Subject: BMJ - Decision on Manuscript ID BMJ-2019-050247

Body: 03-Jun-2019

Dear Dr. Song

Manuscript ID BMJ-2019-050247 entitled "Stress-related disorders and subsequent risk of life-threatening infections: 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 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.

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: Jose Merino (chair), Jamie Kirkham (statistician), David Ludwig, Tim Feeney, John Fletcher, Elizabeth Loder, Helen Macdonald, 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:

- Our statistician made the following comments:
This is a well reported study.
The associations they find in this study are clear - however the reviewers are of the opinion that there are many factors that may be of interest that haven't been accounted for. The authors have performed a number of sensitivity analyses to compensate for different scenarios - I'm of the opinion that they have fully utilised the data they have available to them.
The study quantifies effects that were perhaps expected and summarises these findings in the discussion - more discussion I think is needed on the impact of these findings.

- We would like to see some sensitivity analyses to evaluate how robust the findings are to omitted confounders.

- We wonder if the sibling analyses carry more weight and thereby suggest that the effect really is smaller than the population study suggests. The headline numbers should be from the sibling comparisons as these were chosen to account for more potential confounders. You have enough data for the 95% CIs to be informative.

- Please emphasize severe infections are relatively rare events.

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:
The questions posed are relevant to patients and their carers as I suspect few are aware of the increased risk of life-threatening infections. As someone who suffered a prolonged period of stress, I found the results interesting, although I did not personally experience any severe psychiatric reaction.

There is no indication of the effects of lifestyle, smoking, drug or alcohol use. These might play a greater role in the lives of stress sufferers than in the general population. It is impossible to estimate how much these factors contribute to the raised risk level so I am unsure how relevant the increased risk figures are without lifestyle data.

I would also have liked to see an indication of risk levels for those who have suffered milder stress-related disorders.

There is no advice to those at risk, such as steps they could take to reduce their risk or signs to look out for, or suggestion of further work to produce some. I accept that this study aimed only to verify the link between stress-related disorders and serious infections, but when the results reach the wider public those questions are bound to be asked.

The authors could have benefited from some patient involvement in the design of the study, to help them understand what patients would like to see come out of the study, or indicate what sort of advice they would like to receive from their doctors if they were at increased risk.

Additional Questions:
Please enter your name: Peter Green

Job Title: Retired

Institution: ex-NHS Business Services Authority

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

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If you have any competing interests <A HREF='http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/declaration-competing-interests'target='_new'> (please see BMJ policy) please declare them here:

Reviewer: 2

Recommendation:

Comments:
The authors found that those with a history of stress at a childhood or young age are at greatest risk for life threatening infections due to inflammatory reactions and gene expression, but there is no information on inflammatory markers to support this. There is no information on whether these patients received antibiotics to treat infections, or tranquilizers and sedatives that are frequently prescribed for anxiety, insomnia and other stress related complaints. The only information we have is that SSRI's, "which are recommended for the long-term (beyond one year) risk of life-threatening infections seemed attenuated by persistent use of SSRIs during the first year after the diagnosis of stress-related disorders." No mention is made that these drugs are banned in those under 18 in the U.K. and other countries because of increased suicides. Dr. Fang lists no conflicts of interest, but in a 2018 publication also co-authored with Dr. Sang, he reported income from Pfizer and AbbieVie. Pfizer markets Zoloft (sertraline) an SSRI which was the most prescribed psychiatric drug in the U.S. in 2016. AbbieVie manufactures drugs to treat certain infections. No reference was made to a large body of literature linking various infections to myocardial infarction, stroke and atherosclerosis. The data on siblings does not indicate whether they lived with or were in close contact with those that were infected. The authors mined the information available to them as much as possible, but it is not enough to draw any meaningful conclusions in my opinion, and would reject this unless a revision addresses the caveats noted above.

Additional Questions:
Please enter your name: Paul J. Rosch

Job Title: Clinical Professor of Medicine

Institution: New York Medical College

Reimbursement for attending a symposium?: No

A fee for speaking?: No

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Funds for research?: No

Funds for a member of staff?: No

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Reviewer: 3

Recommendation:

Comments:
The current study by Song et al examines the relation between exposure to stress disorders and the subsequent risk for serious infectious diseases. Because there is much evidence of stress-induced disruptions of immune regulation, and risk for infection after symptom-based measurements of stress, the present study addresses a well-motivated research question. The paper is generally very clear and well-written, and addresses a timely and important topic. I have mostly minor comments.

Introduction, page 5 (page is truncated on the left margin, so row numbers can't be seen in my pdf):
The authors state: "Strong evidence from animal models and human studies suggests a considerable dysregulation of the hypothalamic-pituitary-adrenal axis in response to stress with varying indices of immunosuppression (e.g., impaired humoral and cell-mediated immunity). "

The HPA axis response to stress should not be presented as dysregulation. The response to challenge in this axis represents an adaptive response – as the acute stress response in general. Also, it is not simply related to immunosuppression, and experimental stress, at least of the acute kind, and stress related conditions, at least PTSD, is connected with increased measures of inflammation, while other functional indices seem to be suppressed. The sentence needs to be clarified, not to mislead. This is important also as to judge potential causes of infectious disease, as compromised immunity may increase risk, and other aspects of a complex immune system, like inflammatory overshoot, may contribute to severity.

For a similar reason, consider updating the references (1, 12,13) regarding immune profiles in stress-related disorders.

Methods, page 7: because adaptions have been made to the Swedish classification of stress-related disorders, and includes exhaustion disorder, consider explaining "other stress disorders" more fully.

Because treatment guidelines vary across countries, please state to what country reference 18 applies to regarding SSRI as recommended pharmacotherapy for stress-related disorders.

Page 8: Explain more clearly why history of psychiatric disorders and psychiatric comorbidity was handled differently than other covariates.

Results, page 11 and discussion:
Prior history of psychiatric diseases as well as somatic and infectious diseases were more common among exposed as compared to non-exposed subjects. Does this speak for vulnerability rather than immune dysregulation resulting from the stress disorder? This should be better discussed.

The same need applies to the results on higher risk in subjects without a history of somatic or psychiatric conditions.

Discussion, page 13: It is true that many studies show that higher stress is related to increased risk for infection, but they are experimental in the way that virus is exposed to subjects. The independent variable, stress, is not manipulated, which one might believe. I leave it to the authors if they want to rephrase the sentence or not.

Is it is it reasonable that acute stress reactions, of maximum one month, increase the risk for severe infections? Also, because prior of psychiatric, somatic and infectious diseases were more common among exposed subjects, the authors might discuss in somewhat more detail the issue of possible reasons for seeing the observed higher risk for infectious disease in the exposed group. What role can vulnerability play? For PTSD, there is fairly strong evidence that inflammatory activation is present. Would this apply to severity rather than risk for infection per se? While I appreciate the lack of speculation in the current version of the manuscript, a more thorough discussion would be appreciated in some of these matters.

On a related note: risk for death from serious infections is brought up in the introduction, and I expected this to be analysed as an outcome. If I do not misread, this is not displayed in the manuscript.

On behavioural factors of relevance: consider including sleep, as sleep disturbances are related to psychiatric disorders, and not the least stress-related disorders, including PTSD.

Page 14: Because stress diagnoses are not uncontroversial in terms of precision (for example, aetiology is part of the diagnosis, which stands out from other more descriptive and untheoretical diagnoses), is there a risk for misclassification? Also, these disorders are indicated to vary in frequency in relation to insurance regulation that change over time.

Additional Questions:
Please enter your name: Mats Lekander

Job Title: Professor

Institution: Karolinska Institutet

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

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