PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Cohort study on the effects of depression on atherosclerotic cardiovascular disease risk in Korea
AUTHORS	Jee, Yon Ho; Chang, Hyoungyoon; Jung, Keum Ji; Jee, Sun Ha

VERSION 1 - REVIEW

REVIEWER	Rachel Miller University of Pittsburgh, USA
REVIEW RETURNED	30-Nov-2018

GENERAL COMMENTS	This manuscript describes the association between outpatient visits for depression and the subsequent risk of ASCVD in a Korean cohort who participated in a national health screening program provided by the NHIS. This study provides evidence that the association between depression and increased CVD risk, which has been established in other populations, is similar in an Asian population. The major concern with the study design is that the number of outpatient visits with an ICD 10 code for depression is being used as a proxy for severity of depression, without discussing the limitations of this approach. Specific comments: 1. Abstract: Participants: Should this say “at least twice” rather than just “twice”? This makes it seem that only 2 visits were possible 2. Abstract: Main Outcome measure: The main outcome of ASCVD also included CVD deaths. This should be clearly stated in the abstract. 3. Abstract: Results: In the final sentence, the comparison group should be stated. I.e. it should say the risk of ASCVD was not increased when men received more than 10 depressive treatments compared to 0 outpatient depression visits. As it is written, it reads that more than 10 visits was not increased compared to the risk associated with 1-10 visits. 4. Introduction: the second sentence needs a reference 5. Introduction: This study is not designed to test the hypothesis stated in the first sentence of the third paragraph “This study has a hypothesis that aggressive treatment and management of depression will prevent CVD”. This sentence should be removed.

	6. Methods: The rationale for restricting the analysis to those patients who had at least 2 visits is not stated. Why not include everyone with at least 1 visit, or at least perform a sensitivity analysis doing so? 7. Methods: Measurement variables: First sentence, “demographic” should be “anthropometric” 8. Methods: Using antidepressant medications alone as part of the depression definition has the potential for misclassification of the exposure, if they are prescribed for another indication. This possibility should be added to the limitations in the discussion. 9. Methods: Outcomes: The description of the validation study is not clear. It seems that this validation was a previous study conducted separately from the current study? The years of the validation do not correspond to the current study. If this was a separate prior study, this information should be removed from the Methods section and described in the Discussion. 10. Methods: A major concern regarding the design of the study is that the number of visits with a depression ICD 10 code is being used as a proxy for severity of depression, without acknowledging the limitations of this approach. More visits could actually mean better treated depression (and may be why greater than 10 visits does not correspond to increased ASCVD risk). These possibilities should be examined in the discussion. 11. Statistical analysis: Fourth paragraph, when describing the SES categories, participants are described as “reporting depression”, but as these are not self-reported data this wording should be changed. Did you test for an SES x Depression interaction with respect to ASCVD? The SES results are a bit confusing as currently presented. 12. Statistical analysis: Have you fit any alternative models adjusting for comorbidities? E.g. adjusting for diabetes status rather than fasting glucose? Is information on renal disease available? This is an important risk factor for ASCVD and is also associated with depression, so is likely to be an important confounder. 13. Results: The flow would be improved if the second paragraph is moved to be the first paragraph. Also, in this section, where it says “took depression medication more than 3 times”, I think this should say “were prescribed depression medication at more than 3 visits”. The frequency distributions for the number of visits do no add up to 100%, I am not sure what the percents are? 14. Discussion: Again, a potential explanation for the lack of increased risk with more than 10 visits for depression needs to be discussed. 15. Table 2. The title should say “ Age-Adjusted Incidence Rate per 100,000 and Hazard Ratio for…” and a row showing the n in each group should be added to the table 16. Supplemental Figures: Are these graphs of cumulative incidence? The axis need to be labeled and the titles should be more descriptive.

REVIEWER	Carlos G Santos-Gallego, MD Cardiology Department The Mount Sinai Hospital New York City
REVIEW RETURNED	08-Feb-2019

GENERAL COMMENTS	The aim of the author is to investigate whether depression increases the risk of developing atherosclerotic cardiovascular disease (ASCVD) in a large Korean cohort study. The atuhros study 481355 Koreans, aged 40-80 yo (mean age 52.8, mean BMI 24, 7.5% diabetic, 28% h ypertensive, 12% hypercholesterolemic, 24% current smokers), who underwent health checkup twice in 2002-2005. After a mean follow up of 8 years, depression increased the risk of developing ASCVD by 41% for men and 48% for women, even after adjusting for CVRF. Depression was also associated with stroke in men and in women. Interestingly, the risk of ASCVD did not increase when men received more than 10 depressive treatments for follow-up periods. The authors are to be praised for focusing on the relationship of depression and CVD, which has often been overlooked. The novelty of the article lies on the fact that depression increases ASCVD and stroke independently of CVRF, and on the fact that patients with >10 visits for depression (basically, a surrogate at good long-term management of depression and compliance with antidepressant medication) had a lower risk of ASCVD compared with fewer visits. as the authors focus on whether depression. The proper methodology, the incredibly high sample size (almost half a million patients), and the long follow up (more than 8 years) strengthen the conclusions. The results are robust, the discussion is balanced, the conclusions are supported by the data, and the manuscript is short and reads well. However, this peer reviewer raises the following issues: Major comments: - The authors report the incredibly interesting finding that risk of ASCVD did not increase when men visited more than 10 times for depression. The following tantalizing explanation should be mentioned: proper treatment of depression reduces CV risk, and moer than 10 visits for depression is a surrogate endpoint of treatment compliance, of attending the follow up visits with their doctor, and in general of proper mental treatment. - Do tryciclic antidepressant and SSIR have different effects on ASCVD? Minor comments: - Introduction, second paragraph: The reference to cancer should be deleted as cancer is not the aim of the authors. - The authors should mention an additional mechanism explaining the increased ASCVD in depressed patients: ie depression and anxiety enhance platelet aggregation(please quote the relevant article Eur Heart J. 2010 Jul;31(13):1573-82), which can cause recurrent ACS in secondary prevention.

VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1
Reviewer Name: Rachel Miller
Institution and Country: University of Pittsburgh, USA
Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below
This manuscript describes the association between outpatient visits for depression and the subsequent risk of ASCVD in a Korean cohort who participated in a national health screening program provided by the NHIS. This study provides evidence that the association between depression and increased CVD risk, which has been established in other populations, is similar in an Asian population. The major concern with the study design is that the number of outpatient visits with an ICD 10 code for depression is being used as a proxy for severity of depression, without discussing the limitations of this approach.

Specific comments:

1. Abstract: Participants: Should this say “at least twice” rather than just “twice”? This makes it seem that only 2 visits were possible

Response: We included participants who attended a biennial health checkup at least once between 2002 and 2005. Only for those who attended every two year (eg, attended in 2002 and 2004 OR attended in 2003 and 2005), we averaged their mean value of measurements from two years. Otherwise if participants attended only one health checkup during the period, we used their single measurement. We understand the wording may confuse readers, so now we changed the term to “biennial health checkup”.

2. Abstract: Main Outcome measure: The main outcome of ASCVD also included CVD deaths. This should be clearly stated in the abstract.

Response: we added CVD deaths in Abstract: Main Outcome measure.

3. Abstract: Results: In the final sentence, the comparison group should be stated. I.e. it should say the risk of ASCVD was not increased when men received more than 10 depressive treatments compared to 0 outpatient depression visits. As it is written, it reads that more than 10 visits was not increased compared to the risk associated with 1-10 visits.

Response: we added the comparison group.

4. Introduction: the second sentence needs a reference

Response: we added a relevant reference to the sentence.

5. Introduction: This study is not designed to test the hypothesis stated in the first sentence of the third paragraph “This study has a hypothesis that aggressive treatment and management of depression will prevent CVD”. This sentence should be removed.

Response: we removed the sentence.

6. Methods: The rationale for restricting the analysis to those patients who had at least 2 visits is not stated. Why not include everyone with at least 1 visit, or at least perform a sensitivity analysis doing so?

Response: As we responded for the Reviewer's first comment, we did not restrict the analysis to those who had at least 2 visits. We included participants who attended a biennial health checkup at least once between 2002 and 2005. For those who had multiple measurements for continuous variables (eg, height, weight blood pressure), we used their mean value in order to minimize measurement error. We have described these explanations in our Methods section.

7. Methods: Measurement variables: First sentence, "demographic" should be "anthropometric"

Response: we changed the term to "anthropometric".

8. Methods: Using antidepressant medications alone as part of the depression definition has the potential for misclassification of the exposure, if they are prescribed for another indication. This possibility should be added to the limitations in the discussion.

Response: we defined depression as patient with at least one visit or 3 medications. But we acknowledge that there is limited information on assessment of depression. So we added detail in the Methods section.

9. Methods: Outcomes: The description of the validation study is not clear. It seems that this validation was a previous study conducted separately from the current study? The years of the validation do not correspond to the current study. If this was a separate prior study, this information should be removed from the Methods section and described in the Discussion.

Response: we appreciate your thoughtful comment and agree with your suggestion. We have described the validation study in the Discussion section as a potential limitation of the current study.

10. Methods: A major concern regarding the design of the study is that the number of visits with a depression ICD 10 code is being used as a proxy for severity of depression, without acknowledging the limitations of this approach. More visits could actually mean better treated depression (and may be why greater than 10 visits does not correspond to increased ASCVD risk). These possibilities should be examined in the discussion.

Response: We thank the Reviewer for pointing out the possibilities. We added them in the Discussion.

11. Statistical analysis: Fourth paragraph, when describing the SES categories, participants are described as "reporting depression", but as these are not self-reported data this wording should be changed. Did you test for an SES x Depression interaction with respect to ASCVD? The SES results

are a bit confusing as currently presented.

Response: We tested for an interaction between SES and depression and found that there was no significant interaction.

12. Statistical analysis: Have you fit any alternative models adjusting for comorbidities? E.g. adjusting for diabetes status rather than fasting glucose? Is information on renal disease available? This is an important risk factor for ASCVD and is also associated with depression, so is likely to be an important confounder.

Response: Thank you for your thoughtful comment. We added information on renal disease. And we adjusted for diabetes, hypertension and dyslipidemia instead of fasting glucose, blood pressure and cholesterol level.

13. Results: The flow would be improved if the second paragraph is moved to be the first paragraph. Also, in this section, where it says “took depression medication more than 3 times”, I think this should say “were prescribed depression medication at more than 3 visits”. The frequency distributions for the number of visits do no add up to 100%, I am not sure what the percents are?

Response: we moved the second paragraph and changed the phrases as you suggested. The frequency distributions did not add up to 100% because we did not include the percentage of “none visits”, which was 96.9%. The sum of the percentages is now 100%.

14. Discussion: Again, a potential explanation for the lack of increased risk with more than 10 visits for depression needs to be discussed.

Response: We thank the Reviewer for pointing that out again. We added the explanation in the Discussion.

15. Table 2. The title should say “ Age-Adjusted Incidence Rate per 100,000 and Hazard Ratio for…” and a row showing then in each group should be added to the table

Response: we changed the title and added a row as you suggested.

16. Supplemental Figures: Are these graphs of cumulative incidence? The axis need to be labeled and the titles should be more descriptive.

Response: The graphs are about cumulative incidence. We added a title (“Cumulative incidence of atherosclerotic cardiovascular disease”) and a footnote (*y-axis: cumulative incidence, x-axis: duration of follow-up, year) to the figures.

Reviewer: 2
Reviewer Name: Carlos G Santos-Gallego, MD
Institution and Country: Cardiology Department, The Mount Sinai Hospital, New York City

Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below

The aim of the author is to investigate whether depression increases the risk of developing atherosclerotic cardiovascular disease (ASCVD) in a large Korean cohort study. The atuhros study 481355 Koreans, aged 40-80 yo (mean age 52.8, mean BMI 24, 7.5% diabetic, 28% hypertensive, 12% hypercholesterolemic, 24% current smokers), who underwent health checkup twice in 2002-2005. After a mean follow up of 8 years, depression increased the risk of developing ASCVD by 41% for men and 48% for women, even after adjusting for CVRF. Depression was also associated with stroke in men and in women. Interestingly, the risk of ASCVD did not increase when men received more than 10 depressive treatments for follow-up periods.

The authors are to be praised for focusing on the relationship of depression and CVD, which has often been overlooked. The novelty of the article lies on the fact that depression increases ASCVD and stroke independently of CVRF, and on the fact that patients with >10 visits for depression (basically, a surrogate at good long-term management of depression and compliance with antidepressant medication) had a lower risk of ASCVD compared with fewer visits. as the authors focus on whether depression. The proper methodology, the incredibly high sample size (almost half a million patients), and the long follow up (more than 8 years) strengthen the conclusions. The results are robust, the discussion is balanced, the conclusions are supported by the data, and the manuscript is short and reads well.

However, this peer reviewer raises the following issues:

Major comments:

- The authors report the incredibly interesting finding that risk of ASCVD did not increase when men visited more than 10 times for depression. The following tantalizing explanation should be mentioned: proper treatment of depression reduces CV risk, and more than 10 visits for depression is a surrogate endpoint of treatment compliance, of attending the follow up visits with their doctor, and in general of proper mental treatment.

Response: We thank the Reviewer for his/her appreciation of our work. We added the explanation in the Discussion as your suggestion.

- Do tryciclic antidepressant and SSIR have different effects on ASCVD?

Response:

	SSRI	TCA
Men	1.44 (1.26-1.65)	1.35 (1.29-1.41)
Women	1.62 (1.46-1.79)	1.43 (1.38-1.48)

The table above shows hazard ratio of SSRI and TCA for ASCVD. After adjusting for age, smoking status, systolic blood pressure, cholesterol, fasting blood sugar, taking SSRI has 44% higher risk of ASCVD (HR=1.44; 95% CI 1.26-1.65) and taking TCA has 35% higher risk of ASCVD in men (HR=1.35; 95% CI 1.29-1.41). In women, the HR of taking SSRI was 1.62 (95% CI 1.46-1.79) and the HR of taking TCA was 1.43 (95% CI 1.38-1.48).

Minor comments:

- Introduction, second paragraph: The reference to cancer should be deleted as cancer is not the aim of the authors.

Response: we removed the reference of cancer.

- The authors should mention an additional mechanism explaining the increased ASCVD in depressed patients: ie depression and anxiety enhance platelet aggregation (please quote the relevant article Eur Heart J. 2010 Jul;31(13):1573-82), which can cause recurrent ACS in secondary prevention.

Response: We thank the Reviewer for introducing the relevant article. We added the platelet hypothesis in the Discussion as you suggested.

VERSION 2 – REVIEW

REVIEWER	Rachel Miller University of Pittsburgh, USA
REVIEW RETURNED	03-Apr-2019

GENERAL COMMENTS	Thank you for your attention to my previous comments. I have no new comments to add.

REVIEWER	Carlos G Santos-Gallego, MD Cardiology Department, The Mount Sinai Hospital, New York City
REVIEW RETURNED	21-Mar-2019

GENERAL COMMENTS	The authors have satisfactorily addressed the previously raised issues. This peer reviewer congratulates the authors for a solid, interesting and clinically relevant manuscript.