PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Is having asthma associated with an increased risk of dying from cardiovascular disease? A prospective cohort study of 446 346 Taiwanese adults
AUTHORS	Strand, Linn Beate; Tsai, Min; Wen, Chi-Pang; Chang, Shu-Sen; Brumpton, Ben

VERSION 1 – REVIEW

REVIEWER	Izabela Tuleta Department of Cardiology and Angiology, University of Muenster, Muenster, Germany
REVIEW RETURNED	25-Nov-2017

GENERAL COMMENTS	Strand et al. found an increased risk of dying from cardiovascular diseases, coronary heart diseases and stroke in asthma individuals, especially in those with active asthma. It is a very interesting study, since there are no consistent results in the literature regarding potential link between asthma and cardiovascular diseases. The strength of this study is a very high number of participants, collection of a relatively detailed data on asthma itself and history of cardiovascular diseases and the use of spirometry to exclude COPD. The limitation of the study is the uncertain diagnosis of asthma and, giving the descriptive nature of this work, the inability to prove a causative link between asthma and cardiovascular diseases. Do the authors have any explanation why the association between asthma and cardiovascular diseases/ stroke was stronger for men than for women? Patients who used asthma medication less frequently than daily were grouped together with other patients with only a history of asthma into the same subgroup of “non-active asthma”. This makes this group very heterogeneous. The authors could mention this in the limitations of the study. Please correct some grammatical/spelling errors, e.g. page 17, line 9: The underlying reasons …. “are” instead of “is”.

REVIEWER	Runa Vavia Fenger Danish Medicines Agency, Denmark
REVIEW RETURNED	02-Dec-2017

GENERAL COMMENTS	The question "does asthma lead to CVD mortality" is very difficult to answer in an observational study. If asthma and CVD share pathogenesis, it can lead to first asthma and then CVD. In that case, asthma is certainly not a modifiable risk factor. It should be thoroughly discussed that the study does not give any indication that asthma leads to CVD. Had the authors had the possibility/data to

	test and exclude that a substantial amount of other chronic illnesses or conditions also were associated with CVD, the results would have been more convinging. Exclusion of 140000+ individuals should be discussed. Sensitivity anaylses of ”what would the results look like” if the different scenarios of associations or no associations could be estimated and shown as a sensitivity anayses. Discussion of different types of asthma could be included The residual confounding and validation of registies is only slightly touched upon.

VERSION 1 – AUTHOR RESPONSE

Dear Reviewers,
Thank you for giving us these valuable comments. We have responded point by point to each comment below and included your suggestions in the revised manuscript where appropriate.

Reviewer: 1
Comments to the Author
Strand et al. found an increased risk of dying from cardiovascular diseases, coronary heart diseases and stroke in asthma individuals, especially in those with active asthma. It is a very interesting study, since there are no consistent results in the literature regarding potential link between asthma and cardiovascular diseases. The strength of this study is a very high number of participants, collection of a relatively detailed data on asthma itself and history of cardiovascular diseases and the use of spirometry to exclude COPD. The limitation of the study is the uncertain diagnosis of asthma and, giving the descriptive nature of this work, the inability to prove a causative link between asthma and cardiovascular diseases. Do the authors have any explanation why the association between asthma and cardiovascular diseases/ stroke was stronger for men than for women?

We thank the reviewer for the comments. Unfortunately, we did not have a clear reason why we observed a sex difference in the association. If anything the literature would support that females have worse asthma control than males throughout adulthood, suggesting that we would observe a stronger association in women. However this is not the case. We do not have any further speculation but hope further studies will investigate this finding. We have now clarified the need for further studies on sex differences in the conclusion. (Page 9/ Paragraph 3)

Patients who used asthma medication less frequently than daily were grouped together with other patients with only a history of asthma into the same subgroup of “non-active asthma”. This makes this group very heterogeneous. The authors could mention this in the limitations of the study.

We have now added this comment to the limitations section of the manuscript.(Page 18/ Paragraph 3)

Please correct some grammatical/spelling errors, e.g. page 17, line 9: The underlying reasons …. “are” instead of “is”.

Thank you. We have now made the correction.(Page 17/ Paragraph 1)

Reviewer: 2
The question "does asthma lead to CVD mortality" is very difficult to answer in an observational study. If asthma and CVD share pathogenesis, it can lead to first asthma and then CVD. In that case, asthma is certainly not a modifiable risk factor. It should be thoroughly discussed that the study does not give any indication that asthma leads to CVD. Had the authors had the possibility/data to test and

exclude that a substantial amount of other chronic illnesses or conditions also were associated with CVD, the results would have been more convinging.

We thank the reviewer for the comments. We have recognised the possibility of confounding in the Discussion section. However, we did adjust for diabetes, hypertension, body mass index, total cholesterol, triglyceride, history of heart disease/heart surgery/use of heart drug, and history of stroke in the multivariable analyses. We also conducted two sensitivity analyses – in the first sensitivity analysis we excluded participants with a history of heart disease, heart surgery, use of heart medications and a history of stroke at baseline, and in the second sensitivity analysis we excluded participants with possible chronic obstructive pulmonary disease at baseline. The results of sensitivity analyses were generally similar to those of the main analyses although the statistical precision of effect estimates attenuated due to a decrease in sample size by excluding a significant number of participants.

Exclusion of 140000+ individuals should be discussed. Sensitivity anaylses of ”what would the results look like” if the different scenarios of associations or no associations could be estimated and shown as a sensitivity anayses.

We thank the reviewer for the comment and have added a discussion of this exclusion due to missing information to the limitations section of the manuscript.(Page 19/ Paragraph 1)

Discussion of different types of asthma could be included.

We have now included a brief discussion of different phenotypes in the manuscript.(Page 18/ Paragraph 2)

The residual confounding and validation of registies is only slightly touched upon.

We thank the reviewer for the comments. We now specifically mention an example of residual confounding which might influence the study. We also added a reference showing good accuracy of cause-of-death coding for heart diseases and stroke in Taiwan.(Page 19/ Paragraph 2 and Page 7 / Paragraph 1)