Author’s response to reviews

Title: Western and Modern Mexican dietary patterns are directly associated with incident hypertension in Mexican women: a prospective follow-up study

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Western and Modern Mexican dietary patterns are directly associated with incident hypertension in Mexican women: a prospective follow-up study.

Response to reviewers

We thank the assistant editor and the reviewers for their time and valuable input on our manuscript. We agree that this study shows new information regarding dietary patterns and hypertension, particularly on a population undergoing a nutritional transition and a high prevalence of chronic diseases. We believe we have answered all the comments. We look forward to reading your feedback.

Reviewer #1: Monge et al used data-driven principal component analyses to define dietary patterns and relations with risk of self-reported treated hypertension in a population of 62,913
Mexican women. This study shows interesting data particularly on dietary patterns in Mexico. Their associations with hypertension are also interesting; however, there are few considerations to take into account:

* Title: The title mentions that this is a cross-sectional analysis, while in the Discussion, line 271, this is a prospective study. Considering that the outcome is incidence of hypertension, I am curious about the reason to mention cross-sectional study in the title.

R: Thank you for pointing out this error. We have now changed the title accordingly to: Western and Modern Mexican dietary patterns are directly associated with incident hypertension in Mexican women: a prospective follow-up study.

* Methods, line 110: Why were ~12.000 participants excluded due to unavailable information if it is a cross-sectional study?

R: As the reviewer noted this is not a cross-sectional study but a follow-up study, so we excluded 12,093 participants for whom information after baseline was unavailable

* Methods, line 127: I understand that follow-up time is not available due to unavailable date of diagnosis. However, could you please add the average time between completing the FFQ and hypertension questionnaires? R: Mean follow-up time was 1.7 years (line 210).

It would be good if you could please explain clearer the timing of the questionnaires. Do I understand it correct that the FFQ was completed in 2008 with the hypertension follow-up questionnaire at December 2011? R: While date of diagnosis was unavailable in this study, we could calculate the average follow-up time using the date in which participants completed their questionnaires. Baseline questionnaires were answered during the first phase, which occurred between January 2008 and June 2011. A follow-up questionnaire was administered during a second phase, which occurred between December 2011 and February 2014. Mean follow-up time was 1.7 years.

But the hypertension questionnaire asked about diagnosis of hypertension in the past 2 years. May this have led to the possibility of missed cases? R: The questionnaire did ask about hypertension diagnosis in the past two years, which as the reviewer points out could have led to the possibility of missed cases. However, we believe that the proportion of unreported cases will be small, since mean follow-up time was 1.7±1.1 years. Similarly to the undiagnosed cases, these potential non-reported cases are unlikely to be related to diet. Thus, the misclassification of the outcome is likely a non-differential misclassification, which happens in most cohort studies –
especially with outcomes such as diabetes and hypertension which have a large number of undiagnosed cases. In any case it will underestimate the real association.

Moreover, although it is a large study with a considerable number of HTH cases in 2 years time, this period is relatively short and may explain the borderline associations particularly for the FV dietary pattern with incidence of hypertension. If you have done a power calculation before starting this analysis, it would be good to add details on this. R: As the reviewer states, while this is a large prospective study the short follow-up period may explain the borderline associations. This study has 80% power to detect an OR of 1.17 between Q4 and Q1 of each food pattern.

* Methods, Line 130: Why are people with hypertension, not on treatment not included? Also, it may be good to validate cases in future with data from their GP, if possible.

R: We defined hypertension as participants who self-reported diagnosis and treatment because when conducting a validation exercise (using a confirmatory survey by telephone) we confirmed the presence of hypertension in 89% of participants who reported a clinical diagnosis of elevated blood pressure under treatment, whereas only 50% of cases were confirmed in those who reported a diagnosis without treatment.

We analyzed the data using the less strict definition of hypertension and found a stronger association with all dietary patterns. We defer the decision to the editor whether to include this table as a supplementary table.

### Fruits & Vegetables Pattern

<table>
<thead>
<tr>
<th></th>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
<th>PTrend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age adjusted</td>
<td>Reference</td>
<td>0.94(0.85,1.03)</td>
<td>0.87(0.79,0.96)</td>
<td>0.83(0.76,0.92)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Multivariable</td>
<td>Reference</td>
<td>0.96(0.88,1.06)</td>
<td>0.89(0.80,0.98)</td>
<td>0.87(0.79,0.96)</td>
<td>0.002</td>
</tr>
<tr>
<td>Multivariable + BMI</td>
<td>Reference</td>
<td>1.01(0.91,1.11)</td>
<td>0.90(0.81,0.99)</td>
<td>0.91(0.82,1.01)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

### Western Pattern

<table>
<thead>
<tr>
<th></th>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
<th>PTrend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age adjusted</td>
<td>Reference</td>
<td>1.07(0.98,1.18)</td>
<td>1.10(1.00,1.21)</td>
<td>1.18(1.07,1.29)</td>
<td>0.0008</td>
</tr>
<tr>
<td>Multivariable</td>
<td>Reference</td>
<td>1.08(0.98,1.20)</td>
<td>1.11(1.00,1.23)</td>
<td>1.20(1.08,1.34)</td>
<td>0.0009</td>
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<tr>
<td>Multivariable + BMI</td>
<td>Reference</td>
<td>1.07(0.96,1.19)</td>
<td>1.05(0.94,1.17)</td>
<td>1.14(1.02,1.27)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

### Modern Mexican Pattern

<table>
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<tr>
<th></th>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
<th>PTrend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age adjusted</td>
<td>Reference</td>
<td>1.05(1.01,1.09)</td>
<td>1.05(1.01,1.09)</td>
<td>1.05(1.01,1.09)</td>
<td>1.05(1.01,1.09)</td>
</tr>
</tbody>
</table>
Age adjusted Reference 1.11(1.01,1.22) 1.12(1.02,1.24) 1.14(1.03,1.25) 0.01 1.05(1.01,1.09)

Multivariable Reference 1.11(1.00,1.22) 1.15(1.04,1.27) 1.19(1.07,1.32) 0.001 1.07(1.03,1.11)

Multivariable + BMI Reference 1.05(0.94,1.16) 1.06(0.96,1.18) 1.04(0.93,1.15) 0.52 1.02(0.98,1.06)

* Methods, Line 123: Please address the moderate to weak correlation of protein measured by ffq vs 4-day 24-hr recalls. Underestimation of intake of protein sources may have influenced the results and composition of the dietary patterns.

R: As Walter Willett discusses in Nutritional Epidemiology, it is expected that correlations of nutrients measured by two different dietary assessment tools, such as an FFQ and a 24-hour recall, range from 0.3 to 0.5. While the correlation coefficient of protein measured by the FFQ compared to the multiple 24-hour recalls was 0.32 this value is within the expected range. Additionally, a study using the national health survey (Denova-Gutierrez 2016) shows that the correlation between dietary patterns derived from an FFQ correlate with those derived using 24-hour recalls. Thus, we believe it is unlikely that the dietary patterns would be affected by a possible underestimation of protein.


* Results Line 255 to 261: It would be informative if you could please add the variance explained for the components based on individual food items? How does the variance explained by individual items compare to variance explained by food groups? The number of individual food items per food group may explain the different dietary patterns by component; could you please add more information on this?

R: The variance explained for the three components based on individual food items was 6.8%, 3.9%, and 3.3%, respectively, and slightly lower than the observed with food groups (8.6%, 5.9% and 5.1%). This information was added to the manuscript in line 260. In general it is not practical to run a principal component analysis with all food items because interpretation of the components is more complicated. It is general practice to collapse the individual food items into food groups that may represent distinct lifestyles, such as whole grains, low fat diary, etc.
* Results: Please add the correlations between the 3 dietary patterns?

R: Correlation between the three dietary patterns would certainly be of concern, as the reviewer is implying. To take into account that multicollinearity would be an issue when assessing the association between dietary patterns and any outcome, we derived these dietary patterns using an orthogonal rotation which by definition results in patterns uncorrelated with each other.

* Discussion Line 281-285: Please add references of 'other studies' and the variance explained by those studies for comparison.

R: We added the references to the other studies. The variance explained by all derived patterns in those studies: Hu et al. 1999 (20%) Hu et al. 2000 (17.4%) Khani et al. 2004 (24%), is similar to the total variance explained in our study (19.6%).

* Discussion Line 293: More explanation of 'commonly used index scores' and 'hypothesis-oriented dietary patterns' are needed to make a proper comparison of how these dietary patterns may be comparable to which dietary patterns investigated in this analyses.

R:

In lines 289-291 we added a discussion on the difficulty to compare empirically derived vs hypothesis driven dietary patterns: It is difficult to compare empirically derived and a priori dietary patterns. Some of the advantages of using empirically derived dietary patterns are that they are data driven and allow for the examination of eating behaviors.

We also added specification of the commonly used index scores and dietary patterns that Li et al and Toledo et al used in their studies in lines 297-301:

Li et al. found strong inverse associations between three commonly used index scores (Dietary Approaches to Stop Hypertension, alternative Mediterranean diet, alternative Healthy Eating Index) and hypertension but Toledo et al. found no association with fifteen hypothesis-oriented dietary patterns.[28, 29]

* Discussion Line 296-300: Please rephrase this complicated, long sentence.
R: Thank you for pointing this out. We rephrased the paragraph to: Adjusting for a mediator, in this case BMI, would cause collider bias so the direct association between the dietary patterns and hypertension would not be valid. Line 303.

*Discussion:* Considering the results based on the outcome of self-reported treated hypertension, it seems that, although treated, blood pressure levels are not well controlled. I understand that this study has no available data on actual blood pressure measures, but is any data available on levels of control and adherence to treatment of the treated hypertensive population in Mexico?

R: Please refer to answer on question 4. The reason for using this definition was not because we assume that blood pressure levels are not well controlled but rather for its positive predictive value. However, according to the national health survey, ENSANUT 2012, 55% of diagnosed and treated individuals have a blood pressure ≥140/90. While this does indicate that there is a poor blood pressure control in hypertensive individuals, this would not impact our study because we are analyzing hypertension incidence and not blood pressure control.

*Conclusions, Line 354-355:* Considering that only treated individuals are included, associations may be underestimated and conservative. Also, the number of cases in 2 years time may not have been at sufficient power, which also may explain the borderline results of the FV diet. Considering the available literature and inverse borderline trend of associations, it would be good to weaken the statement of lines 354 and 355.

R: The reviewer has an excellent point. We weakened the statement to: In contrast to previous findings, the Fruits & Vegetables pattern was not significantly associated with hypertension, probably due to misclassification of the outcome. Lines 365-66. We also added the points raised by the reviewer to our discussion, lines 316-17 and 335-39.

*Table 1:* It would be informative if you could please add a percentage of contribution to the food group for each food item.

R: We ordered the food items within each food group to show which item contributed most to each group to address the reviewer’s comment. We add this explanation to the table’s footnote. We believe that adding the percentage contribution for each food item would make this table very complicated.
Reviewer #2: Adriana monge, et al have studied the association of dietary patterns and incident hypertension among 62913 Mexican women. They extracted three dietary patterns using principal component analysis (PCA) and investigated their association with hypertension incidence. Participants who were in the highest quartile of western and Modern Mexican patterns compared to the lowest quartile had higher risk of hypertension, whereas they showed no significant association between fruit and vegetable dietary pattern and incidence of hypertension. Present research is a prospective population-based study, with a large sample size. Self-reported diagnosis of hypertension and low follow up time for determining the incidence of hypertension are major limitations of this study.

Comments:

1- In abstract, a brief descriptive statistics about percent of incident hypertension and mean ± SD of age and body mass index of participants should be mentioned.

R: Done. We have added these descriptive statistics to the abstract.

2- Material and methods, subjects: It would be better if researchers excluded subjects with specific diets such as hypertension and cardio vascular disease, and also pregnant and nursing subjects, because in this two periods of women's life it is likely that dietary patterns undergo a lot of changes.

R: We agree with the reviewer which is why prevalent cases of hypertension (n=11,292), myocardial infarction, stroke or cancer (n=1,772) were excluded from the analysis. The percentage of pregnant participants is low, 1.5% so we did not exclude these participants. However, in this cohort we do not have information on whether or not they are lactating at the moment of answering the questionnaire.

3- The final sample size for data analysis was 62913 subjects, however PCA was conducted on 88082 women. It would be better for PCA to be conducted in final sample size (62913). It is probable that the dietary patterns changed. Due to changing patterns it is suggested to compare the mean of dietary score, the percent of macronutrient, and main demographic variables between this 88082 women used for pattern extractions and whom which excluded using a t test analysis. And if there were no significant differences between two groups, report it in a paragraph at method section.

R: We strongly believe that the ideal population in which to derive data-driven dietary patterns is the whole population with a valid FFQ. Which is why we calculated the dietary patterns in that
population. We are aware that some studies derive specific patterns for a specific disease, however, the patterns we derived are not specific to hypertension but are also used in this cohort in general. The main difference between the ~88,000 participants in which the patterns were derived and this study’s final sample size (~63,000) is the loss to follow-up (~12,000). The supplemental table comparing response vs no response to the 2011 questionnaire is now complemented with % macronutrients and mean dietary score. We consider that the dietary score is not informative per se so we reported and compared their quartile distribution as well. We have also added the p-values from the comparison of independent means using a t-test and chi-square analysis when appropriate. However, we would like to stress out that these results are confounded.

4- The follow up time (1.7 years) for determining the incidence of hypertension based on usual dietary patterns is not a suitable time, please added this issue into your limitation section.

R: Done. We added this important limitation in the discussion, lines 316-17 and 335-39.

5- In page 9, line 193, the authors have stated that "in an exploratory model we also adjusted for BMI (kg/m2) as a potential mediator". Since BMI is a common confounder adjustment variable in hypertension research, this is unclear if researchers considered BMI as a confounder variable or performed a separate exploratory mediation analysis for diagnosis BMI as a mediator variable for incident hypertension. Please, clarify.

R: Yes, BMI is a common confounder adjustment variable when analyzing hypertension. However, in the association between diet and hypertension BMI is a mediator. We have added in the manuscript that we performed an exploratory mediation analysis in line 194-95.

6- Discussion: since the significant relationships were observed between western and modern Mexican patterns with incident hypertension, please add further discussion about the relevance of western and modern Mexican patterns to the hypertension to justify their finding and investigate underlying mechanism, e.g. dietary component and molecular biological studies about the impact of these patterns to the incident hypertension.

R: In lines 310-319 we discuss the foods and dietary components that may be the underlying mechanism by which both patterns are associated with incident hypertension. “Meat, processed meats, sweets and pastries have been associated with increased blood pressure [5, 35] perhaps due to their higher content of saturated fat, sodium, and sugar than fruits and vegetables.[36-38] Consistent with this literature, we found a direct association between both the Western pattern and the Modern Mexican pattern and incident hypertension.” We believe this contributes to the
readers’ understanding of why these patterns are associated with hypertension in the Mexican population, however further discussion of the underlying mechanisms would be beyond the scope of this manuscript. We have added in the discussion that these patterns include frequently consumed foods that could be targeted by public policy in lines 321-324.

7-In repeated analysis of dietary patterns, authors extracted two factors (patterns), by different design of factor analysis such as entering all items of FFQ to analysis; when the number of items which entered to factor analysis increases, it is expected that total variances of covering dietary food items by identified factors decrease, (authors have not mentioned about explained variances by two dietary factors in repeated analysis). It seems that after repeated analysis, not only the fruit and vegetable pattern indicated no significant association with incident hypertension, but also the third pattern (Modern Mexican pattern) - which interestingly reflected the nutrition transition in Mexican population and indicated a new dietary pattern in Mexican women - was eliminated. So I think this repeated analysis does not give us a new finding and it not necessary to be included in the manuscript.

R: We agree with the reviewer that these analyses do not give new findings. However, these are important sensitivity analyses to show that there is methodological consistency and that our findings are not just a methodological artefact. It is important to note that our main analysis is conducted using the 3-component solution.