Author's response to reviews

Title: Mediterranean dietary pattern and depression: the PREDIMED randomized trial

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Version: 2 Date: 7 June 2013

Author's response to reviews: see over
5. Are the discussion and conclusions well balanced and adequately supported by the data?
In general, yes. However, I would not describe the relationship between levels of adherence to diet and depression outcomes as a ‘trend’. They are clearly non-significant and should be described as a negative result.

We agree. Following your suggestion we have toned down our conclusions along the manuscript.

6. Do the title and abstract accurately convey what has been found?
The confidence intervals described in the abstract ((Multivariate Hazard Ratio (HR) and 95% Confidence Interval (CI)=0.78; 0.55-1.11) are slightly discordant with those described in the results section (0.78; 0.55-1.10). Please amend.

You were right. We have amended it in the new version of the manuscript.

Minor Essential Revisions:
1. I would appreciate some small discussion regarding the other dietary condition (VOO) and the depression outcomes. The tables suggest that confining analyses to diabetic patients also strengthened the relationship between the VOO diet and depression outcomes, although non-significant. Importantly, the pattern of associations between the dietary conditions and the depression outcomes is similar to those reported for the primary CVD outcomes in the recent NEJM paper. This could be highlighted.

Following your suggestion, we have added a new paragraph in the discussion section regarding the possible role of virgin olive oil intake in depression risk. Also, we have added a comment regarding the similar pattern for the results observed in this study between the dietary interventions and depression and those reported for CVD in the same sample in the paper recently published in the N Engl J Med (See, please, Estruch et al. N Engl J Med 2013, 368:1279-1290).

2. Our group have also shown that leptin is associated with the risk for MDD and this reference could be included:

Thank you for providing us with this reference. It has been added to the new version.

3. The confidence intervals described in the abstract ((Multivariate Hazard Ratio (HR) and 95% Confidence Interval (CI)=0.78; 0.55-1.11) are slightly discordant with those described in the results section (0.78; 0.55-1.10). Please amend.

OK

4. I would not describe the relationship between levels of adherence to diet and depression outcomes as a ‘trend’. They are non-significant and should be described as a negative result.

OK
This interesting study on the Mediterranean diet and depression is notable for some impressive strengths. The authors point out that randomized controlled trials are a necessary next step in the study of diet and mental health, and they provide one with a very large sample size. Unfortunately their study is limited by some important methodological flaws, some of which can not be remedied. The biggest problem may be that the control group in the study also received a positive diet intervention, which could have masked a larger true effect.

We agree. We mention and acknowledge this limitation in the discussion section. Probably the true effect for the intervention with MedDiet on depression is larger than what we report here, We assume that it would be larger if we would have compared MeDiet versus a typical Western diet, instead of using as comparator a fairly healthy dietary model. But perhaps we would have raised strong ethical issues if our comparator diet would not have been healthy enough.

The outcome used in the study is problematic. A structured assessment would be preferred. Physician diagnosis is biased by treatment-seeking behaviour, as is antidepressant treatment. Furthermore, factors associated with treatment-seeking behaviour may be associated with other lifestyle factors that confound the association between diet and mental health (or could even be associated with the intervention).

We understand your concern and we agree that a structured assessment would be preferred for the case ascertainment of depression. However, the randomized design of our trial precludes most of the possible biases associated with treatment-seeking behaviors or lifestyles. The randomization together with the large sample size of our trial has the capability of adequately balancing these features across the three groups and of avoiding clinically meaningful between-group differences in these behaviors or in lifestyle factors. Furthermore, we have adjusted our estimates for a wide array of variables and the factors that you suggested should need to remain unbalanced even after conditioning for these covariates in order to introduce confounding. This is a very unlikely assumption in a large randomized trial such as this one, even more if it uses also multivariable adjustment as we did. In any case, we have also addressed this remote potential limitation in the discussion section of the article.

Even if there is no bias, under-estimating the true rate of depression in the follow-up period undermines the statistical power of the study, which makes interpretation of the results difficult. Unfortunately, there is nothing the authors can do about this. You are right and we acknowledge this limitation in the discussion section. However, the large sample size somewhat compensates the potential loss of statistical power because of under-estimation of the true rate of depression.

The exclusion of 1,870 individuals who had less than three years of follow-up is unexplained and seems unnecessary in the analytical framework. Is there a biological reason why it would take three years of diet change before an effect on mental health could be observed? This must be discussed in more detail, especially given that mechanisms linking diet and mental health have been proposed but not conclusively defined. From an analytical point of view, there is no reason to exclude these individuals. In the Cox model individuals would be censored at the time at which their follow-up finishes. The authors mention wanting to avoid reverse causality, but I'm not sure how this is possible in an RCT.

We understand your comment about reverse causality. However our previous experience in published observational studies on depression by our group (See, please, Sánchez-Villegas et al. PLoS ONE 2011; 6:e16268; Sánchez-Villegas et al. Med Sci Sports Exerc 2008; 40: 827-34; Sánchez-Villegas et al. Med Clin (Barc.) 2008; 130: 405-7) is that the major threat for this particular association is reverse causality bias. Even in a RCT participants with a subclinical or undiagnosed depression may have a lower
motivation to comply with the prescribed diets. Therefore they are less likely to comply with the intervention precisely because of their subclinical depression at baseline. They will not receive any benefit from the allocated diet because of their low motivation and low compliance due to the pre-existing depression. The issue for reverse causality bias in a RCT is not a consequence of self-selection of a poorer dietary pattern because of the subclinical depression, but it may be a consequence of low compliance with the allocated diet. Eventually some of these persons with subclinical depression will become clinical cases during the early follow-up period, but they are not actual “incident cases”, but pre-existing cases who were undiagnosed at baseline and they received the diagnosis of depression only during the early years of follow-up. The assumption of a sufficiently long induction period is the usual approach to tackle with reverse causality bias in epidemiology.

Related to this, it's not clear why these individuals do not have three years of follow-up. Are they lost to follow-up? If so, an analysis of predictors of missingness is necessary, particularly given that drop-out appears to differ by group, and drop out is likely related to the outcome.

Please remember that this is a multicenter trial and some centers initiated the recruitment only after 2007. The trial was stopped in December 2010. In most of the centers the recruitment lasted from 2003 until 2009. The retention rate was high. Therefore the main reason for having a shorter follow-up of participants is late entry in the trial. We feel that to retain only those participants with a sufficiently long follow-up period ensures the adequate duration of the intervention. It also ensures an appropriate induction period and reduces the likelihood of reverse causality bias related to low compliance due to subclinical depression.

It's awkward to say that "although not significant, a decrease in depression risk was observed". It's true that the observed hazards were lower, but the confidence interval suggests no meaningful difference. Consequently, the term "risk" should be avoided, as should discussion of differences. This follows right through to the conclusion.

Following your suggestion and those made by other reviewers we have toned down our conclusions.

The results on those with diabetes are interesting and make for a good and well-reasoned discussion, but they could also be a result of a type I error considering the number of different sensitivity analyses.

We agree. When several analyses are carried out, some of them could give us statistically significant results only by chance if the overall alpha error is not corrected for multiple testing. However, the magnitude of the association observed within diabetic patients for the intervention with MedDiet+Nuts supports the beneficial role of this dietary pattern in depression within these patients (approximately half of our sample). Commonly used criteria for causality include biological plausibility and the analogy with the results obtained for diabetics in the analysis of MedDiet and cardiovascular disease (See, please, Estruch et al. N Engl J Med 2013; 368:1279-1290). The magnitude of the effect and the temporal sequence also suggest a causal association.

REVIEWER 3
This study addresses an important and so far under-researched topic on dietary pattern and depression. The analyses appear appropriate for the available data and the manuscript is clearly written. However, there are several small grammatical issues that could be improved as detailed below.

Minor essential revisions:
1. I don’t know if this journal has a policy with regard to how people with diabetes are described but I believe it is preferable not to use ‘diabetics’ or ‘diabetic participants’ rather people with diabetes or type 2 diabetes. This needs to be addressed throughout.

Following your suggestions we have changed these terms along the manuscript.

2. First line in abstract, omit ‘the’ at end of line, ie before adherence.
OK

3. Last line of Abstract background, omit ‘in’ before intervention.
OK

4. Abstract methods, start with capital ‘M’ for multicentre.
OK

5. Middle of abstract methods, ‘51% of them had type 2 diabetes’.
OK

6. Abstract conclusions, insert ‘a’ before Mediterranean.
OK

7. Page 5, first line, insert ‘a’ before leading.
OK

8. Second line, delete ‘also’ before ‘the first leading’.
OK

OK

10. Para 3, page 5, delete ‘the’ at end of second last line.
OK

11. Para 4, page 5, insert ‘by’ before carrying out.
OK

12. Last sentence on page 5. Suggest rewrite as:
Thus the aim of this analysis was to assess the effects of two Mediterranean diets on depression risk: MedDiet supplemented with virgin olive oil, and MedDiet supplemented with mixed nuts, in comparison with a low fat control diet.

Following your suggestion we have changed the sentence.

12. In the first para on page 7, use the past tense re physicians and nurses roles.
OK

13. Should energy be reported in kilojoules rather than kilocalories?
The specifications of the journal allow us to use kilocalories rather than kilojoules in all the analyses.

14. Bottom of page 10, ‘…we had complete data from 2,513…’
OK

15. Para 2, page 11, in second last line delete ‘in prospective analyses’.
16. Last para on page 11: available evidence is sparse; interpretation of results from observational studies requires caution; delete rest of sentence after ‘caution’. This design is weak for inferring cause-effect relationships; delete ‘on the other hand’; ‘These large studies generally use food frequency questionnaires...’. Delete ‘they’ so you have ‘generally have been validated’; delete uncontrolled before ‘residual confounding’.

17. Page 12, ‘low insulin secretion has been associated with an increased risk of developing depressive symptoms’.

18. Page 12, ‘The association of leptin with depression could be explained not only by its metabolic properties...’

20. Top of page 13, ‘...the control diet exhibited...’

Following your suggestion we have changed the word in the new version of the manuscript.

Other issues
21. The discussion should at least consider why you found significant results for nuts but not olive oil.

Following your suggestion, we have added a new paragraph in the discussion section about this matter.

22. Page 11, in the description of results from the Australian Longitudinal Study on Women’s Health it is not clear whether the OR relates to cross-sectional or longitudinal analysis.

The OR is related to longitudinal analysis. We have added some information to clarify this point.

23. At the bottom of page 11 when considering the weaknesses of cross-sectional studies you should mention the strong possibility that being depressed could make people eat a less healthy diet and perhaps find a reference for this. This is a specific example where reverse causation could be important.

Following your suggestion we have improved our discussion about this point and included a new reference.

24. Is it possible that the association was stronger in people with diabetes because they were more likely to be diagnosed with depression because they had more contact with various health professionals?

We agree. The better the outcome is ascertained, the lower the probability of a non-differential misclassification bias is. However, all the PREDIMED participants are subjects at high risk of cardiovascular disease with a specially stringent tracking system from the Primary Care Health Centers. This is true in Spain for patients with a diagnosis of diabetes and/or the presence of three cardiovascular risk factors such as hypertension or dyspididemia. So, all of them are continuously contacted by their general practitioners and their follow-up from their health
centers is comprehensive. Please take into account that the frequency of the contacts of citizens with their family doctors is the highest in Spain in comparison with other European Countries due to the universal coverage and the exemption from any out of pocket payment of the Spanish National Health System (please check Martin-Moreno et al. BMJ. 2009;338:b1170)

25. The paragraph on page 13 about walnuts and tryptophan was confusing. I assume you mean that walnuts contain tryptophan and not serotonin. Were walnuts part of the PREDIMED nut intervention?

Walnuts are important sources of serotonin (See, please, Feldman J; Lee E: Serotonin content of foods: effect on urinary excretion of 5- hydroxyindoleacetic acid. Am J Clin Nutr 1985,42:639–643). The authors of a recent clinical trial (See, please, Tulipani S, Llorach R, Jáuregui O, López-Uriarte P, Garcia-Aloy M, Bullo M, Salas-Salvadó J, Andrés-Lacueva C: Metabolomics Unveils Urinary Changes in Subjects with Metabolic Syndrome following 12-Week Nut Consumption. J Proteome Res 2011,10:5047-5058) suggest that walnut consumption leads to a high excretion of several metabolites of serotonin. This high excretion of metabolites could be due, according to these authors, to both a high intake of walnuts and also a high endogenous serotonin turnover following the intake of these food items. This second fact would explain the beneficial role of walnut intake on depression risk among patients with metabolic syndrome.

The Nut intervention group in the PREDIMED trial received 30 g/day of mixed nuts (15 g walnuts, 7.5 g hazelnuts and 7.5 g almonds) (you can see the description of the intervention in the method section of the manuscript).

We have improved this paragraph in the new version of the manuscript.

26. At the bottom of page 13 the argument that the lack of significance in interventions compared with observational studies may be due to lack of variability in intakes for interventions seems odd. Even sub-optimal adherence to an intervention could put people at intake levels beyond those seen in the general population. Many observational studies have been criticised for the homogeneity of the diet of participants. Unless you can actually show data from real studies that supports this I would omit this argument. I do agree on the other hand that because this study is conducted in a Mediterranean population, they may all have higher adherence to the MedDiet than a population in another area, and this might make the effect of the intervention less.

We agree. We have added information regarding the high adherence to the Mediterranean dietary pattern found for all the participants of the PREDIMED trial before and even after the intervention. We used a specific tool (See, please, Schröder H, Fitó M, Estruch R, Martínez-González MA, Corella D, Salas-Salvadó J, Lamuela-Raventós R, Ros E, Salaverría I, Fiol M, Lapetra J, Vinyoles E, Gómez-Gracia E, Lahoz C, Serra-Majem L, Pintó X, Ruiz-Gutierrez V, Covas M: Validation of a short screener for assessing Mediterranean Diet adherence among older Spanish men and women. J Nutr 2011,141:1140-1145) to measure the adherence to this pattern at baseline and during the follow-up. Before the intervention the mean score was 8-9 points for the overall sample (14 maximum; 0 minimum). After six years of follow-up, the control group obtained a mean score of 9 points whereas the two Mediterranean groups obtained a score of 10.5 points (You can see this information in the Supplementary Appendix of the article published recently in the New England Journal of Medicine (Figure S3) (See, please, Estruch et al. N Engl J Med 2013, 368:1279-1290).

We have added a new paragraph in the discussion addressing this point.

27. In the text describing the data in table 1, some differences are note between control group and others but it does not state whether these diffs are significant and this information is not provided in Table 1. It would be worth showing the significance of between group diffs in the table.
The differences found between groups were not significant. Moreover, statistically significant differences have not been recommended to assess if the baseline characteristics are comparable or balanced across the different groups of a clinical trial design. (See, please, Altman et al. Randomisation and baseline comparisons in clinical trials. Lancet 1990; 335: 149-153). Instead these authors deem more important to consider the absolute magnitude of the differences from a clinically meaningful point of view.

28. Table 4, missing ‘confidence’ before ‘intervals’ in title.
   OK

29. In Table 4 footnote ‘Model 2 additionally adjusted ‘for’ ...
   OK

30. Ref 16 has been published, update details in refs.
   OK