Manuscript ID: BMJ-2018-047517.R1

Dear Editor:

Thank you for your second review of our manuscript entitled “Stress-related disorders and risk of cardiovascular disease: a population-based sibling-controlled cohort study” and for the opportunity to submit a revised version for publication in BMJ. In accordance to these extra comments from the reviewers and editors, we have now made additional modifications to our manuscript as indicated point by point below. We hope that these improvements are satisfactory and that you will find our manuscript suitable for publication in BMJ.

Yours sincerely,

Huan Song
On behalf of all co-authors

Center of Public Health Sciences
Faculty of Medicine
University of Iceland
Sturlugata 8, 101 Reykjavík,
Iceland

Responses to the comments of referees*:

*All page and line marks correspond to the line numbers of the '**Revised Manuscript_clean**' version.

** 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.

Authors' responses: Thank you for your comments. We agree and have now corrected the IQRs as the differences between the 75th and 25th percentiles. Please refer to the Table 1 (Page 22) in the revised manuscript.

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.

Authors' responses: Thank you for this important comment. In general, there is no widely accepted term for this group of diseases (i.e., PTSD, acute stress reaction, adjustment disorder and other severe stress reactions), and we have intensely discussed the terminology when drafting this manuscript. This group of psychiatric disorders (F43) is in ICD-10 called "Reaction to severe stress, and adjustment disorders", and in ICD-11 the category is labelled "Disorders specifically associated with stress". In DSM-5, these conditions are included in a new diagnostic category 'trauma- and

stressor-related disorders'. However, the DSM-5 and ICD-11 categories also includes two stress-related attachment diagnoses not included here as they are used specifically for children. (https://dsm.psychiatryonline.org/doi/full/10.1176/appi.books.9780890425596.dsm07). In a series of studies in the Danish population Gradus JL et al. called these diseases ('ICD-10 F43') simply 'stress disorders' (BMJ open 2015; Clin Epidemiol 2017). Similarly, in our recently published paper (Song H, JAMA 2018) focusing on this group of psychiatric conditions in the context of autoimmune disease, we used 'stress-related disorders'.

As the reviewer suggested, 'reactions to severe acute stress' could be proposed as an alternative to 'stress-related disorders'. Yet, this description does not fit the clinical criteria of 'adjustment disorder' where the stressor may be a normal life event, not necessarily severe, acute or transient although experienced as significantly stressful by some individuals (e.g. moving to a new place).

Therefore, to maintain consistency with our previous publication, we prefer to keep the same label as before "stress-related disorders" but are willing to reconsider our position on the editor's request.

Nevertheless, we recognize the reviewer's point of having a clear definition of this category of disorders throughout the paper and whenever we disseminate the results of our study, to avoid any over-interpretation of the findings.

In the 'Abstract', we introduced this definition (Page 2, lines 32-34):
'Participants*: Through the Swedish National Patient Register, 136,637 patients with stress-related disorders, including posttraumatic stress disorder (PTSD), acute stress reaction, adjustment disorder, and other stress reactions, were identified from 1987 to 2013.'*

For the 'Summary box', since this is only a short explanation on the significance of our study, we think it is not necessary to introduce any new definition that not familiar with the readers. We therefore summarize these conditions as 'severe stress reactions to significant life events or trauma'.

(Page 4, lines 62-63)
'*Accumulating evidence suggests a role of severe stress reactions to significant life events or trauma in cardiovascular disease (CVD).'*

(Page 4, lines 69-73)
'*After careful control of familial background (through a sibling design), multiple risk factors, and comorbidities, our results demonstrate that severe stress reactions to significant life events or trauma, indicated by a clinical diagnosis of PTSD, acute stress reaction, or adjustment disorder and other stress reactions, are associated with considerably elevated risk of multiple types of CVDs.*'

In the 'Introduction' part of the manuscript, we further specified the definition of 'stress-related disorders':

(Page 5, lines 88-94)

'Stress-related disorders are a group of psychiatric disorders where one of the diagnostic criteria is the presence of a preceding stressful life event. Depending on the type of stressor, the reported symptoms, and their duration, such disorders are mainly categorized as acute stress reaction, post-traumatic stress disorder (PTSD), and adjustment disorder[14]. The presence of a life-threatening traumatic event is a prerequisite for the former two disorders while adjustment disorder generally refers to physical or psychological distress ('adjustment syndromes'[15]) triggered by an identifiable and significant life change.'

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.

Authors' responses: We agree with your concern about possible misunderstanding of 'familial factors'. In the revised manuscript, we have specified "familial factors" as 'genetic background and early-life environmental factors'.

See 'Abstract' part (Page 3, lines 54-56):

'***Conclusion*** *Stress-related disorders are robustly associated with multiple types of CVDs, independently of genetic background, early-life environmental factors, and psychiatric comorbidity.*'

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.

Authors' responses: Thank you for your comments. As explained above, we have reworded this part as:

(Page 4, lines 62-63)

'Accumulating evidence suggests a role of severe stress reactions to significant life events or trauma in cardiovascular disease (CVD).'

(Page 4, lines 69-73)

'*After careful control of familial background (through a sibling design), multiple risk factors, and comorbidities, our results demonstrate that severe stress reactions to significant life events or*

trauma, indicated by a clinical diagnosis of PTSD, acute stress reaction, or adjustment disorder and other stress reactions, are associated with considerably elevated risk of multiple types of CVDs.'

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.

Authors' responses: We agree and have made the suggested change. In the revised manuscript, we have deleted 'As this study leverages nationwide register data'.

'Method' part (Page 10, lines 217-218)

*'**Patient and Public Involvement***

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study.'

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.

Authors' responses: Thank you for this important comment. We indeed did not consider 'heart failure' as an acute CVD in our analyses and we have now corrected any statements in the manuscript with such inferences. Our analyses on acute CVDs (defined on Page 9, lines 199-203: '*We further analyzed certain acute CVD events, i.e., cardiac arrest, acute myocardial infarction, and acute cerebrovascular disease……*') was limited to cardiac arrest, acute myocardial infarction, and acute cerebrovascular disease (i.e., arachnoid bleeding, intracerebral haemorrhage, or cerebral infarction, Supplementary Table 2)

In addition, we stated in the 'Method' section (Page 7, line 138-140): '*Follow-up of all study participants started from the index date until the first primary diagnosis of CVD (**any or specific subtype**), death, emigration, or the end of follow-up (December 31, 2013), whichever occurred first.*' Thus, in analyses on subtypes of CVDs, both first ischemic heart disease (e.g., MI) and first heart failure, if happened in the same individual, contribute to the calculation of their corresponding type-specific HR. Namely, the HR of 'heart failure' represents the point estimates for heart failure occurring with or without a previous MI.

In the revised manuscript, we have now deleted the inference to that 'heart failure' is an 'acute CVD'

'Discussion' part (Page15, lines 342-346)

'Clinical observations[37,38] suggest that experiencing severe emotional or physical stress may trigger immediate cardiovascular consequences, such as heart attack and sudden cardiac arrest~~, and heart failure,~~ even in apparently healthy individuals. Our results consolidate these reported associations by showing that a clinically confirmed stress-related disorder (requiring a preceding occurrence of a trauma or significant life stressor) is also associated with these acute CVD events.'

We have now also specified 'acute CVD events' in the ´Discussion´ part (Page 16, lines 372-376):

'However, the additional analyses on acute and severe CVD events (i.e., cardiac arrest, acute myocardial infarction, and acute cerebrovascular diseases) that typically resulting in prompt hospital visit and medical care provide further evidence supporting an immediate impact of stress-related disorders on CVD, since such analyses are less likely to be affected by surveillance bias or reverse causality.'

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.

Authors' responses: Thank you for your comment. In the revised Table 1, we have added the number of subjects who developed psychiatric disorders among the unaffected full siblings and the matched unexposed individuals, between three months before and one year after the study entry.

Reviewer: 3

Recommendation:

Comments:

All comments have been suitably addressed.

Authors' responses: Thank you.

Reviewer: 4

Recommendation:

Comments:

The authors have addressed my comments.

Authors' responses: Thank you.