Nutrition Spanish cohort. *Br J Nutr.* 2012;108:2075–82..
34. \*Sotos-Prieto M, Bhupathiraju SN, Mattei J, Fung TT, Li Y, Pan A, Willett WC, Rimm EB, Hu FB. Changes in Diet Quality Scores and Risk of Cardiovascular Disease Among US Men and Women. *Circulation.* 2015;132:2212-9..
35. Mente A, De Koning L, Shannon HS, Anand SS. A systematic review of the evidence supporting a causal link between dietary factors and coronary heart disease. *Arch Intern Med.* 2009 Apr 13;169:659-69.
36. Grosso G, Marventano S, Yang J, Micek A, Pajak A, Scalfi L, Galvano F, Kales SN. A comprehensive meta-analysis on evidence of Mediterranean diet and cardiovascular disease: Are individual components equal? *Crit Rev Food Sci Nutr.* 2017;57:3218-3232.
37. Mayor S. Sixty seconds on . . . the Mediterranean diet. *BMJ* 2018;361:k2667.
38. Ioannidis JPA. The Challenge of Reforming Nutritional Epidemiologic Research. *JAMA* 2018;320:969-70.
39. Agarwal A, Ioannidis JPA. PREDIMED trial of Mediterranean diet: retracted, republished, still trusted? Is republication justified? Continuing follow-up. *BMJ* 2019;364:341.
40. \*\*Giovannucci E. Nutritional epidemiology: forest, trees and leaves. *Eur J Epidemiol.* 2019;34:319-325.
41. \*\*Giovannucci E. Nutritional epidemiology and cancer: A Tale of Two Cities. *Cancer Causes Control.* 2018;29:1007-1014.
42. Mandrola JM. *Medscape* 2018, Nov 22. Mandrola's Top 10 Cardiology Stories of 2018. Available online: [www.medscape.com/viewarticle/906639#vp\\_4](http://www.medscape.com/viewarticle/906639#vp_4) (accessed on Nov 21, 2020).
43. \*\*Li J, Guasch-Ferré M, Chung W, et al. The Mediterranean diet, plasma metabolome, and cardiovascular disease risk. *Eur Heart J* 2020;41:2645–56.
44. \*\*Sharma S, Parry-Williams G, Gati S. The metabolic signature: an emerging paradigm in cardiovascular nutritional health research? *Eur Heart J* 2020;41:2657–9.
45. Hebestreit K, Yahiaoui-Doktor M, Engel C, Vetter W, Siniatchkin M, Erickson N, Halle M, Kiechle M, Bischoff SC. Validation of the German version of the Mediterranean Diet Adherence Screener (MEDAS) questionnaire. *BMC Cancer.* 2017;17:341.
46. Rasmussen E, Fosnacht Morgan AM, Munson R, Ong A, Patel S, Yucus C, Pham A, Patel V, Frigerio R, Lai R, Hillman L, Tideman S, Wang C, Simon KC, Martínez-González MÁ, Maraganore DM. Use of an Electronic Medical Record to Track Adherence to the Mediterranean Diet in a US Neurology Clinical Practice. *Mayo Clin Proc Innov Qual Outcomes.* 2018;2:49-59.
47. Papadaki A, Johnson L, Toumpakari Z, England C, Rai M, Toms S, Penfold C, Zazpe I, Martínez-González MA, Feder G. Validation of the English Version of the 14-Item Mediterranean Diet Adherence Screener of the PREDIMED Study, in People at High Cardiovascular Risk in the UK. *Nutrients.* 2018;10:138.
48. Chervenkov M, Ivanova T, Dimitrova D, Maksimova V, Smilkov K, Ackova DG, Miloseva L, Ruskovska T, Deligiannidou GE, Kontogiorgis CA, Pinto P. Exploring the Validity of the 14-Item Mediterranean Diet Adherence Screener (MEDAS): A Cross-National Study in Seven European Countries around the Mediterranean Region. *Nutrients.* 2020;12:2960.
49. Gregório MJ, Rodrigues AM, Salvador C, Dias SS, de Sousa RD, Mendes JM, Coelho PS, Branco JC, Lopes C, Martínez-González MA, Graça P, Canhão H. Validation of the Telephone-Administered Version of the Mediterranean Diet Adherence Screener (MEDAS) Questionnaire. *Nutrients.* 2020;12:1511.
50. Vieira LM, Gottschall CBA, Vinholes DB, Martinez-Gonzalez MA, Marcadenti A. Translation and cross-cultural adaptation of 14-item Mediterranean Diet Adherence Screener and low-

fat diet adherence questionnaire. Clin Nutr ESPEN. 2020;39:180-189.

## TABLES

**Table 1.** Evidence of the Mediterranean dietary eating pattern on clinical health events.

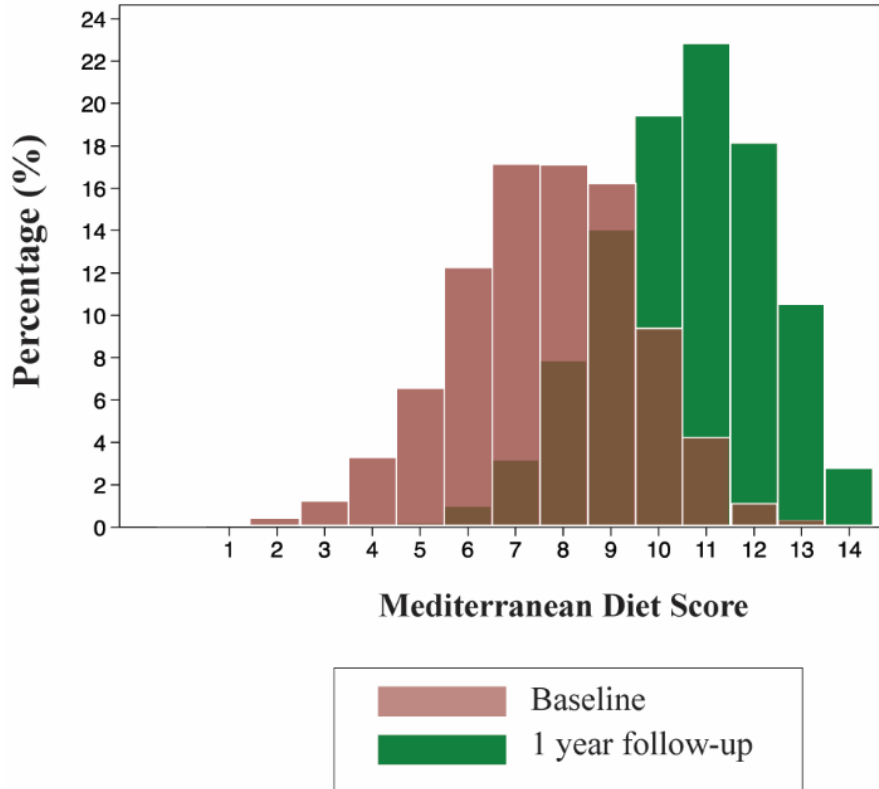
Hazard ratios and 95% confidence intervals<sup>1</sup>

| Outcome                          | Mediterranean diet      | Mediterranean diet      | Both                    |
|----------------------------------|-------------------------|-------------------------|-------------------------|
|                                  | +<br>EVOO               | +<br>Nuts               |                         |
| Type2 diabetes (19)              | <b>0.60 (0.42-0.84)</b> | 0.79 (0.59-1.07)        | <b>0.69 (0.53-0.91)</b> |
| Peripheral arterial disease (20) | <b>0.35 (0.19-0.65)</b> | <b>0.52 (0.31-0.87)</b> | <b>0.44 (0.27-0.69)</b> |
| Atrial fibrillation (21)         | <b>0.62 (0.44-0.86)</b> | 0.87 (0.64-1.18)        | <b>0.74 (0.56-0.96)</b> |
| Breast cancer (24)               | <b>0.32 (0.13-0.79)</b> | 0.59 (0.26-1.35)        | <b>0.43 (0.21-0.88)</b> |
| Heart failure (25)               | <b>0.63 (0.38-1.04)</b> | 0.91 (0.55-1.50)        | 0.76 (0.53-1.08)        |

<sup>1</sup>Hazard Ratios vs. control group

References: 19, 20, 21, 24 and 25.

FIGURES



**Figure 1.** Adherence to the Mediterranean diet in the participants from the 2 PREDIMED active intervention groups at baseline and at 1-year follow-up.