

BMJ -  
Decision on  
Manuscript  
ID  
BMJ-2018-  
047517.R1

**Body:** 20-Feb-2019

Dear Dr. Song

Manuscript ID BMJ-2018-047517.R1 entitled "Stress-related disorders and risk of cardiovascular disease: a population-based sibling-controlled cohort study"

Thank you for sending us your paper. We sent it for external peer review again. We recognise its potential importance and relevance to general medical readers, but I am afraid that we have not yet been able to reach a final decision on it because several important aspects of the work still need clarifying.

We hope very much that you will be willing and able to revise your paper as explained below in the reviewer's comments, so that we will be in a better position to understand your study and decide whether the BMJ is the right journal for it. We are looking forward to reading the revised version and, we hope, reaching a decision.

When you return your revised manuscript, please note that The BMJ requires an ORCID iD for corresponding authors of all research articles. If you do not have an ORCID iD, registration is free and takes a matter of seconds.

Yours sincerely,

Tiago Villanueva  
Associate Editor  
tvillanueva@bmj.com

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In your response please provide, point by point, your replies to the comments made by the reviewers, explaining how you have dealt with them in the paper.

\*\* Comments from the external peer reviewers\*\*

Reviewer: 1

Recommendation:

Comments:

Thank you for the opportunity to evaluate the revised version of the paper. I find that the authors have dealt satisfactorily with my comments to the original manuscript.

One small comment for the new version: In table 1 age and follow up time is now relevantly described with median and IQR - but formally IQR is the distance between the 25 and 75 percentile, that is one figure - the given figures must be the 25 and 75 percentiles themselves.

Best regards  
Henrik Bøggild

Additional Questions:

Please enter your name: Henrik Bøggild

Job Title: Associate professor

Institution: Public Health and Epidemiology, Health Science and Technology, Aalborg University

Reimbursement for attending a symposium?: No

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Reviewer: 2

Recommendation:

Comments:

The current resubmitted manuscript includes details of a population-based cohort study in Sweden exploring the link between psychiatric disorders that occur in response to severe acute stress and the development of CVD. Using novel sibling-controlled and population-matched designs the authors were able to provide information on a large number of participants (ca. 130,000 patients with the disorder, 170,000 full siblings, and 1.4 million unexposed members of the general population). The authors report finding that there was a consistent, increased association between having a disorder and a future CVD event, which was generally robust to all sensitivity analyses. Furthermore, there was a signal suggesting that this association was stronger in the 1st year post diagnosis compared to after 1 year post diagnosis.

The authors have done a very good job of responding to the comments of the reviewers and the manuscript is noticeably better. Below are a couple of extra points which the authors may consider.

In general, the more I think about the terminology of 'stress-related disorders,' which the authors have a very specific concept of, the more I am concerned that people might conflate this with a variety of mood and anxiety disorders. Whilst I appreciate that the disorders that are included in the manuscript aren't clustered in any formal way (e.g., DSM-V), they are responses to severe acute stress and, maybe, this is the way that they

might be best reported throughout the manuscript. The addition of the acute component certainly provides some distinction between PTSD and something like GAD.

Page 3 Line 55 (abstract), rather than familial factors I would suggest that this is changed to familial history. The sibling cohorts share a history, but they may still have different familial factors more broadly.

Page 4 Line 62-63 (summary box), tied to my main comment above, the authors still include the comment "Accumulating evidence suggests a role of psychiatric reactions to severe stress in cardiovascular disease..." and then go on to note that this is derived from males samples and PTSD related research. Depression is another example that could be included in the "psychiatric reactions to severe stress" category and there is ample evidence from samples of men and women about its links to the development and progression of CVD. I would suggest a small rewording of this section to make it clearer that this is specifically focused on reactions to acute severe stress.

In the patient and public engagement section, whilst it is true that because of the nature of the data it was not possible for patients or members of the public to influence study design, these key stakeholders can always be included when generating the research question. I appreciate that this didn't happen in the context of the current study, but this should not be attributed to the fact that the study leveraged a nationwide registry.

Peppered throughout the manuscript, the authors talk about heart failure being an acute CVD. In reality, the majority of non-post MI heart failure comes from slower processes and is predominantly considered a chronic onset condition. Given the way the analyses are set up (i.e., if MI precedes heart failure the MI becomes the incident event not the heart failure) some tempering of the wording for the acute heart failure phenomenon is warranted.

With regards to my previous point about Table 1 only reporting psychiatric comorbidity in the effected cohort only, I appreciate the points raised by the authors around the relatively small proportion of individuals who, outside the effected cohort, may have a psychiatric comorbidity and the adjustment of this variable in the analyses. However, I would still recommend including the rates in all 3 groups. If anything, this would reinforce the above points.

Simon Bacon  
Concordia University

Additional Questions:  
Please enter your name: Simon Bacon

Job Title: Professor

Institution: Concordia University & CIUSSS-NIM

Reimbursement for attending a symposium?: No

A fee for speaking?: No

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Reviewer: 3

Recommendation:

Comments:  
All comments have been suitably addressed.

Additional Questions:  
Please enter your name: Brian Lee

Job Title: Associate Professor

Institution: Drexel University School of Public Health

Reimbursement for attending a symposium?: No

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Reviewer: 4

Recommendation:

Comments:

The authors have addressed my comments.

Additional Questions:

Please enter your name: Angie Wade

Job Title: Professor of Medical Statistics

Institution: UCL Great Ormond Street Institute of Child Health

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