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Considerations to facilitate a US study that replicates PREDIMED

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ABSTRACT

The PREDIMED clinical trial provided strong evidence that a Mediterranean dietary pattern (MedDiet) could help prevent cardiovascular disease (CVD) events in high risk middle-aged/older people. This report considers the feasibility of replicating PREDIMED in the U.S., including recommendations for dietary and behavioral principles. A 14-point Mediterranean diet Adherence Score (MEDAS) guided the PREDIMED MedDiet recommendations. At baseline MEDAS points were ~8.5. During intervention this score increased to nearly 11 in MedDiet vs. 9 in control. In the MedDiet groups, only about 0.5 points of the net 2 point MEDAS increase was attributable to the gratis supplements of olive oil or nuts. An issue in a U.S. replication is the large difference in typical U.S. versus Spanish diet and lifestyle. A typical U.S. diet would achieve a MEDAS of 1–2. A replication is scientifically feasible with an assumption such as that the MedDiet reflects a continuum of specific food choices and meal patterns. As such, a 2 point change in MEDAS at any point on the continuum would be hypothesized to reduce incident CVD. A conservative approach would aim for a randomized 4 point MEDAS difference, e.g. 5–6 points vs. an average U.S. diet group that achieved only 1–2 points.

Contents

Abbreviations: CVD, cardiovascular disease; CWC, California Walnut Commission; EVOO, extra-virgin olive oil; MEDAS, Mediterranean Diet Adherence Score; MedDiet, Mediterranean diet; NHANES, National Health and Nutrition Examination Survey 2011–2012 database; PREDIMED, Prevención con Dieta Mediterránea; RCT, randomized clinical trial.

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1. Background

There is scientific excitement about PREDIMED (PREvención con DIeta MEDiterránea), a randomized clinical trial (RCT) providing "Grade A" evidence that the Mediterranean diet (MedDiet) reduced the incidence of cardiovascular disease (CVD) in Spain [1]. Briefly, PREDIMED was conducted in 7447 Spanish men aged 60–80 and women aged 55–80 years over a median 4.8 years. Participants were free of clinical CVD at baseline, but were high risk, many being overweight or obese, hypertensive (83%), dyslipidemic (72%), or having type-2 diabetes (49%). Some were smokers (14%) or had family history of premature coronary heart disease (22%). An important design feature was that PREDIMED participants were recruited from medical clinics, simplifying access to medical records. Incident CVD was reduced by approximately 30% among participants randomized to either MedDiet plus extra-virgin olive oil (EVOO) or the MedDiet plus nuts (50% walnuts, 25% almonds, and 25% hazelnuts) compared to the control diet group (advice to reduce all dietary fat). A 14-point Mediterranean Diet Adherence Score (MEDAS) guided the PREDIMED recommendations to participants in the two MedDiet groups, while the principles that guided the control group were designed to reduce fat of all types (Table 1); (verbatim MEDAS questions and criteria [1] are given in Table 2).

In contrast to the many long-term RCTs related to pharmaceuticals, there have been relatively few long-term RCTs of dietary interventions. Studies of food are less well suited to the RCT design than are studies of pills [2,3]. Issues in RCTs of foods and dietary patterns include difficulty in masking a food intervention, the centrality of food in daily life, difficulty in maintaining compliance with the prescribed diet, and high cost of this type of study. Furthermore, in RCTs eating one food generally means not eating another, both because of personal food preferences and because isocaloric conditions may be required to maintain body weight. However, PREDIMED successfully circumvented these difficulties. There has been substantial commentary about PREDIMED, with response by the PREDIMED investigators [4].

Interpreting and potentially replicating PREDIMED depends on clearly defining what food combinations were eaten in the intervention and control groups. While PREDIMED generally supports consumption of a MedDiet, what exactly did the PREDIMED trial test? What achieved dietary patterns distinguished the three experimental groups?

Table 1
Dietary recommendations which guided the Mediterranean and control diet groups in PREDIMED.

Dietary recommendations for the Mediterranean diet groups	Dietary recommendations for the control diet group
1. Olive oil used as the main culinary fat	1. Olive oil ≤ 2 tbsp/day
2. Olive oil ≥ 4 tbsp/day	2. Remove visible fat from meat and broth
3. Vegetables ≥ 2 servings/day	3. Meat and processed meat ≤ 1 serving/week
4. Fruit ≥ 3 servings/day	4. Butter and other solid fats ≤ 1 serving/week
5. Red meat and meat products < 1 serving/day	5. Consume only low-fat dairy products
6. Butter, cream, margarine < 1 serving/d	6. Use of sofrito ≤ 2 servings/week
7. Soda drinks < 1 drink/day	7. Fatty fish or and fish/seafood canned in oil ≤ 1 serving/week
8. Wine ≥ 7 glasses/week	8. Solid sweets/industrial bakery products ≤ 1 serving/week
9. Legumes ≥ 3 servings/week	9. Nuts, potato chips, and commercial snacks ≤ 1 serving/week
10. Fish and seafood ≥ 3 servings/week	
11. Cakes, sweets < 3 servings/week	
12. Nuts ≥ 3 servings/week	
13. Poultry > red meat	
14. Sofrito sauce ≥ 2 servings/week	

Information extracted from [1]. The two Mediterranean diet groups were distinguished in that one received gratis extra virgin olive oil, while the other received gratis tree nuts.

The California Walnut Commission (CWC) has had a great interest in PREDIMED from its outset, supplying over 3,000,000 pounds of walnuts to the PREDIMED participants. Motivated by discussion of a National Heart, Lung, and Blood Institute (NHLBI) workshop about the MedDiet held May 2016 [5], a Working Group (constituting the authors of this article) concerned with testing a Mediterranean-style diet in the U.S. was established at the annual CWC Scientific Advisory meeting in July 2016. They subsequently convened to discuss what would be involved in a replication of PREDIMED in the U.S. The conclusions of the Working Group have been presented [6].

The Working Group queried how the PREDIMED trial was conducted and visited the Barcelona PREDIMED site. In Barcelona, they collaborated with PREDIMED investigators and staff at their clinic to discuss the conduct of PREDIMED and review study materials. In addition, to understand the food supply in Barcelona, they visited supermarkets and restaurants and participated in a cooking demonstration. This hands-on experience enabled them to better understand the differences in diet and lifestyle between the Spanish and American cultures and the implications this may have for a replication trial in the U.S. The Working Group subsequently formulated a plan to replicate PREDIMED in the U.S.

2. De Novo Analysis in This Report

As part of this report, a de novo analysis was conducted using the original PREDIMED individual participant repeated MEDAS data. It categorized changes in item-specific responses between PREDIMED baseline and years 1, 3, and 5 according to randomized group.

3. Considerations for a PREDIMED Replication in the U.S.

The theoretical basis for a replication was considered. Understanding the dietary patterns that were actually achieved during the RCT, and how they differed from the lower fat control diet, is necessary because the difference in diet consumed is what PREDIMED actually tested. Besides providing dietary guidance for the MedDiet groups, the 14-point MEDAS assessed compliance in both MedDiet and control groups. In PREDIMED, the base for both treatment and control groups was a traditional Spanish MedDiet and lifestyle, evidenced by a baseline MEDAS (expressed in points) of ~8.5. This relatively high score likely reflects common Spanish culinary positions [7].

In Spain, olive oil (not necessarily extra-virgin) is the main culinary fat, used in food preparation or added at the table. For example, sofrito and other sauces (see supplementary material), which are staples in the Spanish MedDiet (and sofrito is specifically referenced in MEDAS), are typically made with olive oil. Traditionally, fresh foods are purchased daily, meals prepared at home and relatively few pre-prepared and processed foods are consumed. This contrasts with the U.S. where cooking from scratch is rare and commonly consumed meals are assembled from pre-prepared and processed foods [8,9]. In Spain, lunch is traditionally the main meal and lighter fare is served for dinner. Main meals are enjoyed with family and friends and last >20 min. The Spanish also tend to have a more active lifestyle than do Americans. It is likely that the PREDIMED intervention promoted a shift towards more traditional customary behaviors of the MedDiet and lifestyle, including eating meals together. In contrast, the control group was encouraged to move towards a low-fat diet, which in the study setting differed from a Spanish MedDiet, particularly given the central role of olive oil in Spain.

The background culture would differ from PREDIMED in any non-Spanish replication. Dietary patterns are complex and multidimensional, defined in terms of all aspects of food, food preparation, and eating practices accumulated over time. Consequently, it is not possible to define a dietary pattern based on intake on a single day. Although there are various dietary patterns in the Mediterranean geographic region [10–14], the Spanish diet has specific aspects, such

Table 2
Mediterranean Diet Adherence Score (MEDAS) as used in PREDIMED and its estimated values in the Healthy U.S. Mediterranean Style Diet and current average U.S. diet.

MEDAS item	PREDIMED	Healthy U.S. Mediterranean style diet [21]	Healthy U.S. Mediterranean style diet	Average U.S. Diet[a]
Verbatim wording	Criteria for 1 point	U.S. recommendation	MEDAS points	MEDAS points
1) Do you use olive oil as main culinary fat?	Yes	No	0	0 (WG, not reported in NHANES, use of other fats is well known to be widespread)
2) How much olive oil do you consume in a given day (including oil used for frying, salads, out of house meals, etc.)?	4 or more tablespoons (~60 g)	27 g/day vegetable oil	0	0 (NHANES 26.7 g/day total oil, not specifically reported for olive oil)
3) How many vegetable servings do you consume per day? (1 serving = 200 g − consider side dishes as 1/2 serving)	2 or more (at least 1 portion raw or as salad)	2.5 servings/day	1	0 (NHANES 1.64 cup Equivalents/day)
4) How many fruit units (including natural fruit juices) do you consume per day?	3 or more	2.5 servings/day	0	0 (NHANES 0.99 cup Equivalents/day)
5) How many servings of red meat, hamburger, or meat products (ham, sausage, etc.) do you consume per day? (1 serving = 100–150 g)	<1	12.5 oz (350 g)/week	1	1 (NHANES 2.72 oz Equivalents (79 g)/day)
6) How many servings of butter, margarine, or cream do you consume per day? (1 serving = 12 g)	<1	Spread fats 17 g/day	0	0 (WG, not specified in NHANES, many margarines are used widely)
7) How many sweet/carbonated beverages do you drink per day?	<1	Limit added sugar	1	0 (NHANES 1.24 servings/day) Rehm
8) How much wine do you drink per week?	7 or more glasses	≥7 glasses/week (only for habitual drinkers)	1	0 (NHANES 0.86 glasses/d for males and females 20+ years, not reported for habitual consumers only)
9) How many servings of legumes do you consume per week? (1 serving = 150 g)	3 or more	1.5 cups/week	0	0 (NHANES 0.14 cups (28 g)/day)
10) How many servings of fish or shellfish do you consume per week? (1 serving: 100–150 g fish, or 4–5 units or 200 g shellfish)	3 or more	15 oz Equivalents (420 g)/week	1	0 (NHANES 0.60 oz Equivalents (17 g)/day or 4.2 oz Equivalents (119 g)/week, includes both lean and fatty fish, whereas the fatty fish is more predominant in Spain)
11) How many times per week do you consume commercial sweets or pastries (not homemade), such as cakes, cookies, biscuits, or custard?	<3	Limit added sugar and saturated fat	1	0 (WG, not reported in NHANES)
12) How many servings of nuts (including peanuts) do you consume per week? (1 serving = 30 g)	3 or more	5 servings/week (nuts and seeds)	1	0 (NHANES 0.80 oz Equivalents (22 g)/day of nuts and seeds)
13) Do you preferentially consume chicken, turkey or rabbit meat instead of veal, pork, hamburger or sausage?	Yes	Instead of red meat	0	1 (FD, poultry disappearance has been increasing since the 1940s, while beef has been decreasing since the 1970s)
14) How many times per week do you consume vegetables, pasta, rice, or other dishes seasoned with sofrito (sauce made with tomato and onion, leek, or garlic, simmered with olive oil)?	2 or more	No	0	0 (WG, the closest similar foods are salsa and marinara sauce; ingredients and preparation are different)

Notes about Healthy U.S. Mediterranean Style diet:
Item 3 (Vegetables): the criterion component "at least 1 portion raw or as salad" was not addressed.
Item 4 (Fruit): 0 point was awarded because 2.5 servings/day is less than the PREDIMED criterion of 3 servings/day.
Items 5 and 13 (Red meat and Preference for poultry over red meat): The Scientific Report of the 2015 Dietary Guidelines Advisory Committee (DGAC) recommendation is for 12.5 oz Equivalents/week of red meat and 10.5 oz Equivalents/week of poultry, but these are combined along with eggs in the 2015–2020 Dietary Guidelines for Americans (DGA) as 26 oz Equivalents/week. The listed recommendation is the one from DGAC (Table D1.32). Preferential consumption is not addressed in DGAC or DGA; 0 MEDAS points were awarded for item 13 based on the DGAC recommendation.
Items 6, 7, 8, 11 (Butter, soft drinks, wine, commercial bakery goods): These items are linked in the U.S. recommendation for the Healthy U.S. Mediterranean Style diet by the Extra Calories recommendation—which is 260 kcal for the Healthy U.S. Mediterranean Style Diet. For alcohol consumption (not specifically wine), the U.S recommendation is 1 serving/day for women who drink and 2 servings/day for men who drink, which matches the PREDIMED recommendation. However, alcohol is considered in the U.S. recommendation to be extra calories, along with added sugars and solid fats, so if this amount of alcohol is consumed, soft drinks and commercial bakery goods should be decreased. On the other hand for non-drinkers, soft drinks and commercial bakery goods could be increased a little. Spread fats such as butter must also be considered here, because the energy balance won't allow 17 g/d if 100–200 kcals/day come from alcoholic beverages.
Notes for MEDAS points for Average U.S. Diet:
Although American diets are diverse and few individuals would eat an "average diet", the criterion used for assigning MEDAS points relied on the average value in the National Health and Nutrition Examination Survey (NHANES) in 2011–2012. Where NHANES data did not cover an item, food disappearance data was used (for poultry preference over red meat) or the judgment of the Working Group based on experience with American diets was used.
[a] MEDAS verbatim items are cited from Table S1 of [1]. Each MEDAS item is coded yes or no, with 1 point assigned for each "yes". MEDAS points for the U.S. Healthy Mediterranean Style Diet are based on interpretation of the 2015–2020 Dietary Guidelines for Americans [21]. Cell entries for the average U.S. diet are estimated MEDAS score and in parentheses rationales for and comments about judgments about the estimated score. The information for these judgments is derived from several sources [16–18]. Abbreviations for source of the information: NHANES = National Health and Nutrition Examination Survey (1 day recall in 2011–2012), FD = food disappearance data, WG = working group judgment.

as sofrito. While the Working Group acknowledges that subpopulations in the U.S. may achieve a MEDAS score of 4–7 [15], using "What We Eat in America" [16] or other [17] data derived from NHANES as well as food disappearance [18] findings, we estimated that the MEDAS score in this representative sample of Americans was 2, related to preference for poultry over red and processed meat and relatively low average consumption of red and processed meat (rightmost column of Table 2). Assumptions made in harmonizing MEDAS food groups and grams per serving with U.S. data are provided both in the body of and footnotes to Table 2. Table 3 shows the food and nutrient changes that would be required to align the average U.S. diet [16] with the MedDiet in PREDIMED. Notably the MedDiet is higher in total fat, predominately monounsaturated, marine n-3 fatty acids and fiber. Olive oil consumption was not measured in NHANES, but was probably low in the U.S.

Table 3
Dietary intake in the Mediterranean diet groups in PREDIMED compared to average intake in the U.S.

	Mediterranean diet + EVOO	Mediterranean diet + nuts	NHANES 2011–12	Change needed
Nutrient intake				
Energy, kcal/d	2172	2229	2141	–
Carbohydrate, % E	40	40	48	Decrease (type matters)
Protein, % E	16	16	16	–
Total fat, % E	41	42	34	Increase (type matters)
Saturated fat, % E	9	9	11	Decrease
MUFA, % E	22	21	12	Increase
PUFA, % E	6	8	8	None
α-Linolenic acid, g/d	1.3	1.9	NA	NA
Marine n-3 fatty acids, g/d	0.9	0.8	0.1	Increase
Fiber, g/d	25	27	17	Increase
Cholesterol, g/d	339	338	293	None
Food intake				
Virgin olive oil, g/d	50	32	NA	Increase
Refined olive oil, g/d	0.9	10.3	NA	–
Nuts, g/d	10	40	11	Increase
Fruit, g/d	401	406	149	Increase
Vegetables, g/d	340	336	246	Increase
Legumes, g/d	22	22	6	Increase
Whole grains, g/d	27	28	28	None
Refined grains, g/d	181	178	165[a]	None
Pastry, sweets, g/d	17	16	NA	Decrease
Meat, g/d	119	119	118	None
Fish/seafood, g/d	101	103	17	Increase
Dairy, g/d	366	370	399	None

NA = not available.
Derived from the What we eat in America website, accessed January 4, 2018.
[a] Includes pastry, cake, cookies, donuts in addition to refined cereals and cereal products.

In addition, intake of nuts, fruits, vegetables, legumes, and fish and seafood were substantially less in the U.S. than in PREDIMED. The Working Group considered it unrealistic to imagine that a long-term clinical trial that relies even partly on dietary advice would be able to achieve and maintain MEDAS at a level close to that typical of Spain. Therefore, it seems unlikely that the diets reportedly consumed in PREDIMED would be replicable elsewhere. It would be particularly difficult to replicate the low-fat version of the PREDIMED control group, because this dietary pattern still had MedDiet characteristics, and yet was, in a way, antithetical to a "true" MedDiet.

Therefore, as a theoretical basis to support a replication of PREDIMED, the Working Group considered whether the MedDiet might be a continuum; if so, then regardless of where individuals start on the continuum, small increases towards a diet more aligned with the MedDiet should be the focus. It is assumed, but not easily verified, that the MEDAS points are approximately equal in their disease effects. Because MEDAS was the basis for MedDiet advice, the Working Group suggests that it be used to quantify this continuum. In this sense, it would be possible to implement a treatment that moved towards the PREDIMED MedDiet and a control that more closely mimicked the average U.S. dietary pattern. However, neither diet would be at the same point on the MEDAS continuum common to the Spanish MedDiet.

The Working Group also considered an alternate model which postulates that changes in MEDAS affect CVD risk only above a certain threshold. In this case, a realistic goal would be for the treatment group in a U.S. replication to achieve a MEDAS difference of 4 points, for example, treatment group achieving 5–6 points while the controls achieved only 1–2.

The Working Group pointed out that a PREDIMED replication would also have relevance outside the U.S. and Mediterranean regions, where MEDAS is generally low and the encouraged foods would likely differ across geographic areas. These differences pose a unique opportunity, in that a more ambitious goal would be to achieve the PREDIMED treatment dietary pattern as it was done in Spain; if such a goal were achievable, the dietary difference from the control group would be substantial.

4. What Parts of Diet Changed in PREDIMED?

Food changes that occurred in each of the randomized groups, based on an annual food frequency questionnaire, are included in Table 4, as previously reported [1]. In the MedDiet groups, intake of EVOO increased and refined olive oil intake declined. Nut intake increased in the MedDiet plus nuts group. Legumes and fish and seafood intakes increased in both MedDiet groups. This form of diet assessment did not show significant differences for other foods. PREDIMED investigators also reported MEDAS values at 1, 3, and 5 years, without regard to baseline MEDAS (see Table S5 in [1]), with a similar conclusion.

Perhaps because most of the changes reported here in Table 4 involved olive oil (more EVOO absolutely and replacing refined olive oil) and nut intake, Appel and Van Horn's commentary [19] on the primary PREDIMED report [1] noted that EVOO and nuts, provided to the respective treatment groups as gratis supplements, were important in the way that PREDIMED participants implemented their assigned treatments.

Table 4
The quantitative change in key foods between the Mediterranean diet and control diet groups in PREDIMED.

Key foods (g/day)	Mediterranean diet + EVOO	Mediterranean diet + nuts	Control group	*p* value
Virgin olive oil	29	10	3	<0.001
Refined olive oil	−17	−6	−4	<0.001
Nuts	0	18	−3	<0.001
Legumes	2.4	2.4	0	<0.001
Fish or seafood	1.25	2.5	−4	<0.001

The change is follow-up minus baseline. The last available follow-up FFQ for each participant was used. Information extracted from Table S6 in [1].

Furthermore, they suggested that PREDIMED should be regarded simply as a test of EVOO and nut supplements [19], as other aspects of the MedDiet played a minor role in their view. This issue is critical to understanding what PREDIMED actually tested. The Working Group felt that this conclusion [19] understated the role of the general diet in PREDIMED. They performed de novo analysis of MEDAS changes from baseline in the individual mean MEDAS responses at year 1, 3 and 5 and observed that most participants in the MedDiet groups altered their diets in several other ways as well. They found that a large part of the PREDIMED cohort was using olive oil and many participants were regularly consuming nuts at baseline, so the provision of supplemental foods appeared to maintain a dietary behavior rather than change it. In the MedDiet plus EVOO group, the 3 olive oil items accounted for 0.42 to 0.46 points of the ~2 point increase in MEDAS throughout the trial, while in the MedDiet plus nuts group the nut item accounted for 0.47 to 0.53 points of the ~2 point MEDAS increase (Table 5). The remaining sections of Table 5 show that about 55% of participants in both MedDiet groups increased their MEDAS score by 2 or more points, vs. 27–37% in control. Correspondingly, only 25–30% of participants in both MedDiet groups had no change or a decrease in their MEDAS score, vs 48–55% in control. This means that the target foods accounted for ~25% of the overall change in MEDAS score in both treatment arms. The remaining MEDAS items all were part of the ~2 point increase and this came from a range of food combinations for different participants, meaning it would be difficult to isolate any individual food. The exception was that very few participants increased intakes of wine.

These new findings point to a major role within PREDIMED for all MEDAS components except wine. In addition, change in specific MEDAS factors varied between participants in achieving the 30% reduction in incident CVD. Thus, rather than focusing on individual foods in isolation, the dietary pattern comprising these foods should be the main point of interest. This focus on the whole MedDiet is consistent with a recent umbrella review of existing meta-analyses of epidemiologic studies and RCTs, in which robust evidence supported that greater adherence to the MedDiet is associated with a reduced risk of all-cause mortality, CVD, coronary heart disease, diabetes, overall cancer, and neurodegenerative disorders [20].

Two other issues are physical activity and salt intake. Neither was specifically addressed in PREDIMED. The main consideration for physical activity is that it does not act as a confounder, so advice in a U.S. replication would be to maintain current levels, with some general advice for all to lead an active life. A treatment group that was using mostly healthier products, including fresh fruits and vegetables, and avoiding highly processed food would likely result in reduced salt intake, without making that a specific aim.

Table 5
Change in MEDAS points[a] in PREDIMED participants during the trial.

	Year 1	Year 3	Year 5
Number of people providing MEDAS answers[b]			
MedDiet + EVOO	2234	2011	1429
MedDiet + nuts	1962	1627	1089
Control	1706	1281	813
Change points attributable to target food/total change points[c]			
MedDiet + EVOO	0.46/1.65	0.46/1.65	0.42/1.66
MedDiet + nuts	0.52/1.90	0.53/1.96	0.47/1.86
Control	0/0.36	0/0.34	0/0.71
Percent of people with increase 2+ points			
MedDiet + EVOO	50.6	53.9	52.9
MedDiet + nuts	56.8	57.8	56.2
Control	27.2	30.3	37.5
Percent of people with no change or decreased points			
MedDiet + EVOO	30.0	30.8	30.6
MedDiet + nuts	24.8	24.6	26.0
Control	55.2	52.9	47.8

MedDiet, Mediterranean diet; EVOO, extra-virgin olive oil.

[a] Mean MEDAS change = $[\Sigma_{\text{j across participants within treatment group}} \Sigma_{\text{k=1 to 14}} (\text{MEDAS}_{\text{k,year m}} - \text{MEDAS}_{\text{k,year 0}})]$ / number of participants within treatment, where j indexes participant, k indexes MEDAS ítem, and $\text{MEDAS}_{\text{k,year m}}$ and $\text{MEDAS}_{\text{k,year 0}}$ are the ítem values (0 for no, 1 for yes) for ítem k at year m and year 0, respectively.

[b] The numbers randomized were 2543 for MedDiet + EVOO, 2454 for MedDiet + Nuts, and 2450 for Control. The unequal follow-up time of participants in PREDIMED (median follow-up 4.8 y) and greater failure to attend clinic in the control diet arm explain much of the reduction in number of participants not providing MEDAS answers with time.

[c] Mean baseline MEDAS values were 8.7 for both the MedDiet + EVOO and MedDiet + nuts groups and 8.4 for the control diet group.

5. The Mediterranean Dietary Pattern Recommendations in the U.S. Compared With PREDIMED Dietary Patterns

The 2015–2020 Dietary Guidelines for Americans include as options the Healthy U.S.-Style eating pattern, the Healthy Vegetarian eating pattern, and the Healthy Mediterranean-Style eating pattern [21]. The food-based recommendations for these three dietary patterns are similar for the key components of a MedDiet (vegetables; legumes; fruits; nuts; other seeds; and oils). Small differences between the Healthy U.S.-Style eating pattern and the Healthy Mediterranean-Style eating pattern include less dairy but more protein foods recommended in the U.S. Healthy Mediterranean-Style eating pattern.

Comparison of the PREDIMED MedDiet with the U.S. Healthy Mediterranean-Style eating pattern shows notable differences for olive oil, fruits, and legumes (Table 2). Recommendations for nuts, vegetables, fish, and red meat are similar. There are no recommendations for sofrito and wine in the U.S. Healthy Mediterranean-Style eating pattern. Perfect adherence to the U.S Healthy Mediterranean-Style eating pattern would yield MEDAS of 7 points. Points would be lost for olive oil, since no recommendations are made for olive oil to be the main culinary fat, and just 27 g/day of vegetable oil is recommended. The quantity of fruit and legumes recommended in the U.S. Healthy Mediterranean-Style eating pattern is lower than the PREDIMED recommendations. Therefore, to align the U.S. Healthy Mediterranean-Style eating pattern more closely with the PREDIMED recommendations, more emphasis on EVOO is required. Intake of legumes and fruit would also need to increase from 1.5 cups/week to ≥2.25 cups/week and from 2.5 to ≥3 servings/day, respectively. Wine is a MEDAS component, although less than one third of PREDIMED participants drank it. Sofrito or similar sauces would also need to be considered.

6. Intervention Strategies to Achieve a PREDIMED Style Mediterranean Dietary Pattern in the U.S.

PREDIMED used a regular individual face-to-face and group intervention (2 contacts/3 months) plus extensive materials, including a quarterly 1-week menu card, shopping list for ingredients in the menu, and recipes for the menu, in addition to providing either EVOO or nuts at no cost. The intervention was highly successful. To facilitate behavioral change in U.S. adults towards a MedDiet-Style eating pattern, intensive behavior modification interventions should be used. Examples of studies that used this type of intervention are Trials of Hypertension Prevention I [22], PREMIER [23], and Trial of Nonpharmacologic Intervention in the Elderly (TONE) [24]. These studies had an intensive intervention phase of 8–12 weeks that included group and individual sessions to increase knowledge. This was followed by a maintenance phase where contact was less frequent and only group sessions were held. A meta-analysis of 22 RCTs including adults of retirement transition age (54–70 years) showed that face-to-face meetings were the most effective type of dietary intervention to promote a healthy dietary pattern, including the MedDiet [25]. Lara et al. [25] reported that face-to-face interventions resulted in greater dietary change compared to indirect methods.

Increasingly, information communication technologies are being used to change dietary intake and behavior. This approach may include

use of a smartphone app, tablet app, or website. Use of a smartphone app resulted in better compliance, retention, and weight loss compared to a website, or to diary monitoring in a six-month trial [26]. Similarly, in a 14-week RCT, a web-based app intervention increased physical activity level, nutrition knowledge, diet quality, and weight loss, compared to a group that received a single lecture [27]. In PREDIMED older adults were included. Few technology-based dietary interventions have been conducted in older adults, so it is unclear if this approach would be successful in this age group. In one study of older adults (mean age 75 years), a tablet-centered intervention increased physical function more than a brochure only [28]. Interventions based on information communication technologies show promise for changing dietary and lifestyle behaviors in adults and may potentially be more cost-effective.

7. Recommendations of the Working Group

The Working Group found that a U.S. replication study could recruit participants with similar characteristics to PREDIMED participants. Ascertainment of events could be accomplished in a comparable way to what was done in PREDIMED, but with enhanced difficulty in obtaining records; or with differing precision of event ascertainment if electronic medical records were used. Experience to date in U.S. studies is that personal contact is required for event follow-up. More importantly, there are substantial differences between the diet and lifestyle in Spain vs. the U.S. Therefore, consideration about the aspects of PREDIMED that can and cannot be replicated is required. In particular, some assumption of a MedDiet continuum is required, which may be expressed in terms of an aim to create at least a 2-point MEDAS difference between the active and control groups, although with the control diet achieving fewer points. For protection in case there is a threshold relationship of change in MEDAS to CVD risk, it would be prudent to aim for at least a 4-point MEDAS difference, to get the treatment closer to a true MedDiet. Increasing MEDAS to 5–6 points in a MedDiet group, while maintaining the average U.S. diet at 1 or 2 MEDAS points in the control group, both sustained for 5 years, will be challenging and require significant change. In PREDIMED, the provision of gratis EVOO and nuts maintained or increased intake of these key food components of the MedDiet. Provision of these foods and creation of suitable commercially-available sauces, could be replicated in the U.S. and this would be an opportunity for commodity groups to contribute or collaborate. The level of personal involvement with participants in PREDIMED is replicable, given sufficient funding. In PREDIMED, participants were seen twice every three months, once in a group session of approximately 20 people and once in an individual session. The Working Group was confident that a more intensive approach could achieve a substantial shift in MEDAS. If, as is most likely, a PREDIMED replication study were funded by NHLBI, it is clear that some intervention is feasible, but within that spectrum of cost, NHLBI would prefer that the cost be at the lower end. The Working Group pointed out that it is not cost effective to do an intervention trial in which change is not achieved. Therefore, given the likely source of funding, pilot work to identify lower cost, high yield intervention methods are needed before a full study is undertaken. With the likelihood that a PREDIMED replication in the U.S. would involve some private funding, there is a need to manage the partnership to align with responsible recommendations for private sector funding of nutrition studies to avoid perceived conflicts [29,30].

The Working Group disagreed with the conclusions of the NHLBI workshop [5] concerning cost, in light of the conclusions above concerning what intervention strategies have worked in the past. The Working Group also disagreed with the NHLBI workshop conclusion that a true replication could substitute another oil for EVOO. Olive oil in the Mediterranean diet not only provides a good source of unsaturated fatty acids and other healthful bioactives; it also facilitates the consumption of additional vegetables, which, when dressed with or sautéed in olive oil, are much more palatable than when consumed just boiled. Perhaps another unsaturated-fat oil (i.e., refined olive oil, canola, soy or sunflower) could elicit a similar response, but these oils are refined and thus do not contain abundant polyphenols, while EVOO does and significantly contributes to the antioxidant load of the Mediterranean diet. Furthermore, extra virgin canola oil is bitter and not suited for culinary use. Additional benefits of EVOO include that cooking vegetables with EVOO enhances their polyphenol content [31]; and tomato sauces (basically, sofritos) prepared with a higher amount of EVOO contained high levels of polyphenols [32]. Commercial sofritos have been studied and found to be rich in polyphenols [33], although the shelf-life of the commercial products has not been studied.

8. Recommended Treatment Group Goals of a Replication Trial

Based on the PREDIMED experience and considerations of the diet and lifestyle in the U.S., the Working Group recommends that dietary principles in a U.S. replication be modeled after MEDAS. To express this concretely, they developed a list of 10 dietary recommendations plus 1 general behavioral recommendation [34] to shift the U.S. diet towards a MedDiet, displayed in Table 6.

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Competing Interests

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Table 6
10 plus 1 important Mediterranean diet aspects to achieve in the U.S. in the intervention group in a replication of PREDIMED.

1. Use extra virgin olive oil as the main source of added fat
2. Eat vegetables (including salad) at least 2 times/day and legumes at least 3 times/week
3. Fresh fruit should be your daily dessert. Sweets, cakes, ice cream, and similar fatty sugary desserts should be consumed only occasionally
4. Eat daily a handful of nuts such as walnuts, as a snack, dessert or with salads
5. Consume whole grain bread instead of bread made with refined flour
6. Dress your vegetables, pasta, and rice dishes with olive oil, spices, and aromatic herbs instead of commercial sauces[a]
7. Consume fermented dairy products on a daily basis, mainly yogurt and cheese
8. Consume lean red meat no more than twice per week. Prefer poultry to red meat and avoid processed meat products
9. Consume fish at least 3 servings/week (one serving fatty fish) and eggs in moderation (3 times/week)
10. Drink fresh water during and between meals instead of sugar-sweetened or artificially sweetened beverages. If you like wine, drink it with moderation accompanying meals

PLUS: Avoid industrially-made and precooked meals. Better to eat meals at home than out-of-home

[a] Given the predominance of commercial sauces in the U.S., another option may be to work with food manufacturers to improve available commercial sauces. In Spain, commercial sofritos were found to be rich in polyphenols [33], however, polyphenol content was not assessed according to shelf-life. A risk is that commercial sauces must be manufactured for long shelf life, and therefore would not be likely to maintain the level of freshness of a homemade sofrito or other sauce.

Author Contributions

DRJ and KP wrote the first draft; all authors participated equally in discussions and critical review of the article.

Appendix A. Supplementary Data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.metabol.2018.05.001.

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