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Dear Editor:

Thank you for second review of our manuscript entitled “Stress-related disorders and subsequent risk of life-threatening infections: a population-based sibling-controlled cohort study” and for the opportunity to revise and resubmit an improved version for publication in BMJ. In accordance to these extra comments from the reviewer 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 now find our manuscript suitable for publication in BMJ.

Yours sincerely,

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On behalf of all co-authors

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Responses to the comments of referees\*:

\*All page and line marks correspond to the line numbers of the 'Revised Manuscript\_clean' version.

Comments from editor:

We hope very much that you will be willing and able to revise your paper as explained below in reviewer 1's comments regarding toning down the conclusions.

Authors' responses: Thank you for your comment. Please see responses below.

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

Reviewer: 1

Recommendation:

Comments:

Somewhat improved and probably OK to publish but still believe the authors should state that studies such as these can only show an association, not causation.

Authors' responses: Thank you for your comment. We understand and agree with the reviewer's concern about causal inference. We have now gone through the manuscript and made several modifications to avoid inferences on causality as well as added a sentence on this issue in the 'Limitation' part of the discussion.

In the revised manuscript:

Abstract (Page 3, Line 29-31):

*'Conclusion In the Swedish population, stress-related disorders were associated with a subsequent risk of life-threatening infections, after controlling for familial background and physical or psychiatric comorbidities.'*

Discussion, Principal findings of the study (Page 13, Line 253-256)

*'We found that individuals with stress-related disorders, particularly when diagnosed at a young age, were at considerably elevated risk of life-threatening infections, after taking into account sex, familial background, and baseline physical or psychiatric conditions.*

Discussion, Limitation part (Page 14, Line 283-289)

*'Fourth, although the association between stress-related disorders and subsequent risk of fatal infections seems robust, the observational nature of our analysis puts limits in our capability to infer causality or to explore potential mediating pathways. For instance, in spite of efforts to control for disease vulnerabilities (e.g., history of severe somatic diseases, history of other psychiatric disorders, and history of inpatient visit due to any infectious diseases) that differ between exposed and reference groups at baseline, we cannot refute the possibility that unmeasured vulnerability factors still contribute to the reported association.*

Discussion, Meaning of the study (Page 16, Line 309-314)

*'With a specific focus on clinically diagnosed stress-related disorders, we show that severe stress reactions, even in transient form (e.g., acute stress reaction), was associated with elevated subsequent risk of life-threatening infections, both in the short and long term. Importantly, the observed excess risks remained after controlling for most of the known risk factors of the studied infections<sup>33-35</sup>, such as socioeconomic factors, familial background, physical conditions at baseline (including baseline susceptibility to infection), and the occurrence of other severe somatic diseases during the follow-up.*

Discussion, Meaning of the study (Page 17, Line 309-314)

*'Our finding suggesting that exposure to stress-related disorders in early life experience was associated with the largest relative risk increase in life-threatening infections is in line with findings showing that childhood exposure to trauma may have a lifelong impact on susceptibility to disease, through promoting inflammatory reactions<sup>49,50</sup>, interrupting neuropsychological/cognitive development<sup>51,52</sup>, or gene-environment interplay<sup>53</sup>.*

Discussion, Conclusion part (Page 17, Line 348-350)

*'Based on this population-based sibling-controlled cohort study, we found that clinically diagnosed stress-related disorders were associated to subsequently elevated risk of life-threatening infections in the Swedish population.'*

Discussion, Conclusion part (Page 17, Line 352-356)

*'In addition, our findings, subject to replication, suggest an attenuation in the relative risk of life-threatening infections with use of selective serotonin reuptake inhibitors. Further studies are needed to understand the potential mediating role of behavior-related factors in the observed association as well as potential mitigating role of various treatment modalities for stress-related disorders in reducing the excess risk of life-threatening infections.'*

Reviewer: 2

Recommendation:

Comments:

I am happy with the revised version.

Authors' responses: Thank you.