Reviewer’s report

Title: Hypcholesterolemia is an independent risk factor for depression disorder and suicide attempt in Northern Mexican population

Version: 0 Date: 06 Aug 2017

Reviewer: Emily Goldmann

Reviewer’s report:

Dear Authors,

I enjoyed reading this manuscript that describes the findings of a case-control study to assess hypocholesterolemia as a risk factor for MDD and suicide attempt. Exploring the association between mental and physical health is important for reducing comorbidity and furthering our understanding of the etiology of mental disorders. The manuscript is very interesting and well-written. There are a few issues with the study design, statistical analysis and interpretation of findings that require clarification before it is published. Please see below for comments specific to each section.

Introduction:

- The case for this study needs to be further described. Why is it important to study the relationship of interest in this population specifically? Why might findings be different? Are these issues of particular concern in this population? Or is the goal of the study to provide further evidence on a relationship that is inconsistent in the literature? How does this study help us figure out what's really going on, i.e., how does it improve on other studies?

- It would be helpful to briefly summarize the hypothesized explanations for both the positive and negative associations between cholesterol levels and mental health outcomes reported in the literature. How do previous studies try to explain their findings? What are the mechanisms (briefly)?

Methods:

- Does the study population comprise adults (those 18 years or older) only? Please clarify.

- Important: The factors used for matching, as well as the exclusion criteria, need to be justified. Specifically, why did the authors match on BMI? The biggest question is why were subjects with the chronic disease listed and those taking lipid lowering drugs excluded from the study? It is possible that previous studies found a positive association between cholesterol level and MDD because high cholesterol is associated with chronic disease, which is then in turn associated with poor mental health outcomes. Does anyone in the study population have high cholesterol levels? It is possible that there is a non-
linear relationship between cholesterol level and MDD (threshold effects), which may explain the inconsistent findings in the literature. This is something that the authors should consider. The exclusion criteria need to be justified given that they may make the study less generalizable and difficult to compare to other studies in terms of key findings.

- In the DSM 5, I believe it's "major depressive disorder" not "major depression disorder"

- Please describe how suicide attempt was defined/measured in this study

- If presence of MDD and suicide attempt are the dependent variables, I assume they are dichotomous, which would mean logistic regression, not linear regression, was used

- Important: How was matching accounted for in the analysis? Was McNemar's test used? Or conditional logistic regression models? Is that what was meant by "adjusted" and "multiple" when describing the regressions? The study design needs to be reflected in the analysis or, if it has been, this needs to be made more clear. Were regression models adjusted for any additional variables, besides the matching variables? In the models comparing those with and without suicide attempt, depressive symptom severity might be a confounder...

Results:

- Table 1 findings need to be further described in the text. It looks there are some conflicting results -- for some cholesterol variables, levels are lower among those with MDD and suicide attempt; for others, levels are higher. The authors might also explain why all of these different cholesterol variables were assessed in this study. Did the authors hypothesize that there might be different relationships with the outcome? The paper also focuses primarily on hypocholesterolemia when other cholesterol variables were also examined...

- Analysis stratified by sex should be described in the Methods under Statistical Analysis

- p.6 line 127: did the authors mean "showed significant differences in both genders (p<0.05)", instead of p>0.05?

- Regression model results only presented for hypocholesterolemia as the independent variable. What about the other cholesterol variables?

Discussion:

- p. 11 line 190, "Our results showed lower levels of triglycerides in subjects with MDD..." -- This is not what is presented in Table 1; it looks like it is the opposite.

- VLDL levels seem to be higher in MDD as well; this is not discussed
- p. 12 line 204: the study design is case-control not cross-sectional. Perhaps the authors meant that all measures in the study are prevalent not incident and timing was not assessed, so there is some temporal ambiguity.

- It is important to note whether previous studies also excluded individuals with chronic disease and those who were taking lipid lowering medications -- this may make comparison between previous studies' findings and the findings from this study difficult.

- p. 12 line 208 -- is there evidence of this in the literature? Please provide a reference.

- p. 12 lines 211-214: Not clear what is being said. Please clarify.

- The authors state that subjects in the study were from the same sociocultural and economic background. Can the authors confirm that there is really no heterogeneity among subjects in terms of socioeconomic status? This could be an important confounder, though perhaps not available in the dataset.

- How does exclusion of those taking lipid lowering drugs control for potential bias? What bias? This should be clarified in the Methods.

- Generalizability is also a limitation of the study given the exclusion criteria and specific characteristics of the study population.

Tables:

- Where are the percents for female/male distribution?

- Decimal places should be consistent

- What comparison is the p-value column reporting? There were three tests for significant differences, but only one p-value is shown.

- Any p=0.000 should be presented as p<0.001

Overall:

- p-values that are 0.000 should be written as "p<0.001" in the text

- The manuscript is well-written in clear, but there are a few areas that could be clarified/proofread

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

No
Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

No

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

Quality of written English
Please indicate the quality of language in the manuscript:

Needs some language corrections before being published

Declaration of competing interests
Please complete a declaration of competing interests, considering the following questions:

1. Have you in the past five years received reimbursements, fees, funding, or salary from an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

2. Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

3. Do you hold or are you currently applying for any patents relating to the content of the manuscript?

4. Have you received reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript?

5. Do you have any other financial competing interests?

6. Do you have any non-financial competing interests in relation to this paper?

If you can answer no to all of the above, write 'I declare that I have no competing interests' below. If your reply is yes to any, please give details below.

I declare that I have no competing interests
I agree to the open peer review policy of the journal. I understand that my name will be included on my report to the authors and, if the manuscript is accepted for publication, my named report including any attachments I upload will be posted on the website along with the authors' responses. I agree for my report to be made available under an Open Access Creative Commons CC-BY license (http://creativecommons.org/licenses/by/4.0/). I understand that any comments which I do not wish to be included in my named report can be included as confidential comments to the editors, which will not be published.

I agree to the open peer review policy of the journal