Author's response to reviews

Title: Diet quality scores beyond the Mediterranean Diet and depression in the SUN Project.

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Author's response to reviews: see over
This is an interesting study looking prospectively at different scores of dietary quality (MDS, PDP and AHEI-2-10) and depression. This area is currently attracting a lot of interest but this may be the first study to compare different diet quality scores and specifically assess non-linear relationships. The study includes a large number of cases of depression.

Major compulsory revisions

1. Rather than ‘high quality dietary patterns’ the measures are ‘diet quality scores’. Clearly the scores can indicate a ‘poor quality’ diet as well as a ‘good quality’ diet. This should be addressed throughout, including the title.

Following your suggestion we have avoided the use of the term “high quality dietary patterns”. We have replaced “high quality dietary patterns” by “diet quality scores” throughout the manuscript, including the title.

2. Include justification for choosing the three diet quality indices used.

We have used these three indexes as they have been related to mortality or the risk of other non-communicable diseases such as cardiovascular disease as we mention in the discussion section. Moreover, with the exception of the MDS, the other two indexes had not been associated with depression in population studies. We have not included other indexes such as the HEI or the AHEI-2005 because we considered that the AHEI-2010 updates the previous indexes and also adds some new relevant information.

We have slightly modified some paragraphs in the discussion section to better explain why we chose these three dietary indexes.

3. More explanation of the use of residuals from regression of PDP and AHEI on MDS needed. How should the results be interpreted and what is the relevance of this?

The residual models help to explain the results obtained after a regression analysis using MDS as independent variable and adherence to each of the other 2 dietary indexes as dependent variables.

In response to your suggestion, we have developed this idea in more detail in the discussion section. We have included the following paragraph in the discussion section:

“Finally, we have to highlight that, taking into account the observed correlation between the Mediterranean diet and the PDP, the PDP showed additional and relevant information on the association between diet quality scores and depression risk, because the residuals of a regression of PDP on the Mediterranean diet were still significantly associated with depression risk. This was not the case for the AHEI-2010. After eliminating the possible explanation in its variability already accounted for by the Mediterranean diet through the use
of residuals, we observed less important reductions in the risk of depression. This latter finding suggests that common nutrients and food items present in both patterns (AHEI-2010 and Mediterranean diet) could be responsible for the observed reduced risk in depression associated with a good adherence to the AHEI-2010.

4. It is not clear that vitamin D is relevant here as endogenous synthesis is important and sun exposure may have an impact on risk of depression independent of vitamin D level, for example: Acta Neurol Scand. 2014 Feb;129(2):123-31. doi: 10.1111/ane.12155. Epub 2013 Jun 13. Higher levels of reported sun exposure, and not vitamin D status, are associated with less depressive symptoms and fatigue in multiple sclerosis. Knippenberg S1, Damoiseaux J, Bol Y, Hupperts R, Taylor BV, Ponsonby AL, Dwyer T, Simpson S, van der Mei IA.

In response to your suggestion, we have omitted any reference to Vitamin D in the discussion section.

6. On page 18 studies of single nutrients are discussed but the current study does not report on nutrient intakes. Even if only as an appendix perhaps you could estimate nutrients by extremes of the diet quality scores so you could interpret your findings in relation to available nutrient specific data.

We agree with you. We have included additional information on nutrient intake as an appendix in the new version of the manuscript. It shows average intakes of several vitamins, minerals and trace elements within the lowest quintile of adherence to the three considered patterns. Suboptimal intake levels were identified for vitamin E, folate and magnesium (in the latter case only among males).

Also in the discussion make sure differences between cross-sectional and prospective associations are clarified.

Following your suggestion, we have tried to clarify the type of design mentioned in each referenced study included in the discussion section.

Minor essential revisions

In abstract results only PDP and AHEI are shown. Should also provide the HR for MDS which was apparently also inversely associated with depression according to the conclusion.

Following your suggestion we have also included the results obtained for MDS in the abstract.

2. At the top of page 4 the sentence starting ‘However, an emerging field of research...’ needs something added to complete it.
We appreciate the reviewer catching this typo. We have completed the sentence in the new version of the manuscript.

3. This is an area where reverse causality could be particularly important, especially in cross-sectional data, so in the introduction please be clear if referring to cross-sectional or prospective associations.

Following your suggestion, we have clarified this issue in the introduction section.

4. At the top of page 11, ‘Other confounding factors such as marital status...’ not include in final models’. Explain why not included.

We have explained in the new version of the manuscript that the inclusion of these variables in the mathematical models did not materially modify the associations.

5. Bottom of page 14-page 15. This is not results and should be deleted from here.

As you suggested, we have deleted this paragraph from the result section.

6. Throughout the manuscript are some odd expressions that could be improved, for example, on page 18 replace ‘A scarce number of studies...’ with “A few studies...’.

We have deleted this paragraph to avoid mentioning vitamin D.

7. It is not appropriate to compare ‘threshold level of adherence’ for the different diet quality scores as the methods of scoring are so different. It appears that for both PDP and AHEI the threshold is at 60-70% of maximum score so they are similar, where for MDS the threshold is below 50% of max score.

Very interesting comment. We agree with you. We have accordingly toned down the comment on this issue in the new version of the manuscript.

8. Not clear why two sections re specific nutrients in the discussion on page 18 and then page 20

We have included two independent paragraphs as the first one includes longitudinal studies that analyzed the role of micronutrients intake in depression whereas the second paragraph includes studies that have analyzed the association between serum levels (not intake) of different micronutrients and depression in cross-sectional analyses. These second block of studies should represent the nutritional status of depressed and not depressed populations.

9. Are the associations between diet and depression the same if you look just at baseline diet as when the two sets of dietary data are used? This is important to understand as diet measured near diagnosis may be
modified by depression and be due to reverse causality not because it is a prospective risk factor for depression.

The results point to an important reduction in the risk of depression associated to higher adherence to the different dietary patterns in both analyses, for baseline and for updated dietary data. Thus, the probability that the association between adherence to these dietary patterns and depression could be explained by reverse causality is fairly low. Depressed patients are prone to choose unhealthy foods. So, an overestimation of the protective effect of the dietary patterns would be expected in the baseline analysis.

If the reported associations could be explained by reverse causality, we would have found an attenuation of the protective effect of dietary patterns in the repeated measures analysis. However, especially for the Pro-vegetarian Dietary Pattern and for the AHEI the result is just the opposite.

10. While the idea of micro/macronutrient deficits being associated with depression risk is a logical interpretation of the results, ie once the deficit is overcome there is no additional benefit of more of something; it is important to consider the converse association relating to eating less of the foods that score negatively in each diet quality index. For example reducing sugar sweetened beverages or meat might have an impact up to a point but after that reducing further is not of benefit.

This is a very interesting comment. However, this hypothesis is more difficult to develop. Scarce evidences regarding this hypothesis have been published and although suggestive it could be considered less probable than the idea of the presence of suboptimal levels of some micronutrients with important neuropsychiatric properties. For example, function and structure of the nervous systems depends on the concentration of several nutrients such as fatty acids, amino acids, vitamins, minerals and trace elements.

11. Given that you have chosen to look at dietary patterns as risk factors for depression the focus on individual nutrients is odd. Even the conclusion is based on identifying specific micronutrients that might be important. The whole idea of looking at dietary patterns or overall diet is that individual nutrients on their own might have only weak associations with outcomes where a dietary pattern providing a wide range of nutrients could have a stronger association; and that it is difficult to disentangle the association of single nutrients from other nutrients and unknown compounds that are consumed together in different foods.

We agree with you. To analyse dietary patterns has different advantages such as to avoid confounding for other dietary factors or to increase statistical power as the isolated effect of single nutrients are too small, cumulative exposure increases the effect and we are able to avoid multicollinearity and issues related to multiple comparisons.

However, we observed suboptimal intakes for some micronutrients: vitamin E, folic acid and magnesium (below Recommended Daily Allowance) in participants within the first quintile of adherence to the three dietary patterns (Appendix). Thus, not only deficiency in one micronutrient but also deficiencies
in several nutrients could explain the reported results. It is important to clarify that the existence of micronutrient deficiencies among participants in the lowest quintile of adherence to these three dietary patterns is only a possible explanation for the reported results as we have stated in the discussion section.

12. Does the journal have a limit of references include as there are very many and at least one that could be added.
13. Patterns of dietary intake and psychological distress in older Australians: benefits not just from a Mediterranean diet.

We have included this new reference in the last version of the manuscript.

16. Table 1, ‘quantile’ not ‘cauntile’.
   We appreciate the reviewer catching this typo.

17. Table 2. Change table title to ‘diet quality scores’ rather than ‘high quality diet patterns’ (Also Table 3).

   Ok

Is the percentage of post menopause in the table just within women?

Yes. The percentage is based on 8847 women.

Change ‘Unemployment’ to ‘Unemployed’. Fix ‘Dyslipidemia’. Add ‘score’ after the names of diet, eg Mediterranean Diet Score. Don’t need for AHEI and names includes the word ‘Index’.

We have included your suggestions in the new version of the manuscript.

18. Figure 1. Fix the x-axes title by Including a space after ‘Average’ and adding ‘diet score’, eg A) Average Mediterranean Diet Score on x-axis; for AHEI just get add space.

   Ok
Second reviewer
A very interesting and important research paper.

Minor essential/Discretionary level suggestions:

Abstract:
* State the actual population sample size from which the 1,051 cases were drawn from.

Following your suggestion, we have included this figure.

* Clarify "e L-shaped extreme quintiles"

We have clarified this issue in the new version of the manuscript.

* Clarify and justify the "L-shaped" effect. See comments below on this

Following your suggestion, we have avoided the use of the term “L-shaped”. We have replaced “L-shaped” by “non-linear”.

Intro:
* It is true that we can't yet directly correlate these patterns with micro/macro nutrient intake, but it should be clarified that your current research model can't validate this, only if there are general outcome differences between patterns

Ok. As you suggested we have clarified this point in the new version of the manuscript modifying slightly our explanation on the aim of our study.

Methods:
* I appreciate study methods have been published elsewhere but suggest still providing a brief synopsis on what the purpose of the SUN cohort is and what questionnaires where that they filled out

Following your suggestion we have included some additional information on the purpose of the SUN Project and the type of questionnaires that participants have completed.

* I am curious as to how the MDS scale was grouped into: low (score 0–2), low-moderate (score 3), moderate-high (score 4), high (score 5) and very high (6–9). Seems weighted strangely re very high and some having singular scores per rating group

This categorization was used to ensure an adequate distribution of the sample with enough number of participants in each category of adherence.

* Consider reframing "softer and gentle approach" wording for PDP.
We have replaced our previous explanation on the rationale for PDP by the following sentence “a moderate and intermediate approach to a vegetarian diet”.

* Am I right in thinking that all of the sample are classified into variant levels of all three scales? e.g. data not used just for one pattern (I don't think this is the case but just checking)

Data on the whole sample were used for building each of the three different patterns. Therefore, each variable (dietary pattern adherence) has been categorized into quintiles. So, the entire sample has been classified into variant levels of all three scales as you correctly thought.

* I am unclear about the following: "The percentage of confirmed depression was 74.2%; (95% CI=63.3 to 85.1). The percentage of confirmed non-depression was 81.1% (95% CI = 69.1 to 92.9)." Please clarify this further re what confirmation meant or how it was achieved.

Following your suggestion, we have included additional information with some figures to clarify the paragraph.

* Spelling- a participants was considered "a" user of vitamin...

We appreciate the reviewer catching this typo.

Results/Discussion:
* "These findings suggested that deficient nutrient intake related to suboptimal adherence to these high-quality dietary patterns was probably the key factor to account for the raised risk of depression among participants with lower adherence."

Can you really say this is directly related to "nutrient deficiencies" without specific data to intake of individual nutrients?

Although through these analyses we cannot directly associate micro or macronutrient intake with depression risk, a possible explanation for the reported results could be that some micronutrient deficits maybe present in the lowest levels of adherence to diet quality scores. We have included an appendix in the new version of the manuscript to address this issue. We found suboptimal intakes for several micronutrients within the lowest quintiles of adherence to diet quality scores.

* Am I right in thinking with the results and the figures that the moderate adherence to these diets confers the strongest association with depression prevention and that it is weaker with greater adherence or just maintains (with vegetarian pattern)?

Yes, you are right.

If so, need to better explore the reason for this (can't see how it is nutrient related). Some people posit that such effects can be due to psychological
elements of neurotic or obsessive traits—e.g. this pattern is seen in physical activity and exercise, with the highest activity actually having worse mental health.

This is a very interesting comment. However, all the results were adjusted for physical activity, smoking (ex-smokers have been considered participants with important willpower and mentally stronger) or body mass index. Though our adjustment may have controlled for the effect of these behaviors or conditions, imperfect measurements or lack of data for some these traits could also still contribute to explain our reported results, as you have suggested. We have included a comment in the discussion following your thoughts and consequently we have included the following paragraph in the discussion:

“We observed that moderate adherence (but not always the highest level of adherence) to diet quality scores showed the strongest inverse association with depression. It could be speculated that some psychological elements of neurotic or obsessive traits present in some participants classified in the highest category of dietary adherence may contribute to the observed plateau already reached at moderate adherence. An alternative explanation for this plateau is that we observed suboptimal intakes for some micronutrients: vitamin E, folic acid and magnesium (below Recommended Daily Allowance) in participants within the first quintile of adherence to the three dietary patterns (Appendix). Therefore, a threshold effect may exist, and once the threshold is achieved the risk reduction with subsequent improved adherence plateaued. This explanation is also compatible with our observed results”

* “However, the MDS is rich in monounsaturated fatty acids and fish (omega-3) and the AHEI-2010 in nutrients such as polyunsaturated fatty acids” I would have thought as omega-3s are also polyunsaturated fats that this sentence is moot.

We agree. However, although omega-3s are polyunsaturated fatty acids, the type of polyunsaturated fatty acids included in the scoring of the AHEI-2010 can be both omega-3 and omega-6. The differential pro and anti-inflammatory properties of both types of fatty acids deserve a differential consideration. We have included a clarification in the new version of our manuscript.

* On page 19 there is discussion about the micronutrients and the equivocal association with depression, but then on page 20 there are new references and justification for the link between some of these e.g. Zn and depression. Suggest harmonising this passage so that your position based on the evidence is clearer

We have included two independent paragraphs as the first one includes longitudinal studies that analyze the role of micronutrients intake in depression whereas the second paragraph includes studies that have analyzed the association between serum levels (not intake) of different micronutrients and depression in cross-sectional analyses. These second block of studies should represent the nutritional status of depressed and not depressed populations.
* I appreciate that the AHEI takes into account processed foods, sugars, and trans fats, and that you have done previous work showing this type of diet effects mental health outcomes; could a scale have been used applying this approach-focusing on the 'elements' of a poor diet. In other words seeing if your results reflect a higher consumption of processed and fast foods?

This is a good idea and we can work on it in subsequent future manuscripts, we feel that the inclusion of such an assessment in the present manuscript will need a considerably longer extension than the available room for a single manuscript. We focused here on the overall diet quality scores and rather than on single foods.

**Figures:**
* Suggest the need for a footnote clarifying the axis numbering.

Following your suggestion we have included a footnote clarifying the axis numbering.

* Also, it would be good to discuss in more detail what these differential regression patterns are telling us in the discussion.

The following paragraph has been included in the discussion section:

“Finally, we have to highlight that, taking into account the observed correlation between the Mediterranean diet and the PDP, the PDP showed additional and relevant information on the association between diet quality scores and depression risk, because the residuals of a regression of PDP on the Mediterranean diet were still significantly associated with depression risk. This was not the case for the AHEI-2010. After eliminating the possible explanation in its variability already accounted for by the Mediterranean diet through the use of residuals, we observed less important reductions in the risk of depression. This latter finding suggests that common nutrients and food items present in both patterns (AHEI-2010 and Mediterranean diet) could be responsible for the observed reduced risk in depression associated with a good adherence to the AHEI-2010”.

*I am still unsure how this relates to an L-shaped curve meaning it is related to micronutrient deficiencies.

The existence of micronutrient deficiencies among participants in the lowest quintile of adherence to these three dietary patterns is only a possible explanation for the reported results. If that deficit does exist, this fact could explain the shape of the dose-responses curves found for the associations between adherence to these three dietary patterns and depression risk. We have further elaborated on this idea by providing the intakes of micronutrients within lowest categories of adherence in the supplementary material.