BMJ -
Decision on
Manuscript
ID
BMJ-2018-
047517

Body: 18-Dec-2018

Dear Dr. Song

Manuscript ID BMJ-2018-047517 entitled "Psychiatric reactions to severe stress 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 and discussed it at our manuscript committee meeting. 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 report from the manuscript meeting, 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.

Please remember that the author list and order were finalised upon initial submission, and reviewers and editors judged the paper in light of this information, particularly regarding any competing interests. If authors are later added to a paper this process is subverted. In that case, we reserve the right to rescind any previous decision or return the paper to the review process. Please also remember that we reserve the right to require formation of an authorship group when there are a large number of authors.

When you return your revised manuscript, please note that from 30 November 2018 BMJ is mandating ORCID iDs for corresponding authors for all research articles if accepted. Co-authors and reviewers are strongly encouraged to also connect their ScholarOne accounts to ORCID. We firmly believe that the increased use and integration of ORCiD iDs will be beneficial for the whole research community. For those who do not currently have an iD they will be required to register but this is free and takes a matter of seconds.

Tiago Villanueva
Associate Editor
tvillanueva@bmj.com

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Report from The BMJ's manuscript committee meeting

These comments are an attempt to summarise the discussions at the manuscript meeting. They are not an exact transcript.

Members of the committee were: Sophie Cook (chair), Angie Wade (statistician), Elizabeth Loder, Wim Weber, Jose Merino, John Fletcher, Daoxin Yin, Tiago Villanueva

Decision: Put points

Detailed comments from the meeting:

First, please revise your paper to respond to all of the comments by the reviewers. Their reports are available at the end of this letter, below.

Please also respond to these additional comments by the committee:

- Please note that the Patient and Public Involvement (PPI) declaration is missing and there was no acknowledgment to patients for their data. Some of the limitations could have been mitigated by PPI and it is alarming that a study with psychiatric issues linked to morbidity and mortality would be without PPI

- Our statistician made the following comments:
The analyses seem appropriate and I have only minor points to add to the reviewer comments:
1. Follow up time is skew and so should be summarised non-parametrically (table 1). The same may also be true for patient age.
2. Need to remove causal inference in what this study adds.

- One editor would like you to clarify what does it mean that all the individual elements of the composite outcome are raised considering they arise from different conditions? He also wondered if you could include "control conditions" as other outcomes, as well as mortality. For example, some common cancers (e.g. skin and GIT), chest infection, joint surgery, back pain, etc. The results for these would add whether they were raised across the board (stress as a universal risk factor for instance) or only raised for some conditions (stress affecting specific disease mechanisms).

- Another editor wondered how come the 'Family history of cardiovascular disease' is different for exposed and their siblings?

- Another editor suggested that you make it clearer that this looks at the more severely affected people with stress as this is a cohort who were referred to psychiatric services.

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

Comments from Reviewers

Reviewer: 1

Recommendation:

Comments:
As a previous sufferer of stress-related illness I found this paper interesting and reassuring. My illness was some years ago, I have not developed CVD, and this paper suggests my past stress is unlikely to give me an increased risk level. I received very little in the way of care or treatment for my stress illness, other than removing me from the cause and occasional blood pressure checks. I would hope that anyone involved in treating or caring for a victim of severe stress would be alerted to the increased risk of CVD and be vigilant in monitoring the signs. I think this paper would be of interest to a large number of people.
I found the article comprehensive and informative and I have been unable to identify any areas where I wished for more information.
Patients with stress disorders might find it difficult to distinguish between imagined and real symptoms, so increased vigilance from healthcare professionals could be required. For example, I often had feelings of palpitations or felt my heart rate was raised. I also imagined my blood pressure must have been raised. However, none of these were

observed on the occasions I had health checks, leading me to doubt if I would have been able to differentiate these from real physical symptoms if I had experienced any.
The outcomes described in the paper are relevant to patients and clinicians and could form the basis of discussions between them to highlight the increased risk of CVD. This would have to be done sympathetically in order to avoid raising the patients stress levels further.
There is no evidence of patient involvement in this study, which has been produced from large volumes of patient data. Perhaps the authors could have recruited some patients and clinicians to discuss the findings and assess their impact on stressed patients and how clinicians were able to reassure them or put a monitoring plan in place.

Additional Questions:
Please enter your name: Peter Green

Job Title: NHS Project Manager (Retired)

Institution: NHSBSA (Retired)

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

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Funds for a member of staff?: No

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Reviewer: 2

Recommendation:

Comments:
This study is a well-conducted large register-based cohort study using two different approaches in relation to selecting the comparison groups, as both a cohort of siblings and a cohort of birth-year- and sex-matched controls were examined in relation to the exposed group with stress. The study is well argued, designed, analysed and written.
The exposure was based on hospital discharge diagnosis within posttraumatic stress disorders, acute stress reaction or adjustment disorder and the cohorts were followed for incident cases of cardiovascular diseases, likewise based on hospital discharge or death certificates. Adjustment and analyses of interactions were conducted based on register-based information.

The study shows a higher hazard rate ratio for CVD among those exposed to stress-related disorders, higher within the first 6-12 months and with stronger associations with CVD before the age of 50.

Major comments:
Both in the summary box, the introduction and in the supplementary files, the focus is on posttraumatic stress disorder, which is clinically different from acute stress and adjustment disorders. This is to some extent explained, as PTSD has been subject to most research, but it would, in my opinion, be relevant to discuss this further or to change the focus of the text and handle all three types of stress equally. This is also relating to the introduction, stating that most individuals will be exposed to psychological trauma or life events, and clinically this may not necessarily be in the form of stress examined in the study. A more thorough discussion on the type of stress (leading to hospitalization) in comparison to ”stressful life events” could be included.
As the clinical entities have changed over the years it is somewhat surprising that stratification on calendar time yields the same results. This could be discussed further, as it may imply potential bias in the study.
As is rightly discussed, most patients suffering from stress are not hospitalized and will thus not be entering the study, but is treated in general practice. The conditions leading to hospitalization could be the more grave ones, and this could be discussed further, especially as the implications of the study would lead to suggestions to focus on the prevention of CVD. This may be only the more severe ones.
The study finds a long-term (up to 25 years) elevated risk of CVD with an HR of 1.2-1.4. This is somewhat surprising, I think, as stress should wear off if the biological cause is related to an increased workload for the heart (p. 14), and the consistent risk could be the result of residual confounding or unaccounted bias; this could also be discussed in more details.

Minor comments:
The abstract (p. 3-4) gives results from the sibling-controlled study as is also implicated on p. 4, l. 5. The abstract might be reformulated in order to balance the results
The term ”16 individual CVDs” is used in the summary box (p. 5) and elsewhere in the manuscript. It covers diagnoses and thus not necessarily different conditions, and I would suggest rephrasing the term.
table 1: the total number of participants (p. 22, l. 11) in both columns below population-matched cohort seems to be ten times too high.
Several entries should have the ”n (%)” explanation given, eventually just in the heading as a general description and then ”…unless otherwise stated”.
Supplementary files, figure on p. 39. In the legend on p. 40, no explanation of the red line at HR=1 is given. Is the red line necessary?

Henrik Bøggild
Associate professor, MD
Public Health and Epidemiology
Health and Science Technology
Aalborg University

Additional Questions:
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A fee for organising education?: No

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Reviewer: 3

Recommendation:

Comments:
The current manuscript includes details of a population-based cohort study in Sweden exploring the link between PTSD and other similar psychiatric disorders 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.

Overall, this is a well-structured study which extends the current literature exploring PTSD (mostly) and CVD. The study design and samples size are considerable strengths. That being said there are several areas where some further reflection by the authors may enhance the manuscript.

It would seem that the authors are trying to explore the relationship between PTSD and related disorders and CVD. However, they are using the term psychiatric reactions to severe stress, which is rather nebulous. For example, one could argue that certain forms of depressive disorders may appear in response to severe stress, which would also fall under the realm of 'psychiatric reactions to severe stress' (of note, there is an abundance of literature linking depression to CVD). As such, I would suggest that the authors rework their title and be consistent in their wording throughout the manuscript (may be PTSD and similar stress-related disorders?).

Non-effected siblings were matched at the point of diagnosis for the effected sibling. If the non-effected sibling demonstrated a PTSD or similar diagnosis during follow-up how was this handled analytically? Was some kind of censoring included? This may have a notable effect on the course of associations. Of note, due to the 1:10 matching for the general population I don't think this is as much of an issue in those analyses, where any effects are likely to be washed out by the magnitude of the general population.

Table 1 only reports psychiatric comorbidity (i.e., the development of a non-PTSD or related disorder) in the effected cohort only. I am assuming that the siblings and the general population both developed these disorders as well. It would be good to report these in the table. I am also assuming that if the other 2 cohorts had one of these disorders then this was included in the analyses, though I am now not 100% sure that this is correct. As a side-bar this should probably be 'other psychiatric disorders' rather than comorbidity to cover all 3 populations.

In the second paragraph on page 14 the authors speculate that the association between a stressful event (and not disorder) and CVD events (which has been shown in a number of previous studies) might be mediated by severe emotional reactions. However, the data they have make it hard to make this assertion. To be able to study this they would have needed to have 2 groups of individuals who experienced stressful events and then compared those who developed a PTSD or similar disorder vs. those that didn't. I understand where the authors are going with this, but there is some tempering of this assumption which is needed in this paragraph.

At the end of the 2nd paragraph on page 15 the authors argue that because their analyses show similar patterns with acute CVD events as well as non-acute events that this 'diminishes the possible impact of surveillance bias or reverse causality.' I'm not sure why this would be the case, especially for surveillance bias. Furthermore, the fact that heart failure had one of the largest HRs within the first year would strongly suggest reverse causation (HF is unlikely to be caused in a 6 month window) but this is not offset by the findings from the acute events (NB. the HRs for the acute events of MI, hemorrhagic stroke, and Takotsubo cardiomyopathy were all lower than would be expected compared other events). I think most people will appreciate the limitation, without diminishing the importance of the findings, if that sentence was removed.

Minor comments.

The authors use the term gender to describe their population. However, gender is a complex psychosocial construct made up of a number different facets. If this is truly what the authors studied then they should provide details of their conceptualisation of gender and the measures they used to assess it. Alternatively, if they used sex, which is an anatomical/physiological construct usually represented as a binary man/woman variable, then they should adjust their terminology within the manuscript.

There are some inconsistencies in the tables with the use of decimal places which should be corrected.

Figure 2, the forest plots, should be on the same scale so has to help comparisons.

Simon Bacon
Concordia University

Additional Questions:
Please enter your name: Simon Bacon

Job Title: Professor

Institution: Concordia University

Reimbursement for attending a symposium?: No

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Reviewer: 4

Recommendation:

Comments:
Song et al. have produced an excellent manuscript regarding stress disorders and risk of CVD. Although the overall finding of increased risk is not particularly surprising, the novelty here is the use of a sibling-matched analysis to address potential confounding. The manuscript is well-written and analyses conducted thoroughly. Some potential areas for improvement are discussed below.
Introduction
A fundamental argument of this manuscript is that stress increases CVD risk and that persons who have developed a stress disorder are at greater risk. However, this point is not properly supported by the authors. Reference 5 from the Nurses Health Study is used to support this point, but in that study, trauma with no PTSD symptoms vs. trauma with 4+ PTSD symptoms were generally equivalent in increased risk of incident CVD across various model adjustments. That study would support that trauma, regardless of psychiatric disorders or not, is the important determinant of CVD risk. The authors should find evidence that better supports their point (while acknowledging incompatible evidence) …or consider reframing their argument. It should also be noted that the Nurses Health Study participants are all women, and stress disorders and CVD both exhibit sex differences that may make this reference even more unhelpful to the present study.
Methods:
Sibling cohort – this section is presented in a confusing manner. The first paragraph seems to be more relevant to the overall study rather than the specific sibling cohort – a simple fix would be to move the header to the actual paragraph describing the sibling cohort. It also would be helpful to the reader to introduce the rationale for a sibling cohort design here.
The sample selection may be problematic because of potential immortal time bias. The age at index date is 36 +/- 14 years SD, which suggests that there are very young participants included who are very unlikely to be diagnosed with stress disorders (due to lower detection in pediatric populations) and CVD even with long follow-up (due to lower inherent risk). Implementing a minimum age eligibility requirement as well as an assessment of the distributions of the ages of diagnosis of the stress disorders would help mitigate this potential bias.

From a causal inference perspective, the sibling matched analysis still has some problems since shared genetic or environmental confounding is still a possibility. It may make sense to use a case-crossover analysis to better control for this, so that each person is his/her own control. Having this 3rd matching analysis triangulate with the sibling and population-matched analyses would be powerful support of the authors' results.
The authors mention the possibility of surveillance bias in that patients with stress disorders have more healthcare visits and greater likelihood of receiving CVD diagnoses. Sensitivity analyses would be useful to defend against this, e.g.: adjusting/stratifying on number of health care contacts or days in hospital.
Were pain disorders considered as covariates? Pain and pain control are very relevant to stress-disorders.
Table 1: Numbers in the columns do not sum to the listed number of exposed "patients". Also: some standardization of terminology would be helpful, since unexposed and unaffected are seemingly used interchangeably, as well as patients and individuals. Could just use exposed vs. unexposed.

Additional Questions:
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Institution: Drexel University School of Public Health

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