PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Risk of aortic aneurysm and dissection in patients with Sjögren's syndrome: a nationwide population-based cohort study in Taiwan
AUTHORS	Tsai, Yi-Da; Chien, Wu-Chien; Tsai, Shih-Hung; Chung, Chi-Hsiang; Chu, Shi-Jye; Chen, Sy-Jou; Liao, Wen-I; Yang, Chih-Jen; Liao, Min-Tser; Wang, Jen-Chun

VERSION 1 – REVIEW

REVIEWER	Howard Amital Sheba Medical Center
REVIEW RETURNED	03-Mar-2018

GENERAL COMMENTS	The paper of Tsai et al is interesting and through. Dealing with an important issue. A major issue that the authors need to clarify; why wasn't the control group chosen as subjects without Sjogren's syndrome. The current comparison turns the results and methods obscure since it is ca composition of people who pressed claims to the insurance; this is a group of people the readership will find difficult to compare with. I suggest that the control group should be more reasonable and natural.

REVIEWER	Dominic PJ Howard Oxford University, UK
REVIEW RETURNED	12-Mar-2018

GENERAL COMMENTS	This is a large retrospective coding analysis rather than a true population-based study. The 2005 Taiwan longitudinal health insurance database was searched using ICD-9 codes for patients with a new diagnosis of Sjogrens Syndrome. 10941 cases were identified and followed up until 2010 for the occurrence of aortic aneurysms or dissection again using ICD-9 coding retrieval. The same analysis was performed for 43764 matched controls identified from the same database. A small, but significant, difference in aortic aneurysm/ dissection incidence was identified. The true significance of this finding is difficult to determine due to the methodology of the study. I have the following queries: 1.) The abstract states that the controls were propensity matched, but there is no detail in the manuscript on how any propensity matching was performed, how potential confounders were scored, and what type of propensity matching analysis was used. It would appear that the controls were actually extracted from the database and matched for a variety of demographics, co-morbidities, and medications. More information is required on exactly how this was performed as this process can easily lead to significant bias with

	regards to the outcome of interest. 2.) Both SS cases and controls are mostly female. Females are known to have a lower incidence of aortic aneurysms and dissection than males. Yet over the 5-10 year follow-up period over 200 aortic aneurysm and dissection events occurred in 55000 individuals. This would suggest high incidence rates in both cases and controls. The authors need to explain this. Median follow-up time for cases and controls should be included and patient-years follow-up in order to calculate incidence rates. I expect the high event rates maybe a coding issue, as the codes used would identify both non-emergency and emergency aortic aneurysm and dissection diagnoses. Are the codes used restricted to primary discharge diagnosis or any co-morbidity coding? 3.) Following on from above, it would be very useful to have age- and gender- specific incidence figures and graphs for aortic aneurysm and dissection occurrence in the whole health insurance population. The same should be done for Sjögren's syndrome. This would put the study findings in context. 4.) Graphs of Age- and gender- specific rates for aortic aneurysm/dissection in the SS cases and controls would also provide greater clarity for the reader. 5.) The logistic regression analysis is confusing and flawed. Essentially the case and controls have already been matched at baseline, but they are then analysed with logistic regression using the previously matched variables. It is clear that the authors are trying to show that despite other diagnoses occurring during the follow-up period, the diagnosis of Sjögren's syndrome remains independently associated with aortic aneurysm and dissection incidence. Overall, either cases are matched at baseline and then regression analysis is not required, or they are not matched and then regression analysis can be informative. Using both methods doesn't make sense. 6.) The discussion is largely hypothesis generating. It needs to be shortened (particularly paragraphs 2-4) and focused on putting the findings of this study into context with the current literature, and the impact of the findings on clinical care/future research. 7.) Finally, why is study being submitted 8 years after final follow-up period?

REVIEWER	Kate Honeyford Dr Foster Unit, Department of Primary Care and Public Health Imperial College, UK
REVIEW RETURNED	23-Apr-2018

GENERAL COMMENTS	Reviewers Comments In general this is clear and easy to read. The discussion focusses heavily on the possible mechanisms associating SS with AA/AD, which is not directly related to the study. More detail is needed regarding the methodology of the propensity score matching. The implications of the study need to be linked to the conclusion, given an association between SS and AA/AD is found, are there implications for healthcare professionals? Is the abstract accurate, balanced and complete? Objective is clear.

	Methods – you talk about using Cox regression to estimate odds ratios but I am not sure this is what happened. You predominantly used Cox regression to estimate HRs. You don't mention propensity score matching in the methods. I would like the outcome clearer in the methods. "All medical conditions for each case and control were categorized using the International Classification of Diseases, 9th Revision (ICD-9)." Is possibly more detail than necessary, with not quite enough detail on the statistical approach. Results It says that "patients with SS exhibited a significantly increased risk of developing AA and AD (adjusted OR=3.642…" I can't see in the main results where this comes from. They all appear to be HRs. "AA and AD" could be clarified into "AA or AD", as patients are not developing both. Conclusion – clear. Strength and limitations of this study: Did you 'exclude' confounding factors? Or did you adjust for comorbidities. The second point is also about confounders. The fourth point is also hinting at unmeasured variables/confounders. You need to clarify what you are trying to say about confounders. Is the study design appropriate to answer the research question? Yes Are the methods described sufficiently to allow the study to be repeated? I was not clear what is meant by: Please clarify the phrase 'newly diagnosed with SS' followed by 'We excluded patients who were diagnosed with SS…' (Line 12 p9). I am sure there is a clear rationale for excluding some patients but I could not follow it. Some explanation of why patients with specific diseases were excluded and why the baseline variables for matching were selected needs to be provided. The exclusion of certain patients based on pre-existing conditions and the inclusion of certain variables as confounding factors is not clear. Some details regarding the propensity score matching need to be included in the methods. Method of determining the scores, method of matching (eg nearest neighbour), some indication of the method of balance. Also a reason for matching 4:1 should be included. In addition, please state whether all explanatory variables were included in the adjusted models, or whether any variables were excluded. In the results you say that you used a log-rank test – this should be described (briefly) in the statistical analysis.

	There is considerable detail regarding the ICD codes and diseases in the methods which could be in a table (supplementary details?) which would provide more room for details of your statistical approach). Are the discussion and conclusions justified by the results? As a non-medical reviewer it is not clear to me that the detail in the discussion about the possible mechanism of association is justified by the result of the study. Particularly given that you could not control for various lifestyle factors. The conclusion suggests healthcare professionals should be aware of this risk, it might be useful to see in the discussion some reference to whether being aware of the risk might be useful – what actions could be taken. Are the study limitations discussed adequately? I would like to see more detail on limitations, is SS diagnosis accurate? How accurate is other coding? You mention lifestyle factors but you do not make it clear how important you think these are. In the 'What This Study Adds' box you mention human study, but I don't think you discuss this in the main text. In addition, you say you included COPD as a proxy for smoking but this is not mentioned in the methods or justified. Is the supplementary reporting complete (e.g. trial registration; funding details; CONSORT, STROBE or PRISMA checklist)? I could find no evidence of a reporting checklist. Some more specific language points: Introduction Are there more cases in the fourth decade of life? Specifically people in their 30s compared to people in their 40s/50s? Line 28 p6 – 'Estimates of the incidence of AD range from…' would be a clearer way of phrasing this. Detail regarding the AD incidence is provided, but the link with SS is given for AA. Methods Line 52 p7: 'The data analysed in this study…' it is not just described IS the NHIRD used for the nationwide population-based retrospective cohort study or the LHID? Discussion It is not correct to say the study enrolled patients.

VERSION 1 – AUTHOR RESPONSE

Reviewer #1 (Comments to the Author (Required)):

The paper of Tsai et al is interesting and through. Dealing with an important issue.
A major issue that the authors need to clarify; why wasn't the control group chosen as subjects without Sjogren's syndrome. The current comparison turns the results and methods obscure since it is ca composition of people who pressed claims to the insurance; this is a group of people the readership will find difficult to compare with. I suggest that the control group should be more reasonable and natural.

RE: Thank you for your comment. In this study, we aimed to evaluate whether patients with SS exhibit an increased risk of AA or AD. Control candidate sample populations were selected from individuals in the LHID 2005 who lacked a history of SS. The patient and control cohorts were selected by 1:4 matching according to the following baseline variables: age; sex; co-morbidities; and medication use. (Please see page 9, lines 1214-19 and page 10, lines 1-56)

Reviewer #2 (Comments to the Author (Required)):

This is a large retrospective coding analysis rather than a true population-based study. The 2005 Taiwan longitudinal health insurance database was searched using ICD-9 codes for patients with a new diagnosis of Sjogrens Syndrome. 10941 cases were identified and followed up until 2010 for the occurrence of aortic aneurysms or dissection again using ICD-9 coding retrieval. The same analysis was performed for 43764 matched controls identified from the same database. A small, but significant, difference in aortic aneurysm/ dissection incidence was identified. The true significance of this finding is difficult to determine due to the methodology of the study. I have the following queries:

1. The abstract states that the controls were propensity matched, but there is no detail in the manuscript on how any propensity matching was performed, how potential confounders were scored, and what type of propensity matching analysis was used. It would appear that the controls were actually extracted from the database and matched for a variety of demographics, co-morbidities, and medications. More information is required on exactly how this was performed as this process can easily lead to significant bias with regards to the outcome of interest.
RE: Thank you for your comment. We matched the controls with the diseases and medications mentioned on page 9, lines 124-19 and page 10, lines 1-56. These confounders are known as risk or protective factors for AA. The patients with SS and control cohorts were matched 1:4 based on their propensity score matching, for which the matching tolerance was 0.15 with the nearest neighbour method. The independent variables are demographics, comorbidities, medications, and SS. The propensity matching analysis was performed in the logistic regression model. We added these details in the Methods section. (Please see page 10, lines 97-131).

2. Both SS cases and controls are mostly female. Females are known to have a lower incidence of aortic aneurysms and dissection than males. Yet over the 5-10 year follow-up period over 200 aortic aneurysm and dissection events occurred in 55000 individuals. This would suggest high incidence rates in both cases and controls. The authors need to explain this. Median follow-up time for cases and controls should be included and patient-years follow-up in order to calculate incidence rates. I expect the high event rates maybe a coding issue, as the codes used would identify both non-emergency and emergency aortic aneurysm and dissection diagnoses. Are the codes used restricted to primary discharge diagnosis or any co-morbidity coding?
RE: Thank you for your comment. The average annual incidence of AA in Taiwan is 7.35 per 100,000 persons, and the prevalence is 29.04 per 100,000 persons.1 Our study is different from other pure

epidemiological studies. We selected SS cases from the population first and then matched the cases with controls with comorbidities. We also excluded the younger people from our patient selection. Because the case group in our study has a high age and underlying diseases, the finding that they have a higher AA/AD incidence rate is reasonable. The years of follow up and years to AA/AD have been added to the manuscript. (Please see page 11, lines 41-63). We also integrated the first event of AA/AD coding into the distribution analysis in the supplemental material (Please see Supplement Table 4). All patients were coded with AA/AD for the first time in the Inpatient and ER sections. We determined the presence of SS by recording both ICD-9 codes and data from the Registry of Catastrophic Illness Patient Database to increase the accuracy of our diagnosis.

3. Following on from above, it would be very useful to have age- and gender- specific incidence figures and graphs for aortic aneurysm and dissection occurrence in the whole health insurance population. The same should be done for Sjögren's syndrome. This would put the study findings in context.
RE: Thank you for your suggestion. We added figures with age- and sex-specific incidence rates and graphs showing the occurrence of AA/AD and SS in the health insurance research database. (Please see page 12, lines 45-67 and page 12, lines 172-184)

4. Graphs of Age- and gender- specific rates for aortic aneurysm/dissection in the SS cases and controls would also provide greater clarity for the reader.
RE: Thank you for your suggestion. We included figures showing the age- and sex-specific incidence rates and graphs of the occurrence of AA and AD in the whole health insurance population. (Please see page 12, lines 5-7 and page 12, lines 12-14)

5. The logistic regression analysis is confusing and flawed. Essentially the case and controls have already been matched at baseline, but they are then analysed with logistic regression using the previously matched variables. It is clear that the authors are trying to show that despite other diagnoses occurring during the follow-up period, the diagnosis of Sjögren's syndrome remains independently associated with aortic aneurysm and dissection incidence. Overall, either cases are matched at baseline and then regression analysis is not required, or they are not matched and then regression analysis can be informative. Using both methods doesn't make sense.
RE: We agree with your comment. We used Cox regression for this cohort study to investigate the outcomes and clinical characteristics. We corrected the error (logistic regression and odds ratio) mentioned in the manuscript. We believe that the corrected version is easy to understand and makes sense. (Please see page 3, lines 120 and 185 and page 1620, line 13).

6. The discussion is largely hypothesis generating. It needs to be shortened (particularly paragraphs 2-4) and focused on putting the findings of this study into context with the current literature, and the impact of the findings on clinical care/future research.
RE: Thank you for your valuable comment. We refined and shortened the redundant part of the Discussion. We believe that the manuscript is easy to read and understand now. (Please see Discussion paragraphs 2-3). We added these sentences to the Discussion section: "Our research findings should remind healthcare providers of new information that SS patients exhibit an increased risk for AA or AD. Healthcare professionals should be aware of these life-threatening aortic events and aim to make early diagnosis of AA or AD. When SS patients present with chest, back, or abdominal symptoms, the possibility of AA or AD should be considered, with a specific and rapid examination." (Please see page 1617, lines 187-19 12 and page 1720, lines 13-415)

7. Finally, why is study being submitted 8 years after final follow-up period?
RE: Thank you for your comment. We used ICD-9 as a diagnostic code in this retrospective cohort study. In fact, the latest version is ICD-10, which has been used for several years. To ensure that the

diagnoses of patients were consistent, we only used data from the ICD-9 era. Therefore, there is a time gap between the final follow-up and the present time.

Reviewer #3 (Comments to the Author (Required)):

Reviewers Comments

1. In general this is clear and easy to read. The discussion focusses heavily on the possible mechanisms associating SS with AA/AD, which is not directly related to the study. More detail is needed regarding the methodology of the propensity score matching.
RE: Thank you for your valuable comment. We refined and shortened the redundant parts of the Discussion section. We believe that the manuscript is easy to read and understand now. (Please see Discussion paragraphs 2-3). We also added the propensity score matching method to the Methods section. (Please see page 9, lines 156-167 and page 10, lines 97-131)

2. The implications of the study need to be linked to the conclusion, given an association between SS and AA/AD is found, are there implications for healthcare professionals?
RE: We added these sentences to the Discussion section: “Our research findings should remind healthcare providers of new information that SS patients exhibit an increased risk for AA or AD. Healthcare professionals should be aware of these life-threatening aortic events and aim to make early diagnosis of AA or AD. When SS patients present with chest, back, or abdominal symptoms, the possibility of AA or AD should be considered, with a specific and rapid examination.” (Please see page 167, lines 187-192 and page 1720, lines 13-415).

3. Is the abstract accurate, balanced and complete? Objective is clear
RE: Thank you for your comment. We appreciate your affirmation.

4. Methods – you talk about using Cox regression to estimate odds ratios but I am not sure this is what happened. You predominantly used Cox regression to estimate HRs. You don’t mention propensity score matching in the methods. I would like the outcome clearer in the methods. “All medical conditions for each case and control were categorized using the International Classification of Diseases, 9th Revision (ICD-9).” Is possibly more detail than necessary, with not quite enough detail on the statistical approach.
RE: We used Cox regression for this cohort study to investigate to outcomes and clinical characteristics. (Please see page 11, lines 149-1712). We corrected the error (logistic regression and odds ratio) mentioned in the manuscript. We believe that the corrected version is easy to understand and makes sense. (Please see page 3, lines 120 and 185 and page 1620, line 31). The dependent variable is AA or AD. The time variable is the follow-up year. The independent variables are demographics, comorbidities, medications, and SS. We matched the controls with the diseases and medications mentioned on page 9, lines 1514-19 and page 10, lines 1-56. These confounders are known risk or protective factors for AA. The SS patient and control cohorts were matched 1:4 based on their propensity score matching, for which the matching tolerance was 0.15 with the nearest neighbour method. The independent variables are demographics, comorbidities, medications, and SS. The propensity matching analysis was performed in the logistic regression model. We added these details in the Methods section. (Please see page 10, lines 97-131).

5. Results It says that “patients with SS exhibited a significantly increased risk of developing AA and AD(adjusted OR=3.642…” I can’t see in the main results where this comes from. They all appear to be HRs. “AA and AD” could be clarified into “AA or AD”, as patients are not developing both.
RE: We agree with your comment. We used Cox regression for this cohort study to investigate the outcomes and clinical characteristics. We corrected the error (logistic regression and odds ratio) mentioned in the manuscript. (Please see page 3, lines 120 and 185 and page 157, line 1). Additionally, we changed all of the instances of “AA and AD” to “AA or AD” in the manuscript. (Please

see page 3, lines 76, 15,18 and 189; page 4, lines 1 and 5; page 7, lines 102, 113, and 157; page 9, line 910; page 12, line 127; page 1620, line 163; and page 129, lines 7 and 1412). We believe that the corrected version is easy to understand and makes sense.

6. Conclusion – clear.
RE: Thank you for your comment. We appreciate your affirmation.

7. Strength and limitations of this study: Did you 'exclude' confounding factors? Or did you adjust for comorbidities. The second point is also about confounders. The fourth point is also hinting at unmeasured variables/confounders. You need to clarify what you are trying to say about confounders.
RE: Thank you for your valuable comment. The exclusion criteria from our study included Turner syndrome, aortic coarctation, bicuspid aortic valve, Marfan syndrome, and Ehler-Danlos syndrome. These diseases were excluded because they are accompanied by structural abnormalities of the aorta or were genetic disorders. We excluded these conditions because we wanted to evaluate the association between SS and AA/AD and thus minimized the interference of anatomical, congenital, or hereditary problems. Other diseases are matched, because they are known risk or protective factors for AA or AD. We revised the strengths and limitations of this study to clarify our comments about confounders. (Please see page 5, lines 2-910). We believe that the corrected version is easy to understand and makes sense.

8. Is the study design appropriate to answer the research question? Yes
RE: Thank you for your comment. We appreciate your affirmation.

9. Are the methods described sufficiently to allow the study to be repeated?I was not clear what is meant by: Please clarify the phrase 'newly diagnosed with SS' followed by 'We excluded patients who were diagnosed with SS…' (Line 12 p9). I am sure there is a clear rationale for excluding some patients but I could not follow it.
RE: Thank you for your valuable comment. The phrase 'newly diagnosed with SS' means that a patient was not diagnosed with SS prior to 2000. We excluded patients who were diagnosed with SS before 2000. We revised the phrase in the Sampled patients section. (Please see page 9, lines 67-913). We believe that the corrected version is easy to understand and make sense.

10. Some explanation of why patients with specific diseases were excluded and why the baseline variables for matching were selected needs to be provided.
11. The exclusion of certain patients based on pre-existing conditions and the inclusion of certain variables as confounding factors is not clear.
RE: Thank you for your valuable comment. The exclusion criteria from our study included Turner syndrome, aortic coarctation, bicuspid aortic valve, Marfan syndrome, and Ehler-Danlos syndrome. These diseases were excluded because they were structural abnormalities of the aorta or genetic disorders. We excluded these conditions because we wanted to evaluate the association between SS and AA/AD and thus minimized the interference of anatomical, congenital, or hereditary problems. Other diseases were matched because they were known risk or protective factors for AA or AD.

12. Some details regarding the propensity score matching need to be included in the methods. Method of determining the scores, method of matching (eg nearest neighbour), some indication of the method of balance. Also a reason for matching 4:1 should be included.
RE: Thank you for your valuable comment. The SS patient and control cohorts were matched 1:4 based on their propensity score matching, for which the matching tolerance was 0.15 with nearest neighbour method. The independent variables are demographics, comorbidities, medications, and SS. The propensity matching analysis was performed in the logistic regression model. We added these details in the Methods section. (Please see page 10, lines 97-131). We used 1:4 matching,

because a 1:4 case-to-control ratio showed the greatest effective sample size to achieve 80% statistical power.2

13. In addition, please state whether all explanatory variables were included in the adjusted models, or whether any variables were excluded.
RE: Thank you for your comment. The exclusion criteria from our study included Turner syndrome, aortic coarctation, bicuspid aortic valve, Marfan syndrome, and Ehler-Danlos syndrome. These diseases were excluded because they were structural abnormalities of the aorta or genetic disorders. We excluded these conditions because we wanted to evaluate the association between SS and AA/AD and thus minimized the interference of anatomical, congenital or hereditary problems. Other diseases were matched because they were known risk or protective factors for AA or AD. We listed the variables in Table 3 to provide information for the readers. Compared to other known risk factors of AA/AD, such as male sex, old age, and hypertension, SS has a relatively higher adjusted hazard ratio for AA/AD development. We think that this information will be useful and interesting for BMJ open readers.

14. In the results you say that you used a log-rank test – this should be described (briefly) in the statistical analysis.
RE: Thank you for your valuable comment. We added the description “Kaplan-Meier curve with log-rank test” to the Statistical analysis section. (Please see page 11, lines 152-173). We believe that the corrected version is easy to understand.

15. There is considerable detail regarding the ICD codes and diseases in the methods which could be in a table (supplementary details?) which would provide more room for details of your statistical approach).
RE: Thank you for your valuable comment. We integrated the ICD-9-CM code of these diseases into a table in the supplementary material (Supplement Table 1). (Please see page 10, lines 175-196). We believe that the revised version is easy to understand.

16. Are the discussion and conclusions justified by the results? As a non-medical reviewer it is not clear to me that the detail in the discussion about the possible mechanism of association is justified by the result of the study. Particularly given that you could not control for various lifestyle factors. The conclusion suggests healthcare professionals should be aware of this risk, it might be useful to see in the discussion some reference to whether being aware of the risk might be useful – what actions could be taken.
RE: Thank you for your valuable comment. We added these sentences to the Discussion section: “Our research findings should remind healthcare providers of new information that SS patients exhibit an increased risk for AA or AD. Healthcare professionals should be aware of these life-threatening aortic events and aim to make early diagnosis of AA or AD. When SS patients present with chest, back, or abdominal symptoms, the possibility of AA or AD should be considered, with a specific and rapid examination.” (Please see page 167, lines 187-192 and page 1720, lines 13-415).

17. Are the study limitations discussed adequately? I would like to see more detail on limitations, is SS diagnosis accurate? How accurate is other coding? You mention lifestyle factors but you do not make it clear how important you think these are. In the ‘What This Study Adds’ box you mention human study, but I don’t think you discuss this in the main text. In addition, you say you included COPD as a proxy for smoking but this is not mentioned in the methods or justified.
RE: Thank you for your valuable comment. We determined the presence of SS by recording both ICD-9 codes and data from the Registry of Catastrophic Illness Patient Database to increase the accuracy of our diagnosis. (Please see page 9, line 7-9). The accuracy of the diagnoses in the NHIRD, particularly diagnoses of major diseases (e.g., acute coronary syndrome and stroke), has been corroborated. 3 4 (Please see page 8, lines 10-11). Cigarette smoking is the most important

risk factor of COPD. 5-7 Therefore, we included COPD as a proxy for smoking. We added these points to the Discussion to clarify the limitations of our study. (Please see page 1020, lines 67-98).

18. Is the supplementary reporting complete (e.g. trial registration; funding details; CONSORT, STROBE or PRISMA checklist)? I could find no evidence of a reporting checklist.
RE: Thank you for your valuable comment. The funding details are provided on page 21, lines 113-169. The STROBE checklist had been uploaded with the revision files.

19. Some more specific language points: Introduction Are there more cases in the fourth decade of life? Specifically people in their 30s compared to people in their 40s/50s?
RE: Thank you for your suggestion. We added figures with age- and sex-specific incidence rates and graphs showing the occurrence of AA/AD and SS from the health insurance research database. (Please see page 12, lines 45-67 and page 12, lines 172-194).

20. Line 28 p6 – 'Estimates of the incidence of AD range from…' would be a clearer way of phrasing this. Detail regarding the AD incidence is provided, but the link with SS is given for AA.
RE: Thank you for your valuable comment. We revised the section to make it clear and easier to read and understand. (Please see page 6, lines 12-134).

21. Methods Line 52 p7: 'The data analysed in this study…' it is not just described IS the NHIRD used for the nationwide population-based retrospective cohort study or the LHID?
RE: Thank you for your valuable comment. The data analysed in this study were acquired from the Longitudinal Health Insurance Database 2005 (LHID 2005), which is a subgroup database of the Taiwan National Health Insurance Research Database (NHIRD) and is used for nationwide population-based retrospective cohort studies. (Please see page 8, lines 12-45 and page 9, lines 56-89).

22. Discussion
It is not correct to say the study enrolled patients.
RE: Thank you for your comment. We will shift the word 'enrolled' to 'included' to clarify our meaning. (Please see page 137, line 102). We believe that the corrected version is easy to understand and makes sense.

References

1. Wang SW, Huang YB, Huang JW, et al. Epidemiology, Clinical Features, and Prescribing Patterns of Aortic Aneurysm in Asian Population From 2005 to 2011. Medicine 2015;94(41):e1716. doi: 10.1097/md.0000000000001716 [published Online First: 2015/10/16]
2. Hong EP, Park JW. Sample size and statistical power calculation in genetic association studies. Genomics Inform 2012;10(2):117-22. doi: 10.5808/GI.2012.10.2.117
3. Cheng CL, Kao YH, Lin SJ, et al. Validation of the National Health Insurance Research Database with ischemic stroke cases in Taiwan. Pharmacoepidemiology and drug safety 2011;20(3):236-42. doi: 10.1002/pds.2087 [published Online First: 2011/02/26]
4. Mao CT, Tsai ML, Wang CY, et al. Outcomes and characteristics of patients undergoing percutaneous angioplasty followed by below-knee or above-knee amputation for peripheral artery disease. PloS one 2014;9(10):e111130. doi: 10.1371/journal.pone.0111130
5. Wright JL, Churg A. Animal models of cigarette smoke-induced COPD. Chest 2002;122(6 Suppl):301S-06S.
6. Churg A, Cosio M, Wright JL. Mechanisms of cigarette smoke-induced COPD: insights from animal models. American journal of physiology Lung cellular and molecular physiology 2008;294(4):L612-31. doi: 10.1152/ajplung.00390.2007

7. Mannino DM. Smoking and Emphysema: Looking Beyond the Cigarette. Chest 2015;148(5):1126-27. doi: 10.1378/chest.15-1454

VERSION 2 – REVIEW

REVIEWER	Dominic PJ Howard Oxford University, UK
REVIEW RETURNED	21-Jun-2018

GENERAL COMMENTS	The revised manuscript is greatly improved and the majority of the reviewers queries appear to have been responded to.

REVIEWER	Kate Honeyford Imperial College, London, UK
REVIEW RETURNED	02-Jul-2018

GENERAL COMMENTS	The revisions now make the paper easy to understand and the methods can be followed. Within the methods: p13: It is not clear what is meant by the phrase 'Patients had a tracking time < 6months.' Please give a reason for the exclusions (you mention it in the response to reviewers and in the discussion but it should be stated briefly in the methods. It is not clear what is meant by the sentence 'The independent variables were demographics, co-morbidities, medications, and SS.' It is not clear what this sentence adds: The propensity matching analysis was performed in the logistic regression model. Details of the PSM should be in the statistical analysis section (or at least in one neat paragraph – nearest neighbour, 1:4 matching, logistic regression) This should be easily repeatable for some who wants to do a similar PSM. It is all there it is just not that easy to find. Somewhere I would like to see what variables were included in the Cox regression – ideally in statistical analysis section – you can point the reader to a table. (I think it is Table 3). It is common to say 'we retained all explanatory variables in the fully adjusted model' or something. Results p14 (I think you may have lost some text relating to PSS (maybe just an initial) on editing.) The phrase 'We integrated….' I think should be 'We have included…' I'm not sure but it is not clear what is meant. Discussion The limitations section is still limited to confounding variables – there are limitations in using administrative data (you are reliant on coding which can have errors) and there are limitations in any statistical approach (including PSM)

VERSION 2 – AUTHOR RESPONSE

Point-by-point response to the Reviewers

Reviewer #3 (Comments to the Author (Required)):

1. It is not clear what is meant by the phrase ‘Patients had a tracking time < 6months.’ Please give a reason for the exclusions (you mention it in the response to reviewers and in the discussion but it should be stated briefly in the methods.

RE: Thank you for your comment. Previous studies have demonstrated that both SS and AA/AD are induced by chronic inflammation.1-4 We considered AA/AD events that occurred with less than 6 months of tracking time to have a relatively low association with the SS. Therefore, we excluded the patients who had a tracking time less than 6 months in order to decrease the probability of including AA/AD cases that went undiagnosed before SS diagnosis. We have added these details in the Methods section (Please see page 9, lines 17-18).

2. It is not clear what is meant by the sentence ‘The independent variables were demographics, co-morbidities, medications, and SS.’

RE: Thank you for your comment. We have refined and added the following sentence to the Discussion section: The dependent variables were AA and AD. We believe that the manuscript is now easier to read and understand. (Please see page 10, line 13)

3. It is not clear what this sentence adds: The propensity matching analysis was performed in the logistic regression model.

RE: Thank you for your comment. We moved this sentence to the Statistical analysis section and revised it as: Propensity matching analysis was performed in the logistic regression model. The potential confounders were index year, gender, age, comorbidities, and medications. The match tolerance was 0.15 with the nearest neighbour method. The study comparison cohort-matching ratio was 4-fold (study: comparison = 1:4). We believe that the manuscript is now easier to read and understand. (Please see page 11, lines 7-10)

4. Details of the PSM should be in the statistical analysis section (or at least in one neat paragraph – nearest neighbour, 1:4 matching, logistic regression) This should be easily repeatable for some who wants to do a similar PSM. It is all there it is just not that easy to find.

RE: Thank you for your comment. We moved this sentence to the Statistical analysis section and revised it as: Propensity matching analysis was performed in the logistic regression model. The potential confounders were index year, gender, age, comorbidities, and medications. The match tolerance was 0.15 with the nearest neighbour method. The study comparison cohort-matching ratio was 4-fold (study: comparison = 1:4). We believe that the manuscript is now easier to read and understand (Please see page 11, lines 7-10)

5. Somewhere I would like to see what variables were included in the Cox regression – ideally in statistical analysis section – you can point the reader to a table. (I think it is Table 3). It is common to say ‘we retained all explanatory variables in the fully adjusted model’ or something.

RE: Thank you for your comment. We have refined and added the following sentence to the Statistical analysis section: As shown in supplement table 4, all explanatory variables in the fully adjusted model

were retained. We believe that the manuscript is now easier to read and understand. (Please see page 11, lines 16-17)

Results

p14

6. (I think you may have lost some text relating to PSS (maybe just an initial) on editing.)

RE: Thank you for your comment. We have presented the result of the subgroup analysis of PSS and SSS in the Results section (Please see page 13, lines 6-9). The subgroup analysis revealed that patients with PSS or SSS both exhibited significantly increased risks for developing AA/AD compared to patients without SS (adjusted HR = 1.753, 95% CI = 1.108-9.382, P = 0.042; adjusted HR = 3.693, 95% CI = 2.520-5.411, P < 0.001, Table 4).

7. The phrase 'We integrated….' I think should be 'We have included…' I'm not sure but it is not clear what is meant.

RE: Thank you for your valuable comment. We will change the word 'integrated' to 'have included' to clarify our meaning. (Please see page 13, line 9). We believe that the corrected version is easier to understand and makes more sense.

Discussion

8. The limitations section is still limited to confounding variables – there are limitations in using administrative data (you are reliant on coding which can have errors) and there are limitations in any statistical approach (including PSM)

RE: Thank you for your valuable comment. We have added the following sentences to the limitations section: This is a database study using NHIRD. All medical conditions for each case and the controls were categorized using the ICD-9-CM, in which diagnostic codes (up to five each) are coded. There may be a small number of coding errors or missing information when using this kind of administrative data, and limitations are bound to exist in any statistical method, even the propensity score matching. We believe that the manuscript is now easier to read and understand. (Please see page 20, lines 12-17)

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