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Dear Editor:

Thank you for the thorough review of our paper 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 the BMJ. We appreciate the insightful comments from the editors and reviewers; please find our point-by-point responses to these comments below.

We have now performed additional analyses and revised the manuscript in accordance with the important issues raised by the editors and reviewers. We believe that the quality of the manuscript has, as a result, been significantly improved. While we are certainly willing to make further revisions on your request, we hope that you will find the present version of our manuscript suitable for publication in the BMJ.

Yours sincerely,

Huan Song
On behalf of all co-authors

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Responses to the comments of the editorial committee and referees*:
*All page and line marks correspond to the line numbers of the '**Revised Manuscript_clean**' version.

Detailed 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.
Authors' responses: Thanks for the positive comments!

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.
Authors' responses: We agree. We have now further emphasized the impact of these findings with reference to the high incidence of stress-related disorders in the general population.

In the revised manuscript, we wrote:
'Meaning of the study', Discussion section (page 16, line 311-316):
'Although relatively rare, severe infections contribute substantially to the global burden of disease due to high fatality rate, risk of long-term complications, and extremely high health care expense[36,37]. In contrast, stress-related disorders are quite common in the general population. The reported lifetime prevalence of PTSD in Sweden was 5.6% in 2005[38], and our data suggest at least 10-times higher prevalence for other stress-related disorders, underscoring the considerable clinical significance and public health implications of our findings.'

'Conclusion', Discussion section (page 17, line 344-352):
'Based on this population-based sibling-controlled cohort study, we found that individuals diagnosed with stress-related disorders were subsequently at elevated risk of life-threatening infections in the Swedish population. Despite of its relatively low absolute risk, the high fatality of life-threatening infections calls for increased clinical awareness among individuals with stress-related disorders, especially those diagnosed at younger age. In addition, our findings, subject to replication, suggest a potential reduction in risk of these life-threatening infections with the 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 the influence of various treatment modalities for stress-related disorders in reducing the excess risk of life-threatening infections.'

- We would like to see some sensitivity analyses to evaluate how robust the findings are to omitted confounders.
Authors' responses: Besides the sensitivity analyses in the original manuscript, we have now performed a new sensitivity analysis where we additionally adjusted for substance use and sleep related diagnoses during follow-up (as a binary variable) in the Cox models. In addition, since the risk of endocarditis and meningitis is relatively high among individuals with anatomic defects (i.e., congenital heart disease or congenital diseases of never system), we extracted such information from National Patient Register and Medical Birth Register, and repeated the main analyses after excluding individuals with these conditions.

In the revised manuscript, we wrote:
'Covariates', Method part (page 9, line 142-147)
'*For sensitivity analyses on somatic comorbidities and behavior-related factors, data on the presence of severe somatic diseases (as defined above) and substance use/sleep-related diseases (Supplemental Table 1) after the index date were also extracted from the National Patient Register. Anatomic defects (i.e., congenital diseases of heart and nervous system) are risk factors for severe infections[27], and therefore were identified from the National Patient Register and Medical Birth Register (available in 1973 onwards).*'

'Statistical analysis', Method part (page 10, line 187-194)
'In addition, to alleviate concerns that the observed associations were accounted for by the poorer health conditions or suboptimal behaviors of exposed patients than unexposed individuals after the diagnosis of a stress-related disorder, we restricted our analyses to participants without a history of severe somatic diseases and additionally adjusted the Cox models by the presence of severe somatic conditions (as time-varying variables), or substance use/sleep related diagnoses (as a binary variable) during follow-up. Lastly, to address the increased infection risk owing to anatomic defects, we repeated our analyses after excluding subjects with congenital diseases of heart or nervous system.'

Results part (page 13, line 243-248)
'Restricting the analyses to individuals without any diagnosis of severe somatic diseases, injury, or infectious diseases within 1 year prior to the index date, or individuals without anatomic defects yielded largely identical results as the main analyses (Supplementary Tables 5 and 6). Moreover, while additional adjustments for severe somatic diseases during follow-up didn't substantially modify the estimates, the HRs, especially those from population-based analyses, were attenuated after additionally adjusting for the presence of substance use/sleep-related diagnoses (Supplementary Table 7).'

- 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.

Authors' responses: Thank you for the comments. We totally agree with the editors that the sibling-based analyses should be given more weight since it stringently controlled for more potential confounders. In the revised manuscript, the sibling-based analysis was taken as the main analysis. We have rephrased the 'Abstract', 'Methods', and 'Results' parts so that the estimates from sibling-based analyses get more attention.

For instance, in 'Abstract' part (page 3, line 17-23), we wrote:
'Compared to the unaffected full siblings, patients with stress-related disorders were at increased risk of life-threatening infections (hazard ratios 1.47, 95% confidence intervals1.37 to 1.58, for any stress related disorder and 1.92 (1.46 to 2.52) for PTSD). The corresponding estimates in the population-based analysis were similar (hazard ratios for any stress-related disorder: 1.58, 95% confidence intervals 1.51 to 1.65, P for difference between sibling- and population-based comparison=0.09; for PTSD: 1.95 (1.66 to 2.28), P for difference=0.92).'

'Statistical analyses', Methods part (page 9, line 152-156)
'In the sibling cohort, all models were stratified by family identifier, and adjusting for sex, birth year, education level (<9 years, 9-12 years, >12 years, or unknown), family income (top 20%, middle, lowest 20%, or unknown), marital status (single, married or cohabiting, or divorced/widow), history of severe somatic diseases (yes or no), history of other psychiatric disorders (yes or no), and history of inpatient visit due to any infectious diseases (yes or no).'

'Statistical analyses', Methods part (page 10, line 176-178)
'We repeated the main analyses in the population-based cohort, where we used conditional Cox models stratified by matching identifiers (sex, birth year, and county of birth), adjusting for family history of major life-threatening infections (yes or no), and all abovementioned covariates.'

Results part (page 11, line 208-220)
'During the follow-up, 4,843 individuals with incident life-threatening infections were identified —2,197 among exposed patients and 2,646 among unaffected full siblings, with a crude incidence rate of 2.7 and 1.7 per 1,000 person-years, respectively. After controlling for all covariates, we observed an association between stress-related disorders and life-threatening infections: hazard ratios was 1.47 (95% confidence interval 1.37 to 1.58 for any stress-related disorder, 1.92 (1.46 to 2.52) for PTSD (Figure 2), 1.43 (1.29 to 1.58) for acute stress reaction, and 1.48 (1.33 to 1.64) for adjustment disorder and other stress reactions (Supplementary Figure 1). Stress-related disorders were associated with all studied life-threatening infections, with hazard ratios varying from 1.39 (1.16 to 1.65) for deaths due to infections of other origin to 1.63 (1.23 to 2.16) for meningitis. The population-based comparisons corroborated the abovementioned associations (Figure 2 and Supplementary Figure 1) as differences between the estimates in the sibling-based and population-based analysis were not statistically significant (hazard ratios for any stress-related disorder: 1.58(1.51 to 1.65), P for difference between within-sibling and population-based comparison=0.09; for PTSD: 1.95 (1.66 to 2.28), P for difference=0.92).'

Please refer to the revised manuscript for all these changes.

- Please emphasize severe infections are relatively rare events.
Authors' responses: In the revised manuscript, we have emphasized the life-threatening infections are severe but rare events.

'Meaning of the study', Discussion section (page 16, line 311-312):
'Although relatively rare, severe infections contribute substantially to the global burden of disease due to high fatality rate, risk of long-term complications, and extremely high health care expense[35 36].'

'Conclusion', Discussion section (page 17, line 346-348):
'Despite of its relatively low absolute risk, the high fatality of life-threatening infections calls for increased clinical awareness among individuals with stress-related disorders diagnosed, especially those diagnosed at younger age.'

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.

Authors' responses: Thank you for raising this important point. We do not have direct information about these lifestyle factors, and this is definitely a notable limitation of our study.

'Strengths and weaknesses of this study', Discussion part (Page 14, line 275-278)

'Second, we have limited information on some important behavior-related factors (e.g., smoking, drug and alcohol use) and our sensitivity analyses reveal considerable mediating effect of these factors on the observed associations. Further research with detailed data on lifestyle is warranted.'

However, the effect of comorbid substance-use disorder, as one type of psychiatric comorbidities, has been clarified in our analyses—we reported further elevated HRs among exposed patients with comorbid substance use disorders. In the revised manuscript, we further explored the contribution of behavior-related factors to the association of stress-related disorders with infections, by performing a sensitivity analysis where the **diagnoses of substance use and sleep-related diseases** (as a binary variable, yes/no), including substance-use disorders, substance-use related somatic diseases, and sleep disorders that occurred during follow-up (after the diagnosis of stress-related disorders), were additionally adjusted in the Cox regression model.

'Covariates', Method part (page 10, line 142-145)

'*For sensitivity analyses on somatic comorbidities and behavior-related factors, data on the presence of severe somatic diseases (as defined above) and substance use/sleep-related diseases (Supplemental Table 1) after the index date were also extracted from the National Patient Register.'*

'Statistical analysis', Method part (page 10, line 187-194)

'In addition, to alleviate concerns that the observed associations were accounted for by the poorer health conditions or suboptimal behaviors of exposed patients than unexposed individuals after the diagnosis of a stress-related disorder, we restricted our analyses to participants without a history of severe somatic diseases and additionally adjusted the Cox models by the presence of severe somatic conditions (as time-varying variables), or substance use/sleep related diagnoses (as a binary variable) during follow-up. Lastly, to address the increased infection risk owing to anatomic defects, we repeated our analyses after excluding subjects with congenital diseases of heart or nervous system.'

Results part (page 13, line 245-248)

'Moreover, while additional adjustments for severe somatic diseases during follow-up didn't substantially modify the estimates, the HRs, especially those from population-based analyses, were attenuated after additionally adjusting for the presence of substance use/sleep-related diagnoses (Supplementary Table 7).'

In the 'Meaning of the study', Discussion part, we also added more statements about behavior related factors (page 16 line 325-333):

'Alternative explanations for the impact of severe stress reactions on life-threatening infection include behavior-related changes after the diagnosis of a stress-related disorder. In present study, as we observed further elevated relative risk among exposed patients with comorbid substance-use disorders, as well as attenuated excess risk after additionally adjusting for substance use/sleep-related diagnoses during follow-up, it is therefore possible that behavioral factors (e.g., smoking, alcohol or drug use, and sleep disturbance) at least partially mediate the observed association, through increased possibility of pathogen exposure (e.g. needle sharing among drug users[46]) and/or inducing immune dysfunction[47]. Nevertheless, it is unlikely that such behavioral factors can fully explain the rise in fatal infection-related consequences, especially those that appear shortly after a stress-related disorder diagnosis.'

In the 'Conclusion', Discussion part, we added (page 16 line 349-352):

'Further studies are needed to understand the potential mediating role of behavior-related factors in the observed association as well as the influence of various treatment modalities for stress-related disorders in reducing the excess risk of life-threatening infections.'

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

Authors' responses: Thank you for the comment. Our efforts for exploring the severity of stress-related disorder on the studied association include:

- To address the type of stress-related disorder (indicating varying severity): PTSD is the most severe stress-related disorder, and our analyses indeed revealed that patients with PTSD were at higher excess risk of developing life-threatening infection, compared to other milder forms of stress-related disorders, e.g. adjustment disorder, acute stress reaction, unspecified reactions to stress (Figure 2 and Supplementary Figure 1).

- By the status of psychiatric comorbidity: the presence of psychiatric comorbidity might indicate a more severe and symptomatic stress reaction. Therefore, we performed subgroup analyses by the occurrence of psychiatric comorbidity and found further elevated HR among patients with comorbid other psychiatric disorders (See supplementary Figure 2). According to this analysis, a milder stress-related disorder---- adjustment disorder without any psychiatric comorbidity, was associated with about **40%** increased risk of life-threatening infection.

- By the type of psychiatric care received at diagnosis: **in the revised manuscript, we added a subgroup analysis by the type of psychiatric care received at diagnosis**. As expected, we obtained higher relative risks for individuals diagnosed with stress-related disorders in inpatient care, compared to those diagnosed in outpatient care (see Table R1 below, which also Supplementary Table 3 in revised manuscript). Here, we see the relative risk for milder stress-related disorder --- adjustment disorder diagnosed at outpatient care is around 1.34 (increased by **34%**), according to sibling-based analyses.

  Finally, in the revised manuscript, we added comments about the generalizability of our findings and the need to address the potential role of sub-clinical stress-related disorders in life-threatening infections.

Table R1 Relative risks of life-threatening infections among stress-related disorder patients, sub-grouped by the type of psychiatric care received at diagnosis, ***compared to full siblings or matched unexposed individuals***

	Type of psychiatric care received at diagnosis	Sibling-based analysis		Population-based analysis	
		Number of cases (incidence rate, per 1 000 person-years), exposed/siblings	Hazard ratios (95% confidence intervals)*	Number of cases (incidence rate, per 1 000 person-years), exposed/unexposed	Hazard ratios (95% confidence intervals)†
Any stress-related disorder	Inpatient	1351(2.92)/1648(1.71)	1.52 (1.39 to 1.67)	2065(3.20)/9422(1.39)	1.66 (1.57 to 1.75)
	Outpatient	846(2.41)/998(1.65)	1.39 (1.25 to 1.56)	1227(2.52)/6262(1.28)	1.48 (1.38 to 1.58)

Posttraumatic stress disorder	Inpatient	94(3.20)/109(1.81)	1.81 (1.27 to 2.57)	136(3.36)/591(1.39)	2.15 (1.74 to 2.65)
	Outpatient	76(2.67)/66(1.33)	2.29 (1.44 to 3.65)	108(2.71)/450(1.13)	1.71 (1.35 to 2.18)
Acute stress reaction	Inpatient	682(2.79)/875(1.71)	1.44 (1.27 to 1.64)	1077(3.15)/4970(1.38)	1.60 (1.48 to 1.72)
	Outpatient	331(2.40)/395(1.66)	1.41 (1.18 to 1.69)	493(2.55)/2531(1.30)	1.49 (1.35 to 1.66)
Adjustment disorder and other stress reactions	Inpatient	575(3.04)/664(1.70)	1.57 (1.37 to 1.81)	852(3.23)/3861(1.39)	1.67 (1.53 to 1.82)
	Outpatient	439(2.38)/537(1.69)	1.34 (1.15 to 1.56)	626(2.47)/3281(1.29)	1.44 (1.31 to 1.58)

* Cox models were stratified by family identifiers, and adjusted for sex, birth year, education level, family income, marital status, history of severe somatic diseases, history of other psychiatric disorder, and history of inpatient visit due to infectious disease.
† Cox models were stratified by matching identifiers (sex, birth year, and county of birth), and adjusted for education level, family income, marital status, history of severe somatic diseases, history of other psychiatric disorder, history of inpatient visit due to infectious disease, and family history of major life-threatening infections.

In the revised manuscript, 'Statistical analyses', Method part (page 10, line 170-173)
'*To study the potential impact of severity and complexity of stress-related disorder on the studied associations, we assessed hazard ratios by the presence of psychiatric comorbidity (any psychiatric comorbidities, as well as by specific type, including depression, anxiety, and substance use disorders) and by the type of psychiatric care received at diagnosis (inpatient or outpatient).'*

Results part (page 12, line 229-231)
'Additionally, we obtained higher hazard ratios for stress-related disorders that diagnosed through inpatient hospital care, than those from outpatient specialist care (Supplementary Table 3, P for difference= 0.009 according to population-based analysis).'

'Strengths and weaknesses of this study', Discussion part (page 15 line 286-288)
'Fifth, this study only involved patients who received a clinical diagnosis of stress-related disorders through a hospital visit, thus the generalizability of our findings to individuals with less severe stress reaction or daily stress needs further assessment.'

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.
Authors' responses: Thank you for your comments. In this project, besides demonstrating the association, we explored whether primary pharmacological treatment for stress-related disorder modified the subsequent risk of life-threatening infection among patients with stress-related disorder. Although the effectiveness and extent of SSRIs use among young individuals is still debated (Lagerberg T, Molero Y, D'Onofrio BM, et al. Antidepressant prescription patterns and CNS polypharmacy with antidepressants among children, adolescents, and young adults: a population-based study in Sweden. Eur Child Adolesc Psychiatry. 2019 Jan 19. doi: 10.1007/s00787-018-01269-2.), our results suggest an attenuated risk after the persistent use of SSRI, indicating **effective treatment of stress-related disorder may not only relieve psychological symptom burden but also potentially reduce future risk of subsequent health risk, e.g. life-threatening infections**.

Unfortunately, although trauma-focused psychotherapy has the highest priority for PTSD treatment in many countries including Sweden, we do not have such data in our dataset. Further studies are needed to explore the potential role of psychotherapy in the observed associations. In the revised manuscript, we added ('Strengths and weaknesses of this study', 'Discussion' part, page 14 line 278-282)

'Third, although trauma-focused psychotherapy was given the highest priority for PTSD treatment in many countries including Sweden[19], we have no such data available for analyses. Future well-designed studies exploring the influence of psychotherapy, alone or with pharmacological treatment, on the association between stress-related disorder and subsequent risk of severe infections are highly motivated.'

'Conclusion', Discussion section (page 17, line 348-352):
'In addition, our findings, subject to replication, suggest a potential reduction in risk of these life-threatening infections with the 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 the influence of various treatment modalities for stress-related disorders in reducing the excess risk of life-threatening infections.'

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.
Authors' responses: Thank you for your comments. This study leverages Swedish administrative health utilization data for a historical analysis addressing the primary hypothesis. Such register-based studies are, in accordance with Swedish law, conducted without an informed consent, or consultation with patients, after an ethical review by a Regional Ethics Committee (in this case in Stockholm). We regret that patients were not invited to comment on the study design or interpretation of the result during the research process; and **we have plan to involve patients in our future studies**.

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.
Authors' responses: Thank you for your comment. In this study, we reported an association between clinically confirmed diagnosis of stress-related disorder and subsequently increased risk of life-threatening infections; the association seems indeed stronger among individuals exposed to stress-related disorder at younger ages. As the reviewer mentioned, in the discussion part, to explain our findings, we proposed several possible mechanisms, including inflammation and epigenetic modification, based on a large body of evidence from previous studies in various fields. For the notion that 'early trauma/stress can lead to long-term inflammatory change', besides the reference cited in our manuscript, other literature also provides supportive evidence by focusing on inflammatory biomarkers, such as:

- Baumeister D, Akhtar R, Ciufolini S, Pariante CM, Mondelli V. Childhood trauma and adulthood inflammation: a meta-analysis of peripheral C-reactive protein, interleukin-6 and tumour necrosis factor-α. Mol Psychiatry. 2016 May;21(5):642-9.
- Danese A, Moffitt TE, Harrington H, Milne BJ, Polanczyk G, Pariante CM, Poulton R, Caspi A. Adverse childhood experiences and adult risk factors for age-related disease: depression, inflammation, and clustering of metabolic risk markers. Arch Pediatr Adolesc Med. 2009;163:1135–43.
- Taylor SE, Lehman BJ, Kiefe CI, Seeman TE. Relationship of early life stress and psychological functioning to adult C-reactive protein in the coronary artery risk development in young adults study. Biol Psychiatry. 2006;60:819–24.

- Danese A, Moffitt TE, Pariante CM, Ambler A, Poulton R, Caspi A. Elevated inflammation levels in depressed adults with a history of childhood maltreatment. Arch Gen Psychiatry. 2008;65:409–15.
- Danese A, Pariante CM, Caspi A, Taylor A, Poulton R. Childhood maltreatment predicts adult inflammation in a life-course study. Proc Natl Acad Sci U S A. 2007;104:1319–24.

It is true that we do not have biological information, e.g., inflammatory markers or genetic data, in our data set. However, our hypothesis is based on the findings of the cited research on the potential biological mechanisms, while the unique contribution here is the vigorous test of the studied association in a large population with sibling-based comparison.

In the revised manuscript, one meta-analysis entitled 'Childhood trauma and adulthood inflammation: a meta-analysis of peripheral C-reactive protein, interleukin-6 and tumour necrosis factor-α' has been added to our reference list, highlighting the well-established psycho-biologic sequel of stress in younger individuals and matches well our main findings.

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.

Authors' responses: Thank you for this important comment. In the revised version of the manuscript, we now clearly emphasize that the SSRI treatment is indeed only recommended for adults (see below). However, SSRI and other antidepressants use among the young is actually increased in Sweden (and other countries), despite recommendations (Lagerberg T, Molero Y, D'Onofrio BM, et al. Antidepressant prescription patterns and CNS polypharmacy with antidepressants among children, adolescents, and young adults: a population-based study in Sweden. Eur Child Adolesc Psychiatry. 2019 Jan 19. doi: 10.1007/s00787-018-01269-2.).

'Stress-related disorders', Method part (page 7, line 110-112)
'Albeit debates on the appropriateness of use for young patients[19], this medication has been widely used[20] and recommended as the first-line pharmacotherapy for adults with stress-related disorders (e.g., in Sweden[21], UK[22], and US[23])'

Although SSRIs are the recommended first-line pharmacotherapy for adults with stress-related disorders in most countries, we understand the reviewer's concern that we only performed analyses on SSRIs, instead of other medications. Actually, **we did perform analyses on other psychotropic medications** that are commonly used among patients with stress-related disorders (see results shown below in Table R2), and we did not find similar effect of other antidepressants or other psychiatric medications, as SSRIs, on the association of stress-related disorders with life-threatening infections .

Table R2 Crude incidence rate (IR) and Hazard ratios (HRs) with 95% confidence intervals (CIs) for life-threatening infections among patients with stress-related disorders*, ***compared between subgroups with difference medication status***

	Selective serotonin reuptakes inhibitors	Other antidepressants	All other psychiatric drugs

	Number of cases (IR, per 1 000 person-years)	HR (95% CI)†	Number of cases (IR, per 1 000 person-	HR (95% CI) †	Number of cases (IR, per 1 000 person-years)	HR (95% CI) †
Drug user€						
No	582(2.72)	Reference	574(2.54)	Reference	504(2.37)	Reference
Yes	133(2.63)	0.81 (0.66 to 0.98)	141(3.63)	1.07(0.88 to 1.31)	211(4.04)	1.28(1.07 to 1.54)
P for difference		0.0318		0.4751		0.0073
Average dosage level (by median)						
Not user	582(2.72)	Reference	574(2.54)	Reference	504(2.37)	Reference
Low dose	62(2.32)	0.77 (0.63 to 0.93)	59(3.12)	0.96(0.73 to 1.27)	90(3.42)	1.17(0.92 to 1.49)
High dose	71(2.98)	0.86 (0.69 to 1.07)	82(4.12)	1.18(0.92 to 1.50)	121(4.67)	1.39(1.11 to 1.73)
P for trend‡		0.0896		0.2741		0.0030
Duration (by tertiles)						
Not user	582(2.72)	Reference	574(2.54)	Reference	504(2.37)	Reference
Short	29(3.10)	0.96 (0.66 to 1.40)	49(3.71)	1.18(0.87 to 1.58)	48(2.65)	0.95(0.70 to 1.29)
Median	54(2.74)	0.85 (0.64 to 1.13)	39(3.10)	0.92 (0.66 to 1.28)	72(4.40)	1.40(1.08 to 1.83)
Long	50(2.33)	0.70 (0.52 to 0.94)	53(4.07)	1.13 (0.84 to 1.51)	91(5.15)	1.50(1.17 to 1.91)
P for trend‡		0.0137		0.5691		0.0003

* Restricted to patients diagnosed after July 2005, and with more than one year of follow-up (n=74,691).
† Cox models were adjusted for age at index date, sex, county of birth, education level, family income, marital status, history of severe somatic diseases, history of other psychiatric disorder, history of inpatient visit due to infectious disease, family history of major life-threatening infections, and combination use of other psychiatric drugs (yes/no). The first year after the study entry was excluded.
€ We defined drug users as individuals with two or more dispensations of the specific drug within the first year after a stress-related disorder diagnosis.
‡ *P* for trend was calculated using Wald test.

We did not report the results of the analyses of other psychiatric drugs in our paper because these are ranked less important for PTSD treatment, in preference to SSRIs, and we fear **readers might easily misinterpret these results**. Since we extracted medication information from Prescribed Drug Register, our data are subjected to indication bias (i.e., the use of the treatment is relevant to the severity of the condition) which is most likely why we obtained higher HRs for patients with other antidepressants/ other psychiatric drugs, compared to patients without such a treatment. Consequently, this finding can easily be misinterpreted as 'taking these psychiatric medications may increase the risk of life-threatening infection'.

Due to the abovementioned reasons, we have opted to only report the analyses of SSRI treatment, but **we are open to reconsider our position on the editor's request. .**

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.

Authors' responses: The reviewer's concern about conflicts of interest is important but based on misunderstanding. Assuming the reviewer is referring to our paper on stress-related disorders and

autoimmune disease publish in JAMA in 2018 (*https://jamanetwork.com/journals/jama/fullarticle/2685155)*, Dr. Fang only reported a research grant from Karolinska Institutet (see quoted below). Dr. Tomasson, a co-author in our previous paper but not the current one, declaimed personal fees from Pfizer and AbbVie. Please note ***Dr. Tomasson is not a co-author of this paper***; and we, again, the authors of this paper declare no conflict of interest – relevant sources funding are clearly stated in the corresponding section.

'Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Fang reported receiving grants from the Karolinska Institutet. Dr Tomasson reported receiving personal fees from Pfizer and Abbvie……' (https://jamanetwork.com/journals/jama/fullarticle/2685155)

No reference was made to a large body of literature linking various infections to myocardial infarction, stroke and atherosclerosis.

Authors' responses: Thank you for your comment. Yes, we are aware of evidence showing a potential link between infections and various cardiovascular diseases (e.g. infection→ myocardial infarction). While we do not see how cardiovascular risk after the infection (i.e., the outcome here) relates to the validity of the reported association of interest (stress-related disorder → life-threatening infection), we did consider that other various somatic illnesses (including myocardial infarction, stroke) and associated risk of stress-related disorder, might confound the reported association. We therefore adjusted all our analyses for history of any major somatic illness. In addition, our sensitivity where severe somatic diseases (including myocardial infarction, stroke) occurred during follow-up was additionally adjusted obtained virtually unchanged estimates, suggesting these somatic conditions cannot heavily biased the observed associations.

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.

Authors' responses: We totally agree with the reviewer that, there is no guarantee that full siblings lived together or were in close contact with each other. However, it is still reasonable to assume that the majority of full siblings are raised in the same household, at least during early age. First and foremost, full siblings share 50% of their genetic makeup. Thus, the application of between-sibling comparisons should serve its main role, which is **to control for unmeasured confounders, e.g. genetic background and early familial factors**.

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.

Authors' responses: Thank you for the encouraging remarks on our study!

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.
Authors' responses: Thank you for this important comment. The requested changes have been made.
In the revised manuscript, 'Introduction' part (page 5, line 51-54):
'Strong evidence from animal models[2] and human studies[1,3] suggests a considerable modulation of the hypothalamic-pituitary-adrenal axis in response to stress, with altered biological functions such as compromised immunity (e.g., impaired humoral and cell-mediated immunity)[1] and increased inflammatory reactivity[1].'

'Meaning of the study', 'Discussion' part (page 16 line 317-324):
'Initial attempts of explaining the documented 'stress-infection' association were concentrated on altered circulating glucocorticoids and their role in suppression of cell-mediated and humoral immunity[38 39], potentially underlying increased vulnerability to infections among stressed individuals. Yet, studies testing the association between glucocorticoid levels and risk of infections have yielded mixed results[40-43]. A recent hypothesis places focus on the underlying inflammation, induced by glucocorticoid receptor resistance ensuing overproduction of inflammatory cytokines[6 44]. This notion gains support from several studies, including the present one, implying that stress experience prior to infections may exacerbate the severity of infections[4 45]'

For a similar reason, consider updating the references (1, 12,13) regarding immune profiles in stress-related disorders.
Authors' responses: Requested change has been made. In the revised manuscript, we added a newly published review paper, summarizing the modulations of inflammatory markers among individuals with PTSD.

14. Speer K, Upton D, Semple S, et al. Systemic low-grade inflammation in post-traumatic stress disorder: a systematic review. J Inflamm Res 2018;11:111-21.

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.

Authors' responses: Thank you for the important comment. As the reviewer has correctly pointed out, since 2005, exhaustion disorder was introduced to Swedish classification of stress-related disorder as 'F43.8A', which made the Swedish ICD-10 a bit different from the international ICD-10. In the revised manuscript, we have listed all specific disorders under the category of "other stress disorders" in the Supplementary Table 1. Also, we now address this change in the discussion.

'Strengths and weaknesses of this study', Discussion part (Page 14, line 271-275)

'Also, changes in the definition and diagnostic criteria of stress-related disorders over the study period may have influenced the observed associations. For instance, since 2005, exhaustion disorder has been introduced into the Swedish ICD-10 system, which results in a small difference between the Swedish and the international ICD-10 code category 'F43'. However, similar results were obtained from a stratified analysis by calendar periods, suggesting a minor influence of these factors.'

Here, we further present a sensitivity analysis showing largely similar IRs and HRs as the results of main analyses, after the exclusion of exposed patients with F43.8A diagnosis (Table R3). Given the small number of affected patients (n=3969), this sensitivity analysis was not considered informative, and therefore we did not include in the revised manuscript. **Nevertheless, we are certainly willing to reconsider our position upon editor or reviewer's request.**

Table R3 Crude incidence rate (IR) and hazard ratios (HRs) with 95% confidence intervals (CIs) for life-threatening infections among patients with stress-related disorder ***compared to matched unexposed individuals or full siblings***, excluding patients without diagnosis of exhaustion disorder*

	Sibling-based analysis		Population-based analysis	
	Number of cases (IR, per 1 000 person-years), exposed/siblings	HR (95% CI)†	Number of cases (IR, per 1 000 person-years), exposed/unexposed	HR (95% CI)€
Any stress-related disorder	2183(2.71)/2620(1.69)	1.48 (1.38 to 1.58)	3276(2.92)/15563(1.34)	1.58 (1.52 to 1.65)
Posttraumatic stress disorder	170(2.94)/175(1.59)	1.92 (1.46 to 2.52)	244(3.04)/1040(1.26)	1.95 (1.66 to 2.28)
Acute stress reaction	1012(2.65)/1268(1.69)	1.43 (1.29 to 1.58)	1569(2.93)/7500(1.35)	1.56 (1.47 to 1.66)
Adjustment disorder and other stress reactions	1001(2.74)/1177(1.69)	1.49 (1.34 to 1.65)	1463(2.88)/7023(1.34)	1.56 (1.46 to 1.66)

* Sample size for analysis in the sibling cohort: 100,095 in exposed group and 179,629 in sibling group; in the population-matched cohort: 140,950 in exposed group and 1,409,500 in unexposed group.
† Cox models were stratified by family identifiers, and adjusted for sex, birth year, education level, family income, marital status, history of severe somatic diseases, history of other psychiatric disorder, and history of inpatient visit due to infectious disease. € Cox models were stratified by matching identifiers (sex, birth year, and county of birth), and adjusted for education level, family income, marital status, history of severe somatic diseases, history of other psychiatric disorder, history of inpatient visit due to infectious disease, and family history of major life-threatening infections.

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

Authors' responses: Requested changes have been made. Besides the cited US guideline, we now also added more references introducing recommendations for PTSD treatment in other European countries.

'Stress-related disorders', Method part (page 7, line 108-112)
'We further obtained information on the dispensation of selective serotonin reuptake inhibitors (Anatomical Therapeutic Chemical [ATC] code 'N06AB') within the first year after the diagnosis of a stress-related disorder, from the Swedish Prescribed Drug Register (July 2005-). Albeit debates on its appropriateness when use among young patients[19], this medication has been widely used and recommended as the first-line pharmacotherapy for adults with stress-related disorders (e.g., in Sweden[20], UK[21], and US[22]).'

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

Authors' responses: We defined a diagnosis of other psychiatric disorders from 3 months before to 1 year after the first diagnosis of stress-related disorders as comorbidities of stress-related disorders because we observed a dramatic increase in the cumulative incidence of other psychiatric disorders during the 3-months prior to a diagnosis of stress-related disorders, compared to more than 3 months before such diagnosis (Figure R1). We suspect that this increment is related to the trauma or stressful life event leading to the diagnosis of the stress-related disorder. Therefore, this condition may indicate a more severe and symptomatic stress reactions (i.e., an index of severity). While a diagnosis of other psychiatric disorders occurs more than 3 months before the diagnosis of stress-related disorders is more likely an independent disorder, and thereby is considered as "history of other psychiatric disorders".

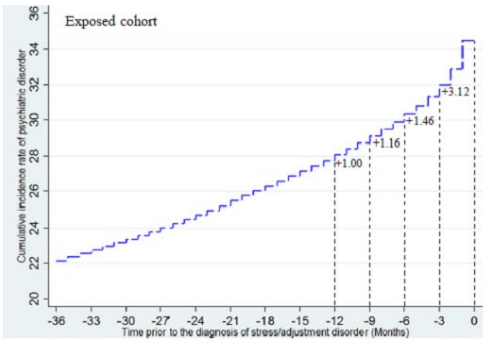

Figure R1 Cumulative incidence rate of other psychiatric disorders before a stress-related disorder

During the analyses, 'history of other psychiatric disorders' was taken into account as a confounder (being adjusted in the Cox model) and a possible effect modifier (through subgroup analyses); and the subgroup analyses for psychiatric comorbidity was mainly used as a proxy for the severity of stress-related disorder and targeted for testing if severe stress-related disorder (with psychiatric comorbidities) was more strongly associated with the outcome.

In the revised manuscript, we have added explanations about the rational of considering 'history of psychiatric disorders' and 'psychiatric comorbidity' separately.

'Covariates', Method part (page 8, line 127-132):
'Given that co-occurring psychiatric disorders may also be related to the trauma precedes the diagnosis of stress-related disorder, and represent more severe stress reactions, we considered other psychiatric diagnoses from 3 months before to 1 year after the diagnosis of stress-related disorder as 'psychiatric comorbidity'. In contrast, other psychiatric disorders documented more than 3 months before the diagnosis of a stress-related disorder were considered as 'history of other psychiatric disorders'.'

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.
Authors' responses: Thank you for the comment. We certainly agree with the reviewer that the baseline psychological and physical condition is different between exposed and unexposed groups, which might suggest that exposed patients are in general more vulnerable to infections, than unexposed individuals. However, we carefully considered these factors in our analyses.

- These potential confounding factors were always adjusted for in the Cox models.
- Our subgroup analyses further indicate that the observed associations existed independently of the status of these factors, and the magnitude of the association appears to be stronger in the less 'vulnerable' group ---- e.g., in Table 2, we observed increased risk of infections for both subgroups with and without a history of severe somatic disease, and the HR was significantly higher among patients without history of these conditions.

- The vulnerability to diseases, either due to genetic or environmental background, tends to be shared between full siblings. Therefore, the between-full sibling comparison is one attempt to control for such unmeasured confounders. In our study, we did not see a substantial difference between the results from population-based and sibling-based analyses, indicating that the vulnerability issue, if any, should not have heavily contributed to our observation.

As the reviewer mentioned, we observed higher **relative risk (not absolute risk)** among individuals without a history of severe somatic diseases/a history of other psychiatric disorders, compared to individuals with such a history. Technically, the higher HR for the former subgroup is likely due to the lower absolute risk of life-threatening infection among individuals without a history of severe somatic diseases/ a history of other psychiatric disorders. Namely, with a given absolute risk difference, it is easier to obtain a higher relative risk for the subgroup with a lower baseline risk.

We agree with the reviewer, that in spite of the above indications that the reported association is independent of past vulnerabilities, caution is needed in the interpretation. We have therefore made some changes in the Discussion section to emphasize this point:

'Strengths and weaknesses of this study', Discussion part (Page 14, line 282-285)
'Fourth, 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, 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.
Authors' responses: Thank you for the comment. We understand it may not be accurate to call these studies 'experimental', without careful descriptions. In the revised manuscript, we have added more details about the quoted studies, to clarify the meaning of 'experimental'.

'Comparison with other studies', Discussion part (page 15, line 290-296):
'*With few comparable data, our results reinforce the 'stress-infection' link illustrated in pervious experimental studies. Back in the early 1990's, Dr. Cohen reported a prospective yet non-randomized study involving 394 healthy volunteers who received viral challenge (nasal drops containing a low dose of respiratory viruses) after questionnaire-based psychological stress assessment[4]. This study demonstrated that psychological stress was associated with an increased risk of acute respiratory infections in a dose-response manner; and similar conclusions were also made in following relevant research[5,29,30].'*

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.
Authors' responses: Thank you for this important comment. The reasons why transient forms of stress-related disorder, e.g., acute stress reaction, are associated with elevated risk of severe infections can be that the focus here is on **clinically confirmed acute stress reaction, from either the inpatient or outpatient register**, which may be an indication of severity and complexity. Patients with milder forms

of the acute stress reaction, detected through primary care (from where we have no data) or not passing through the health care system at all are not involved in our analyses. Given a severe acute stress reaction-condition in the beginning, the lack of PTSD diagnosis at the following stage does not necessarily mean the disappearance of psychological symptoms. In addition, since many of psychiatric comorbidities that commonly co-occurred with acute stress reaction, such as depression, can also lead to chronic inflammation in the body, it is perhaps not surprising that acute stress reaction was associated with increased subsequent risk of severe infections. Finally, acute stress reaction may also result in the increased risk of severe infection through behavior-related changes, e.g., smoking or sleep disorders.

About the vulnerability, as we stated above (in last page), we do not find any evidence that the observed association was heavily confounded by the underlying vulnerability to infections. Nevertheless, we remain cautious in our interpretation and now state that we cannot rule out the role of such factors.

'Strengths and weaknesses of this study', Discussion part (Page 14, line 282-285)
'Fourth, 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.'

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.

Authors' responses: As we stated in 'Life-threatening infections', 'Methods' part (Page 8, line 120-121), *'death with these infections as the underlying cause of death from the Cause of Death Register*' was included in the definition of "life-threatening infections" and was used for identifying incident cases of severe infections that were not preceded by a clinical diagnosis in National Patient Register. We did not do analyses for death due to these specific severe infections specifically because of the small number of events and therefore the little statistical power, particularly for analyses on subtypes of stress-related disorders.

However, we did separate analyses for 'deaths due to other infections' (other than these specific types of serious infections). Please refer to the Figure 2 --- the corresponding HR for any stress-related disorder was 1.39 (1.16−1.65) from sibling-based analysis and 1.64 (95% CI 1.48−1.81) from population-based analysis. This result supports the notion that in addition to the increased risk of getting infected, stress-related disorder may also lead to elevated risk of getting more persistent or fatal infections.

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.

Authors' responses: Thank you for this important comment. In the revised manuscript, we have performed an additional analysis examining the potential role of behavioral factors, i.e. **diagnoses of substance use and sleep-related diseases** (as a binary variable, yes/no), in explaining the reported association. These include substance-use disorders, substance-use related somatic diseases, and sleep disorders occurring during follow-up (after the diagnosis of stress-related disorders for the exposed group for example), was additionally adjusted in the Cox regression model.

In the revised manuscript, we wrote:
'Covariates', Method part (page 10, line 142-144)
'*For sensitivity analyses on somatic comorbidities and behavior-related factors, data on the presence of severe somatic diseases (as defined above) and substance use/sleep-related diseases (Supplemental Table 1) after the index date were also extracted from the National Patient Register.'*

'Statistical analysis', Method part (page 10, line 187-193)
'In addition, to alleviate concerns that the observed associations were accounted for by the poorer health conditions or suboptimal behaviors of exposed patients than unexposed individuals after the diagnosis of a stress-related disorder, we restricted our analyses to participants without a history of severe somatic diseases and additionally adjusted the Cox models by the presence of severe somatic conditions (as time-varying variables), or substance use/sleep related diagnoses (as a binary variable) during follow-up. Lastly, to address the increased infection risk owing to anatomic defects, we repeated our analyses after excluding subjects with congenital diseases of heart or nervous system.'

Results part (page 13, line 245-248)
'Moreover, while additional adjustments for severe somatic diseases during follow-up didn't substantially modify the estimates, the HRs, especially those from population-based analyses, were attenuated after additionally adjusting for the presence of substance use/sleep-related diagnoses (Supplementary Table 7).'

In the 'Meaning of the study', Discussion part, we also added more statements about behavior related factors (page 16 line 325-333):

'Alternative explanations for the impact of severe stress reactions on life-threatening infection include behavior-related changes after the diagnosis of a stress-related disorder. In current study, as we observed further elevated relative risk among exposed patients with comorbid substance-use disorders, as well as attenuated excess risk after additionally adjusting for substance use/sleep-related diagnoses during follow-up, it is therefore possible that behavioral factors (e.g., smoking, alcohol or drug use, and sleep disturbance) at least partially mediate the observed association, through increased possibility of pathogen exposure (e.g. needle sharing among drug users[46]) and/or inducing immune dysfunction[47]. Nevertheless, it is unlikely that such behavioral factors can fully explain the rise in fatal infection-related consequences, especially those that appear shortly after a stress-related disorder diagnosis.'

In the 'Conclusion', Discussion part, we added (page 16 line 349-352):

'Further studies are needed to understand the potential mediating role of behavior-related factors in the observed association as well as the influence of various treatment modalities for stress-related disorders in reducing the excess risk of life-threatening infections.'

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.

Authors' responses: We agree with the reviewer that there is a possibility of misclassification of the exposure --- e.g., overlap (or not a clear-cut distinction) between diagnoses of adjustment disorders and mood and anxiety disorders. Such misclassification of the exposure, provided that it is non-differential to the subsequent outcomes, would tend to yield lower estimates of the real association. In addition, we are not aware of any change in insurance/reimbursement regulation regarding stress-related disorders during the study period in Sweden. But it is true that incidence of stress-related disorder shows a constant increase since 2002. In the revised manuscript, we performed a more detailed stratification analyses by calendar year at the index date: 1987-2000, 2001-2004, 2005-2013 (results shown in below and **Table 2**

in the revised manuscript) ---- albeit varied point estimates, we observed no considerable changes in HRs by calendar year period.

Table R4 Hazard ratios (HRs) with 95% confidence intervals (CIs) for life-threatening infections among patients with any stress-related disorder, ***compared to full siblings or matched unexposed individuals***, by calendar year at index date

	Sibling-based analysis		Population-based analysis	
	Number of cases (IR, per 1 000 person-years), exposed/siblings	HR (95% CI)*	Number of cases (IR, per 1 000 person-years), exposed/unexposed	HR (95% CI)†
1987-2000	1019(2.82)/1330(1.72)	1.51 (1.37 to 1.67)	1564(3.10)/7401(1.39)	1.66 (1.56 to 1.77)
2001-2005	696(2.52)/833(1.69)	1.31 (1.16 to 1.48)	1035(2.70)/5183(1.34)	1.45 (1.34 to 1.57)
2006-2013	482(2.74)/483(1.60)	1.64 (1.43 to 1.88)	693(2.81)/3100(1.25)	1.60 (1.48 to 1.74)

* Cox models were stratified by family identifiers, and adjusted for sex, birth year, education level, family income, marital status, history of severe somatic diseases, history of other psychiatric disorder, and history of inpatient visit due to infectious disease.
† Cox models were stratified by matching identifiers (sex, birth year, and county of birth), and adjusted for education level, family income, marital status, history of severe somatic diseases, history of other psychiatric disorder, history of inpatient visit due to infectious disease, and family history of major life-threatening infections.