**ADDITIONAL QUESTIONS AND ANSWERS**

**(February-March, 2019)**

**Can the PREDIMED protocol deviations detected in 2017 be labeled as “serious”?**

As we described in great detail in the republication of our [N Engl J Med paper](https://www.nejm.org/doi/full/10.1056/NEJMoa1800389), the protocol deviations had little impact on the results and conclusions of the study. In particular,

1. The re-analyses of the data, taking into account the deviations, yielded virtually the same results.
2. The deviations were related to some imperfections in randomization procedures, but only affected a small subset of participants in the trial. The aim of randomization is to balance baseline covariates. The observed imbalances in baseline covariates were minimal and, in any case, they operated *against* the hypotheses of the trial, with 6% more women in the control group than in the Mediterranean diet+nuts group, and 5% more participants with high LDL-cholesterol (>130 mg/dl) in the Mediterranean diet+extra virgin olive oil group than in the control group (Please check [Table S23, page 86, of the Supplemental Appendix, also freely available at nejm.org](http://www.predimed.es/)).

All other observed imbalances in a huge set of compared baseline variables (please check [Tables 2 and S23](http://www.predimed.es/)) among the 3 randomized arms of the trial were negligible in their absolute sizes.

**Did the interventions test only single food supplementations instead of a typical Mediterranean diet?**

No. The trial tested the change in the **overall** dietary pattern, not only in supplemental food items.

Please find below the proportion of participants who complied with each level of the validated 14-item score assessing adherence to an overall [typical Mediterranean Diet pattern (MEDAS)](https://www.ncbi.nlm.nih.gov/pubmed/21508208) at baseline.

|  |  |
| --- | --- |
| Baseline:  The 3 groups combined | |
| Baseline score | Percentage |
| 0 | 0.07 |
| 1 | 0 |
| 2 | 0.03 |
| 3 | 0.28 |
| 4 | 1.31 |
| 5 | 3.63 |
| 6 | 7.34 |
| 7 | 13.8 |
| 8 | 19.32 |
| 9 | 19.28 |
| 10 | 18.29 |
| 11 | 10.54 |
| 12 | 4.7 |
| 13 | 1.16 |
| 14 | 0.24 |

There were significant changes in adherence to the overall dietary pattern in the 2 intervention groups vs. the control group after one year. These differences can be assessed by comparing each level or category in the 14-item score of [Mediterranean Diet adherence](https://www.ncbi.nlm.nih.gov/pubmed/21508208) after 1-year intervention between intervention and control groups:

|  |  |  |
| --- | --- | --- |
| After 1-y intervention | | |
| 1-y score | Percentage in  Control | Percentage in intervention\* |
| 0 | 0.06 | 0 |
| 1 | 0 | 0 |
| 2 | 0 | 0 |
| 3 | 0.12 | 0.02 |
| 4 | 0.47 | 0.02 |
| 5 | 1.87 | 0.21 |
| 6 | 6.8 | 1.00 |
| 7 | 13.01 | 3.19 |
| 8 | 19.57 | 7.86 |
| 9 | 22.91 | 14.05 |
| 10 | 17.4 | 19.41 |
| 11 | 11.48 | 22.84 |
| 12 | 4.98 | 18.13 |
| 13 | 1.35 | 10.46 |
| 14 | 0 | 2.72 |

\*Both intervention groups merged together.

Please check also Figure 5 in [Circ Res 2019;124:779-798](https://www.ncbi.nlm.nih.gov/pubmed/30817261)**.**

This substantial contrast in adherence to the overall dietary pattern (and not only in supplemental foods) was maintained throughout the whole duration of the trial, as reported in The New England Journal of Medicine original paper and its republication. Please check [pages 41-43 of the Supplemental Appendix](http://www.predimed.es/).

**Is peculiar to the PREDIMED trial the use of a primary endpoint which was a composite of three types of major cardiovascular events (stroke, myocardial infarction and death from cardiovascular causes)? Is the PREDIMED trial flawed because the reductions in some components of the composite outcome did not reach the conventional limit for statistical significance?**

The use of a composite cardiovascular primary end-point is the standard practice in RCTs of cardiovascular medicine:

* [ODYSSEY trial](https://www.ncbi.nlm.nih.gov/pubmed/30403574): The primary end point was a composite of death from coronary heart disease, nonfatal myocardial infarction, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization.
* [FOURIER trial](https://www.ncbi.nlm.nih.gov/pubmed/28304224): composite of cardiovascular death, myocardial infarction, or stroke.
* [VITAL trial](https://www.ncbi.nlm.nih.gov/pubmed/30415637): a composite of myocardial infarction, stroke, or death from cardiovascular causes.
* [REDUCE-IT trial](https://www.ncbi.nlm.nih.gov/pubmed/30415628): a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina.
* [EMPAREG trial](https://www.ncbi.nlm.nih.gov/pubmed/26378978): the composite outcome was death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.

In all these trials, because the primary endpoint was defined as a composite outcome, including non-fatal events, the estimates for the individual components of that composite outcome should be considered secondary. They are less relevant because:

1. trials are usually underpowered to assess individual components of the composite outcome.
2. stroke (which is much more commonly ischemic than hemorrhagic), myocardial infarction and cardiovascular death share most etiological and pathophysiological mechanisms involved in atherosclerosis, therefore the use of a composite end-point is more robust, coherent and respectful with the biological plausibility of the assessed effects.
3. the use of separate components as individual outcomes is affected by problematic statistical issues of competing risks that are not easily addressed in conventional analyses. From the point of view of the statistical analyses, also the selection of a composite cardiovascular primary end-point is more powerful and avoids complicated issues in the analyses related to competing risks.

Therefore, the use of the composite CVD outcomes as the primary endpoint in the PREDIMED trial is fully justified.

**Were the effect sizes of PREDIMED inflated because the trial was stopped early after interim analyses showed benefit?**

The original planned duration of the PREDIMED trial was 6 years. The trial was stopped after 4.8 years of median follow-up based on the recommendation of the Data and Safety Monitoring Board. It would not be ethical to continue the trial if the investigators are aware that being allocated to one arm of the trial was causing significant harm to volunteer participants under strict ethical requirements. Their informed consent was given under this requisite of stopping the trial in case the differences in results between the three arms crossed pre-established boundaries. The Institutional Review Board also approved the trial under such premises. One of the reasons why an independent Data and Safety Monitoring Board is appointed in these trials is the need to prematurely stop the trial if sufficient evidence of early benefit or harm arises. This is also the reason why stopping rules are set in advance in the protocols of randomized trials. In PREDIMED, the independent Data and Safety Monitoring Board recommended to stop the trial after 4.8 years of median follow-up because the threshold established a priori in the protocol had been reached.

The stopping of the trial ahead of time with respect to its initially planned duration may be associated with overestimation or underestimation of the effect, but this is an assumption yet to be tested empirically.

**Was it a problem for the PREDIMED trial that some systematic reviews (or a section of some clinical guidelines) did not include its results?**

[Systematic reviews on Mediterranean diet and cardiovascular health published after 2013 usually did include the PREDIMED](https://www.ncbi.nlm.nih.gov/pubmed/30817261) trial. Only two systematic reviews published after publication of the PREDIMED trial did not include the PREDIMED results. First, in a systematic review using [an uncommon, nonspecific, definition of the Mediterranean diet (merely 2 or more of 7 components)](https://annals.org/aim/fullarticle/2607786/effects-health-outcomes-mediterranean-diet-restriction-fat-intake), they explicitly stated that the reason for excluding the PREDIMED trial was that the intervention in the control group was not minimal ([page 12](http://www.ncbi.nlm.nih.gov/pubmed/23939686)), given that they “only considered trials where the comparison group was no intervention or minimal intervention (e.g., a leaflet to follow a dietary pattern with no person-to-person intervention or reinforcement).” ([page 5](http://www.ncbi.nlm.nih.gov/pubmed/23939686)). Another [review](https://www.ncbi.nlm.nih.gov/pubmed/26068959) did not include PREDIMED because it focused on the effect of *saturated fat*, not on the traditional Mediterranean dietary pattern as a whole. These omissions do not represent any problem for the PREDIMED trial.

In one section of British clinical guidelines, the authors stated that the results of PREDIMED were difficult to interpret “because the control group was advised to reduce their fat intake and to follow some of the components of the Mediterranean diet”. The authors misinterpreted the design of the PREDIMED trial. The fact (appropriately described in our original publications) was that the control group received advice to follow a low-fat diet in accordance with the recommendations by the American Heart Association (AHA) back in 2002 (step-I AHA diet), at the time when the PREDIMED trial was designed. Though the outdated step-I low fat diet of AHA-2002 included some general recommendations that may coincide with aspects of the traditional Mediterranean dietary pattern (e.g., increasing vegetable consumption), it is a completely different approach from the current perspective of modifying overall dietary patterns. In the PREDIMED trial, the designed comparison was between the advice to follow a low-fat diet (control) and the advice to follow a high-fat traditional Mediterranean diet (2 intervention groups) enriched with extra-virgin olive oil and mixed nuts. This information was fully available from the very beginning in our protocol and does not pose any risk of bias for PREDIMED.

**Is the analysis of reported baseline characteristics conducted by Carlisle correct when applied to PREDIMED as to raise questions of potential fraud or non-random “sampling”?**

First, the appropriate term in randomized trials is not random “sampling” but [random *allocation*](https://www.bmj.com/content/343/bmj.d7453) . This was incorrectly characterized in the title of the article by [Carlisle](https://www.ncbi.nlm.nih.gov/pubmed/28580651) and also by some commentators.

Second, the Stouffer-Fisher method of combining P values used by Carlisle is built on some [assumptions that are untenable, as](https://www.ncbi.nlm.nih.gov/pubmed/28786843) reported by [Mascha et al](https://www.ncbi.nlm.nih.gov/pubmed/28786843). We already showed in our Supplementary appendix available at [nejm.org](http://www.nejm.org/). (page 8), that the Stouffer-Fisher method is based on at least two assumptions that are not met in PREDIMED:

1. The method assumes uncorrelated variables, but there were actually very strong correlations among several continuous variables at baseline in PREDIMED;
2. It also assumes simple randomization, whereas we used stratified randomization.

Of note, the approach of the Stouffer-Fisher method is only statistical, not epidemiological or clinical. From an epidemiological and clinical point of view, the main issue that should be addressed is the potential for confounding, which represents a threat to scientific validity. Randomization is used specifically to preempt confounding, because, when applied to large samples, it usually removes imbalances of relevant size in potentially confounding baseline covariates. Nevertheless, the Stouffer-Fisher method, merely based on p values for between-group comparisons of independent variables at baseline, does not assess the absolute size of those differences and, therefore, cannot appraise the potential for confounding. Absolute sizes of differences in relevant covariates across groups [(and not p values)](https://www.ncbi.nlm.nih.gov/pubmed/28938715) are what really matters regarding potential confounding. As mentioned above, a detailed examination of the PREDIMED trial reveals that such absolute differences in measured variables were clinically negligible. Our sensitivity analyses taking into account any imbalance in baseline covariates did not alter the results.

**Can the imperfections related to the enrolment of household members without randomization, assignment of participants to study arms based on small clinics or inconsistent use of randomization tables be considered “serious”?**

As stated on [page 8 of our Supplementary Appendix](http://www.predimed.es/), “After the trial was in progress, the Steering Committee approved the enrollment of household members of already enrolled participants, without randomization. The protocol was not amended to reflect this change and the original report of the trial did not explain this change to the protocol. If fulfilling entry criteria, members of the household of randomized participants were invited to participate and allocated to the same intervention group as their household member. This was done to allow recruitment of household members and 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”.

The second enrolled partners of a previous participant (n=425) represented only 5.7% of PREDIMED participants, with proportions of 4.8% of the control group, 6.7% of the Mediterranean diet+extra-virgin olive oil group, and 5.5% of the Mediterranean+nuts group. The appropriate approach to handle this clustering within a couple (two partners randomized together) is to use a robust estimator of the variance to account for intra-cluster correlation. The changes in the estimates of effect after applying this correction of the variance were negligible and the results remained intact. Therefore, there is no reason at all to label this fact as a “serious” irregularity.

In only 1 of 11 recruitment sites (site D), 467 participants (6.2% of total PREDIMED participants) were allocated to the arms of the trial using small clinics as unit of allocation. This procedure was applied in 11 of the 14 clinics from site D. The average size of these clusters was 42 participants per cluster. Of these 11 clusters, 2 were allocated to MedDiet+extra-virgin olive oil, 5 allocated to MedDiet+nuts and 4 allocated to the control group. This allocation in groups introduced only very small imbalances in the baseline covariates (as stated above) and these imbalances were corrected by considering the 11 small clinics as clusters, by applying robust estimators of the variance accounting for the clustering effect and also by additionally adjusting for propensity scores built with 30 baseline covariates. This was the main analysis, as agreed with the editors of the New England Journal of Medicine, the independent reviewers, and the independent statistical reviewers appointed by the New England Journal of Medicine for the republication of our trial. After appropriately assessing these 2 issues (households and small clinics), the results only changed in the second decimal place and only by 1 or 2 units. Moreover, when we compared both Mediterranean diet groups combined together versus the control group ([Figure 3 of the republication in The New England Journal of Medicine, 2018](http://www.predimed.es/)), the results did not change *at all* with respect to our original publication.

In addition, the complete removal of the second members of the households together with the complete exclusion of site D (where some participants were allocated in clusters) not only preserved the original results, but actually rendered a stronger protective effect by the Mediterranean diet (please check [Figure 2 of our republished main article, Figure S2 of the Supplementary Appendix and pages 8-17, 36-38 and 48-50 of the Supplementary Appendix](http://www.predimed.es/)).

There are various ways of applying randomization procedures or using randomization tables. The apparent inconsistent use of randomization tables in sites B and I did not introduce any imbalance in the baseline characteristics at those sites and therefore does not represent any compromise for the randomized design of the PREDIMED trial.

**Is republication justified?**

Similar retractions and republications were previously made by other journals and they have been encouraged by the [editors](https://www.ncbi.nlm.nih.gov/pubmed/25706962) of [top medical journals](https://www.ncbi.nlm.nih.gov/pubmed/26509425).

According to the [Lancet’s editorial](https://www.ncbi.nlm.nih.gov/pubmed/25706962), retraction and republication is another example of correcting the scientific literature and “[it should be considered by journal editors in the interests of readers, research users, and the scientific community](https://www.ncbi.nlm.nih.gov/pubmed/25706962)”. We agree that “[encouraging authors to be active participants in the correction process is essential, and stigma should be minimized in cases of honest error](https://www.ncbi.nlm.nih.gov/pubmed/29531079)”.

The [main message](https://www.ncbi.nlm.nih.gov/pubmed/29531079) on these actions should be that normalizing error correction is necessary to advance in the enterprise of pursuing the truth.

As [Jenkins et al](https://www.ncbi.nlm.nih.gov/pubmed/30285332) suggested in a letter to the editor of The New England Journal of Medicine after the republication of our article, the decision by the editors to accept our proposal of retraction and republication of our paper may “[lead to this process becoming standard practice in the future for articles in which the authors have noted irregularities that cannot be corrected by corrigenda or errata](https://www.ncbi.nlm.nih.gov/pubmed/30285332)”. We fully agree with them that “[the advantage of this approach is that the medical and scientific community is not left in limbo, not knowing whether a reanalysis will show no effect, a blunted effect, or the same effect, on the primary and important secondary outcomes](https://www.ncbi.nlm.nih.gov/pubmed/30285332)”.

Therefore, in these cases of honest errors the republication of the article can be often the best solution. In fact, republications are becoming more and more [common](https://www.ncbi.nlm.nih.gov/pubmed/30056841).

Republications seem well justified because they contribute to increase scientific knowledge, they are advantageous for the Journals, raising public trust in science, and they can provide detailed answers to potential doubts that might have arisen in some sectors of the scientific community.

**Did the republication make it clear that it was a reanalysis and republication?**

In the republished version of the main PREDIMED paper, we stated in the Introduction that [“we have withdrawn our original report and now publish a new report” (page 2),](http://www.predimed.es/) so that the reader knows that the paper is a republication from a previous paper. In addition, [a note on the retraction and republication](https://www.ncbi.nlm.nih.gov/pubmed/29897867) of our paper was separately published by the Journal editors.

Also, in the [Supplementary Appendix](http://www.predimed.es/), the list of changes introduced in the new version of the manuscript is presented right after the list of the PREDIMED investigators, so that it was made clear from the very beginning that it was a republication.

**Were assessors not blinded because of the unmasked design?**

Unlike a drug trial, a randomized trial testing an overall dietary pattern cannot be masked to participants, because obviously they know what they eat. But, as stated on [page 4 of our republished article](http://www.predimed.es/), members of the end-point adjudication committee were completely blinded to the intervention groups.

*Ad hoc* reviews of all medical records of the study participants were conducted by blinded study physicians in order to collect the information on clinical events, which was afterwards verified by the end-point adjudication committee. These procedures were deemed as appropriate by the Data and Safety Monitoring Board.

Therefore, there was little bias related to “unmasked design” or to unmasked “data collection, data arbitration or data adjudication”.

**Did the PREDIMED trial ever randomize “villages”?**

No. We randomized clinics in 11 sites across Spain. This was clearly described in our protocol and publications.

**Did the reanalysis excluding imperfectly randomized patients satisfy the P value boundary required for early stopping of the trial?**

Yes, that reanalysis did satisfy the P value boundary. The trial was stopped at the 4th interim analysis, as we report on [page 5 of the republished version in The](http://www.predimed.es/) New England Journal of Medicine.

* The rules to stop the trial, established in our [protocol (page 22),](https://www.nejm.org/doi/suppl/10.1056/NEJMoa1800389/suppl_file/nejmoa1800389_protocol.pdf) were: "The 2- sided p-values for stopping the trial at each interim analysis (1st to 4th) are respectively 5\*10-6, 0.001, 0.009 and ***0.02 for benefit***,...".
* The reanalysis after exclusions of site D and couples gave a 2-sided p value=0.007 for Mediterranean diet+extra-virgin olive oil versus control and a 2-sided p value=0.006 for Mediterranean diet+nuts versus control.

Therefore, as stated above, the removal of second household members and site D found *stronger* (not weaker) associations with *more significant* (not less significant) p values, as can be easily deduced when reading the new version from the upper limits of the confidence intervals for the hazard ratios (upper limits 0.89 and 0.89) when removing these subjects, versus the complete-case analysis (upper limits=0.91 and 0.94). [Please check Figure 2 of the new paper.](http://www.predimed.es/)

**Is the dataset of PREDIMED available for independent investigators?**

We agree that the sharing of data from the PREDIMED study would be desirable. However, this should be done in a responsible way and satisfying Institutional Review Boards (IRB) requirements, as we explain below. Our first responsibility is with participants from the PREDIMED trial and they did not explicitly encompass data sharing during their informed consent process.

Data sharing should be conducted in a structured and responsible manner. Following, an editorial published in The New England Journal of Medicine, “[many of us who have actually conducted clinical research, managed clinical studies and data collection and analysis, and curated data sets have concerns about the details](https://www.ncbi.nlm.nih.gov/pubmed/26789876)”. One important concern is that “[someone not involved in the generation and collection of the data may not understand the choices made in defining the parameters](https://www.ncbi.nlm.nih.gov/pubmed/26789876)”.

The data sharing plan for the PREDIMED study is detailed on [page 93 of the Supplementary Appendix at nejm.org](http://www.predimed.es/). According to this plan, the dataset (including data dictionaries) is available in order to make possible the replication of the main analyses used for the published article. However, due to the restrictions imposed by the Informed Consent and the IRB, *bona fide* investigators interested in analyzing the PREDIMED dataset may submit a brief proposal and statistical analysis plan to the corresponding author. Upon approval from the Steering Committee and IRBs, the data will be made available to them using an onsite secure access data enclave.

**Are analyses of the CVD events data with expanded follow-up available?**

They will be, together with the all-cause mortality data.

**Are analyses of the full mortality data with expanded follow-up available?**

In the near future, we will submit for publication our analyses of all-cause mortality during the expanded follow-up period, in which we will also address apparent inconsistencies or small differences in the total number of deaths (or deaths from different causes) as reported by some of our papers. These small differences were related to the use of several datasets with different degrees of updating of the events during the last 10 years. We are working thoroughly on a detailed analysis of all-cause mortality during the expanded follow-up period, considering all updated sources of information. We invited commentators to send us a detailed protocol and a statistical analysis plan if they were also interested in collaborating in these or other analyses with our data sets, in order to work together with us and to avoid overlappings.

As can be deduced from [our published papers available at our web page](http://www.predimed.es/publications.html), the PREDIMED data have always been available upon request and our universities and hospitals have welcomed collaborators coming from all parts of the world to work with us. In fact, many investigators from the U.S. and other countries have visited our centers in Spain during these years and have used or are currently using our data base. They are very familiar with the procedures and data sets of PREDIMED, have analyzed our data and published many peer-reviewed papers.

Of note, all-cause mortality is not the most appropriate end-point in a nutritional intervention trial, because it lacks specificity for the effects of changing the overall dietary pattern. It is obvious that not all causes of death are equally influenced by diet.

PREDIMED was a primary cardiovascular prevention trial. All-cause mortality is not the most appropriate outcome when studying the effects of a high-quality dietary pattern on cardiovascular health. As stated in the [Supplementary Appendix (page 28)](http://www.predimed.es/), most cases of the primary cardiovascular endpoint (65%) were *non-fatal*. Consequently, the rationale is that using total mortality as the primary end-point is not the most appropriate choice and it will likely lead to further dilution of the true association, given that all-cause mortality includes many deaths not causally attributed to low-quality dietary patterns and also will exclude most cases of our *a priori* defined end-point.

This view is in full agreement with the design of most landmark cardiovascular randomized trials when they customarily select a composite primary end-point of cardiovascular events (usually, non-fatal stroke, non-fatal myocardial infarction and cardiovascular death, as mentioned above) instead of selecting all-cause mortality as their primary end-point.

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