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Complete List of Authors:	Song, Huan; University of Iceland; Karolinska Institutet, Medical Epidemiology and biostatistics Fall, Katja; Karolinska Institutet, Dept of Medical Epidemiology and Biostatistic Fang, Fang; Karolinska Institutet, Department of Medical Epidemiology and Biosta Erlendsdóttir , Helga ; University of Iceland Lu, Donghao; Karolinska Institutet, Mataix-Cols, David; Karolinska Institutet, Department of Clinical Neuroscience, Center for Psychiatry Research; Institute of Psychiatry, Psychology and Neuroscience. King's College London, Department of Psychosis Studies Fernández de la Cruz, Lorena; Karolinska Institutet, Clinical Neuroscience D'Onofrio, Brian; Indiana University, Department of Psychological and Brain Sciences Lichtenstein, Paul; Karolinska Institutet, Department of Medical Epidemiology Gottfreðsson, Magnús ; University of Iceland; Landspítali University Hospital, Department of Infectious Diseases Almqvist, Catarina; Dept of Medical Epidemiology and Biostatistics Valdimarsdttir, Unnur; Centre of Public Health Sciences, University of Iceland, Department of Medicine
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Stress-related disorders and subsequent risk of life-threatening infections: a population-based sibling-controlled cohort study

Huan Song, postdoctoral fellow[1,2,3], Katja Fall, associate professor[2,4], Fang Fang, associate professor[2], Helga Erlendsdóttir, biomedical scientist [5,6], Donghao Lu, postdoctoral fellow[2], David Mataix-Cols, professor [7,8], Lorena Fernández de la Cruz, assistant professor [7,8], Brian M D'Onofrio, professor[2,9], Paul Lichtenstein, professor[2], Magnús Gottfreðsson, professor[5,10], Catarina Almqvist, professor[2,11], Unnur A Valdimarsdóttir, professor [1,2,12]

1. Center of Public Health Sciences, Faculty of Medicine, University of Iceland, Reykjavík, Iceland

2. Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden

3. West China Biomedical Big Data Center, West China Hospital, Sichuan University, China

4. Clinical Epidemiology and Biostatistics, School of Medical Sciences, Örebro University, Örebro, Sweden

5. University of Iceland, Faculty of Medicine, Iceland.

6. Department of Clinical Microbiology, Landspítali University Hospital, Iceland.

7. Centre for Psychiatry Research, Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden.

8. Stockholm Health Care Services, Stockholm County Council, Stockholm, Sweden.

9. Department of Psychological and Brain Sciences, Indiana University, Bloomington.

10. Department of Infectious Diseases, Landspítali University Hospital, Reykjavik, Iceland.

11. Astrid Lindgren Children's Hospital, Karolinska University Hospital, Stockholm, Sweden

12. Department of Epidemiology, Harvard T H Chan School of Public Health, Boston, MA, USA

Correspondence to: Huan Song, MD, PhD, Center of Public Health Sciences, Faculty of Medicine, University of Iceland, Sturlugata 8, 101 Reykjavík, Iceland (telephone: +354-694 8388; e-mail: huan@hi.is; huan.song@ki.se). ORCID number: 0000-0003-3845-8079.

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Abstract

Objective To assess whether severe psychiatric reactions to trauma and other adversities were associated with subsequent risk of life-threatening infections

Design Population- and sibling- matched cohort study.

Setting Swedish population.

Participants 144,919 patients with stress-related disorders, including posttraumatic stress disorder (PTSD), acute stress reaction, adjustment disorder, and other stress reactions, were identified from 1987 to 2013. For comparison, we included 184,612 full siblings of these exposed patients and 1,449,190 matched unexposed individuals from general population.

Measurements Diagnoses of severe infections with high mortality rates (i.e., sepsis, endocarditis, meningitis, and other central nervous system infections) were identified through the Swedish National Patient Register. We also extracted deaths with these infections or infections of any origin from the Cause of Death Register. Controlling for multiple confounders, we used Cox models to estimate hazard ratios of these life-threatening infections.

Results The average age at diagnosis was 37 years and 38% of exposed patients were male. During a mean follow-up of 8 years, the incidence rate of life-threatening infections was 2.9, 1.7, and 1.3 per 1,000 person-years among the exposed, sibling- and matched unexposed- cohorts, respectively. 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). Stress-related disorders were associated with all studied life-threatening infections, with the highest magnitude observed for meningitis (sibling-based analysis: hazard ration 1.63 (1.23 to 2.16)) and endocarditis (1.57 (1.08 to 2.30)). Younger age at diagnosis of stress-related disorders and the presence of psychiatric comorbidity, especially substance use disorders, yielded greater hazard ratios, while persistent use of selective serotonin reuptake inhibitors throughout the first year after diagnosis of a stress-related disorder was associated with attenuated hazard ratios.

Conclusion Stress-related disorders are associated with a subsequent increased risk of life-threatening infections, independent of familial background and physical or psychiatric comorbidities.

Key words Reaction to severe stress; posttraumatic stress disorder; adjustment disorder; life-threatening infections; infection-related death; cohort study

Summary box

What is already known on this topic

Psychological stress may increase susceptibility to infections through compromised immunity. A series of experimental studies on humans and other animals suggest a link between psychological stress and acute infectious respiratory illness, while data on more severe, life-threatening infections, such as meningitis and sepsis, are limited.

What this study adds

Based on a nationwide population-based sibling-controlled analysis of 144,919 patients diagnosed with stress-related disorders, this is the first study to demonstrate a robust association between stress-related disorders and the subsequent risk of life-threatening infections —including sepsis, endocarditis, central nervous system infections, and fatal infections of any other origin. The association is more pronounced among individuals diagnosed with a stress-related disorder at a younger age, and those with psychiatric comorbidities. The long-term use of selective serotonin reuptake inhibitors was associated with attenuated risk of life-threatening infections after diagnosis of stress-related disorders.

Introduction

Excessive or prolonged psychological stress compromises several physiological systems which may increase the individual's susceptibility to disease[1]. 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]. Correspondingly, individuals exposed to psychological stress have been reported to have higher risk of respiratory virus infections[4-6] paralleled with reduced immune responses to several antiviral/bacterial vaccines[7-10].

Stress-related disorders, including posttraumatic stress disorder (PTSD), acute stress reaction (also known as acute stress disorder), adjustment disorder, and other stress reactions, refer to a group of psychiatric conditions that are preceded and triggered by an identifiable trauma or other life stressors[11]. With considerable variation in response to adverse events, individuals with stress-related disorders may represent a population with the most severe physiologic dysregulation as a result of severe stress[1]. Indeed, populations with PTSD and other stress-related disorders have been reported to have disrupted immune profiles[1,12-14] and increased risk of various autoimmune diseases[15]. Yet, data on major infections in general and life-threatening infections particularly are currently lacking. Therefore, taking advantage of nationwide registers in Sweden, providing complete information on medical diagnoses and family links, we conducted a population-based sibling-controlled cohort study to explore the association between stress-related disorders and subsequent risk of life-threatening infections.

Methods

Study Design

We first identified all Sweden-born individuals who received their first diagnosis of stress-related disorders between January 1, 1987 and December 31, 2013 (n=156,537; Figure 1) from the Swedish

National Patient Register. The National Patient Register has nationwide data from inpatient care since 1987, and specialist outpatient care since 2001. The exposed cohort was then linked to other health registers in Sweden, utilizing the national identification numbers that are uniquely assigned to all Swedish residents.

We excluded patients diagnosed below age of 5 (n=139)[16], with a history of any life-threatening infection before the diagnosis of the stress-related disorder (n=4,311), with conflicting information (died or emigrated before the diagnosis, n=24), or with missing information on county of birth (n=21). Further, to ensure the complete family links from the Swedish Multi-Generation Register[17], we excluded 7,123 patients born before 1932, leaving 144,919 patients for analysis. Patients with stress-related disorders were considered as 'exposed' from the date of their diagnosis (i.e., the index date).

Sibling cohort

To control for familial confounding[16], we constructed a sibling cohort where we compared exposed patients with their unaffected full siblings. Through the Multi-Generation Register, we identified 184,612 full siblings (of 71.1% [103,072] of all exposed patients) who were free of stress-related disorders and life-threatening infections at the date of diagnosis of the exposed patient (i.e., the index date).

Population-matched cohort

The comparison of the exposed patients to the general population was performed using a matched cohort design. We then randomly selected 10 individuals per exposed patient from the Total Population Register who were free of stress-related disorders and life-threatening infections at the diagnosis date of the exposed patient. (i.e., the index date). The unexposed individuals were individually matched to the exposed patient by sex, birth year, and county of birth.

Follow-up

Follow-up of all study participants started from the index date until the occurrence of any or a specific type of life-threatening infection, death, emigration, or the end of follow-up (December 31, 2013), whichever occurred first. The follow-up for unaffected full siblings or unexposed individuals was additionally censored if a diagnosis of stress-related disorder appeared after the index date.

Stress-related disorders

We defined stress-related disorders as any first inpatient or outpatient visit with the main diagnosis of stress-related disorders registered in the National Patient Register according to the 9th Swedish revisions of the International Classification of Diseases (ICD-9) codes 308, 309 or ICD-10 F43. Stress-related disorders were further divided into PTSD (ICD-9: 309B; ICD-10: F43.1), acute stress reaction (ICD-9: 308, 309A; ICD-10: F43.0), and adjustment disorder and other stress reactions (ICD-9: 309X; ICD-10: F43.8, F43.9, details in Supplementary Table 1). Because PTSD might initially be diagnosed as other stress-related disorders (e.g., acute stress reaction[18]), we considered all patients receiving a PTSD diagnosis within one year after their first stress-related disorder diagnosis to be PTSD patients.

We further obtained information on the dispensation of selective serotonin reuptake inhibitors (Anatomical Therapeutic Chemical 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 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]). We defined users of selective serotonin reuptake inhibitors as patients with two or more dispensations of this drug. We calculated the average dosage by dividing cumulative Defined Daily Dose by the time interval (days) from the first to the last dispensation; and this time interval was also considered as the length of selective serotonin reuptake inhibitors treatment.

Life-threatening infections

We identified incident cases of severe infections characterized by high fatality (i.e., sepsis, endocarditis, meningitis, and other central nervous system [CNS] infections), as any first inpatient or outpatient visit with these infections as the main diagnosis from the National Patient Register, or death with these infections as the underlying cause of death from the Cause of Death Register. In addition, we identified all lethal infections of any other origin by identifying deaths with other infections documented as the underlying cause of death from the Cause of Death Register (Supplementary Table 1).

Covariates

Data on education level, family income, and marital status were obtained from the Longitudinal Integration Database for Health Insurance and Labor Market study database. Other psychiatric disorders are commonly diagnosed around the diagnosis of stress-related disorders[24,25]. Given that co-occurring psychiatric disorders may also be related to the trauma preceding the diagnosis of stress-related disorder, and as such 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'. We further obtained information on history of severe somatic diseases (including myocardial infarction, congestive heart failure, cerebrovascular disease, chronic pulmonary disease, connective tissue disease, diabetes, renal diseases, liver diseases, ulcer diseases, and HIV infection/AIDS)[26] and history of inpatient visit due to any infectious disease (as an indicator of baseline susceptibility to infectious diseases). All abovementioned diagnoses were obtained from the National Patient Register, with corresponding ICD codes shown in Supplementary Table 1. Family history of major life-threatening infections was defined as any diagnosis of or death due to sepsis, endocarditis, meningitis, and other CNS infections among biological parents and full siblings of the study participants, according to the National Patient Register or the Cause of Death Register. Except for the 'history of other psychiatric disorder' and 'psychiatric comorbidity', we updated

information until the index date (i.e., baseline) for all other covariates. 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 from 1973 onwards).

Statistical analysis

We estimated the association between stress-related disorders and risk of life-threatening infections using hazard ratios with 95% confidence intervals, derived from conditional Cox regression models. Time since the index date was applied as the underlying time scale.

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). We first considered stress-related disorders as one group, and then by diagnostic categories of PTSD, acute stress reaction, and adjustment disorder and other stress reactions. Also, in addition to a diagnosis of any life-threatening infection, we separately examined the risk of sepsis, endocarditis, meningitis, other CNS infections, and deaths due to infections of any other origin.

In subgroup analyses, we calculated the hazard ratios by sex (male or female), time since index date (<1 year, 1-5 years, 6-9 years, or ≥10 years), calendar period at the index date (1987-2000,2001-2004, or 2005-2013), history of severe somatic diseases (yes or no), family history of major life-threatening infection (yes or no), history of other psychiatric disorders (yes or no), and history of inpatient visit due to any infectious diseases (yes or no). The differences of sub-grouped hazard ratios were assessed by

introducing interaction terms to the Cox models or by computing Wald tests. In addition, to examine potential effect modification by age at index date on the interested association, we applied restricted cubic splines on age and integrated it to the Cox models by adding an interaction term[28]. Age-varying hazard ratios were estimated and visualized thereafter.

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 comorbidity, 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). Within one year after the diagnosis of a stress-related disorder, we considered the psychiatric comorbidity as a time-varying variable.

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. We compared hazard ratios between sibling and population-based analyses using a z-test[29]. Further, restricting to exposed patients diagnosed a stress-related disorder after July 2005 and with more than one-year of follow-up, we compared the beyond one-year risk of life-threatening infections between subgroups of patients with different status of selective serotonin reuptake inhibitors use.

To test the robustness of the observed associations, we performed several sensitivity analyses. To rule out the possibility that the observed risk increase was due to a pre-existing or co-occurring medical condition, we excluded from the analysis individuals with any diagnosis of severe somatic diseases, injuries and poisonings, or infectious diseases (see codes in Supplemental Table 1) within 1 year prior to the index date. 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 defect, we repeated our analyses after excluding subjects with congenital diseases of heart or nervous system. All analyses were conducted in SAS statistical software, version 9.4 (Cary, NC) and STATA 15 (StataCorp LP).

Patient and Public Involvement

No patients were involved in proposing the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study. There are no plans to directly disseminate the results of the research to study participants or the relevant patient community. The dissemination to the Swedish population (which constitutes the study population) will be achieved through a media outreach (e.g. press release and communication) upon publication of this study.

Results

In total, the sibling cohort accrued 2,370,354 person-years, with an approximately 8-year average duration of follow-up. The mean age at entry was 37 years (Table 1), and 38.3% of the exposed patients were male. Prior history of other psychiatric disorders, severe somatic diseases, and inpatient stay due to infectious diseases were more common among exposed patients than among their full siblings (34.8% vs 12.6%, 16.5% vs 12.8%, and 30.9% vs 23.8%, respectively). In addition, exposed patients tended to have lower family income and were more likely to be divorced or widowed (Table 1).

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).

Based on both sibling and population-based analyses, the observed associations did not differ by sex, calendar period, family history of life-threatening infections, or history of inpatient stay due to infectious disease (Table 2 and Supplementary Table 2), but seemed stronger among participants without a history of severe somatic diseases (*P* for interaction<.001 in population-based analysis), without history of other psychiatric disorders (*P* for interaction<.001 in population-based analysis), and within the first year after the diagnosis of a stress-related disorder (*P* for difference<.001 in population-based analysis). Moreover, an age-dependent risk pattern suggested a linear decline in hazard ratios with increased age at diagnosis (Figure 3).

Additionally, we obtained higher hazard ratios for any stress-related disorder diagnosed through inpatient hospital care, than those from outpatient specialist care (Supplementary Table 3, *P* for difference= 0.009 according to population-based analysis). For patients with stress-related disorders other than PTSD, the presence of psychiatric comorbidity, especially comorbid substance use disorders, was linked to further elevated relative risk of life-threatening infections in both sibling and population-based analyses (Supplementary Figure 2).

Among exposed patients diagnosed after July 2005 (n=74,691), we found that use of selective serotonin reuptake inhibitors after the diagnosis of a stress-related disorder was associated with lower

beyond one-year risk of life-threatening infections (user compared to non-user: hazard ratio=0.81 (0.66 to 0.98), *P*= 0.032). Indeed, persistence in use of selective serotonin reuptake inhibitors throughout the first year after a stress-related disorder diagnosis was associated with a linear attenuation in the relative risk of subsequent life-threatening infections (hazard ratio =0.96 (0.66 to1.40), 0.85 (0.64 to 1.13), and 0.70 (0.52 to0.94) for ⩽179, 180-319, and ⩾320 days of use, respectively, *P* for trend=0.014; Supplementary Table 4).

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 did not substantially modify the estimates, the HRs, especially those from the population-based analyses, were attenuated after additionally adjusting for the presence of substance use/sleep-related diagnoses during follow-up (Supplementary Table 7).

Discussion

Principal findings of the study

To our knowledge, this is the first population-based and sibling-controlled study exploring the association between stress-related disorders and subsequent risk of life-threatening infections. We found that individuals with stress-related disorders, particularly when diagnosed at a young age, were at considerably elevated risk of experiencing life-threatening infections, independently of sex, familial background, and baseline physical or psychiatric conditions. Psychiatric comorbidities, especially substance use disorders, were associated with further risk elevation whilst the long-term (beyond one year) risk of life-threatening infections seemed attenuated by persistent use of selective serotonin reuptake inhibitors during the first year after the diagnosis of a stress-related disorder.

Strengths and weaknesses of this study

The major merit of our study was the use of large population-based cohort with a complete follow-up up to 27 years and the comparison within full siblings to address the a priori concern for familial confounding[16]. Information bias was minimized because the diagnosis and registration of exposure and outcome were compiled prospectively and independently. Also, because most of the outcomes of interest (e.g., sepsis, meningitis) are aggressive diseases, characterized by sudden-onset and severe symptoms, the influence of surveillance bias or delayed diagnosis should be minor, if any. Furthermore, the large sample size provided sufficient statistical power for detailed subgroup analyses; and the availability of rich sociodemographic and medical information enabled considerations of a wide range of important confounding and mediating factors.

Notable limitations include: first, the late establishment of Swedish Outpatient Register (2001-) potentially leads to the underestimated number of stress-related disorder cases, especially the milder forms. 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 sub-analysis of different calendar periods, suggesting a minor influence of these factors. 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. Third, although trauma-focused psychotherapy was given the highest priority for PTSD treatment in many countries including Sweden[21], 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. 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. Fifth, this study only involved patients who received a clinical diagnosis of stress-related disorders through a hospital or specialist visit, thus the generalizability of our findings to individuals with less severe stress reaction or daily stress needs further assessment.

Comparison with other studies

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[5,30,31]. However, since common respiratory viral infections are the predominant disease models in all aforementioned investigations, it has remained unclear whether the stress-induced immune modulation can lead to more severe infection-related consequences.

Consistent with our findings, one recent cohort study[32] indicated that a higher perceived stress level was moderately associated with the 1-year and 10-year risk of sepsis in a sample of 30,183 community-dwelling adults from US aged 45 years or older. Although suggestive, this study was based on one-time measurement of psychological stress in an aged population, with limited control of familial- and co-morbidity factors.

Meaning of the study

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), may increase the subsequent risk of life-threatening infections, both in the short and long term. Importantly, the observed excess risks seemed

relatively independent of most of the known risk factors of the studied infections[33-35], 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. 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.

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[39,40], 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[41-44]. A recent hypothesis places focus on the underlying inflammation, induced by glucocorticoid receptor resistance ensuing overproduction of inflammatory cytokines[6,45]. This notion gains support from several studies, including the present one, implying that stress experience prior to infections may exacerbate the severity of infections[4,46].

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[47]) and/or inducing immune dysfunction[48]. 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.

Our finding suggesting that individuals exposed to stress-related disorders in early life experience 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[49,50], interrupting neuropsychological/cognitive development[51,52], or gene-environment interplay[53]. Indeed, the extent of epigenetic modifications, measured as gene-expression changes, were up to 12 times higher in the childhood trauma-exposed individuals with PTSD compared to childhood trauma-free PTSD individuals[53]. These results constitute a molecular basis implying potentially more extensive biological disruptions, and thereby worse health outcomes for younger, rather than older, patients with stress-related disorders.

Conclusions

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.

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Footnotes

Contributors: Study concept and design: HS, UV; data analysis: HS, UV, KF, FF; data interpretation: UV, HS, KF, FF, HE, DL, DMC, LFC, BDO, PL, MG, CA; drafting of the manuscript: HS, UV, KF, FF, HE, DL, DMC, LFC, BDO, PL, MG, CA. HS and UV had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data. HS and UV are guarantors of the article.

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Ethical approval: The study was approved by the Regional Ethics Review Board in Stockholm, Sweden (Dnr. 2013/862-31/5).

Data sharing: No additional data available.

Transparency: The study guarantors (HS and UV) affirm that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Figure legends:

Figure 1 Study design

* Major life-threatening infections of interest include sepsis, endocarditis, meningitis, and other central nervous system infections (excl. meningitis).

Figure 2 Crude incidence rate (IR) and hazard ratios (HRs) with 95% confidence intervals (CIs) for life-threatening infections among patients with any stress-related disorder and posttraumatic stress disorder, ***compared to full siblings or matched unexposed individuals***

CNS, central nervous system.
[a] 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.

[b] 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.

Figure 3 The association between stress-related disorder and life-threatening infections by age at the index date

* Restricted cubic splines were applied on age at index date, with 5 knots placed at 5, 27.5, 50, 72.5, and 95 quantiles of the distribution of outcome events. Then, age-varying hazard ratios were predicted based on fully adjusted Cox models where interaction terms between stress-related disorder and splined age profiles were added. In sibling-based analysis, the 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 inpatient visit due to infectious disease, and history of other psychiatric disorder.

† In population-based analysis, the cox models were stratified by matching identifiers, i.e., sex, birth year, and county of birth, and adjusted for education level, family income, marital status, history of severe somatic diseases, history of inpatient visit due to infectious disease, history of other psychiatric disorder, and family history of major life-threatening infections

Table 1 Characteristics of the study cohorts

	Sibling cohort		Population-based cohort	
	Exposed cohort	Sibling cohort	Exposed cohort'	Matched unexposed cohort
Number of participants	103072	184612	144919	1449190
Age at index date, mean±SD, year	37.0±13.9	38.0±15.1	37.2±14.3	37.2±14.3
Follow-up time, mean±SD, year	7.8±6.4	8.5±6.8	7.9±6.5	8.1±6.6
% of male	38.3%	51.0%	38.3%	38.3%
Education level, n (%)				
<9 years	4191 (4.1)	11919 (6.5)	6453 (4.4)	58565 (4.0)
9-12 years	73505 (71.3)	126305 (68.4)	103252 (71.3)	941393 (65.0)
>12 years	23839 (23.1)	41569 (22.5)	32625 (22.5)	426442 (29.4)
Unknown	1537 (1.5)	4819 (2.6)	2589 (1.8)	22790 (1.6)
Yearly family income level, n (%)				
Lowest 20%	22941 (22.3)	33782 (18.3)	32847 (22.7)	247467 (17.1)
Middle	56877 (55.2)	95927 (52.0)	79051 (54.6)	799409 (55.2)
Top 20%	13160 (12.8)	29946 (16.2)	18292 (12.6)	254009 (17.5)
Unknown	10094 (9.8)	24957 (13.5)	14729 (10.2)	148305 (10.2)
Marital status, n (%)				
Single	58791 (57.0)	100525 (54.5)	82425 (56.9)	823667 (56.8)
Married or cohabiting	30730 (29.8)	66694 (36.1)	42868 (29.6)	514251 (35.5)
Divorced or widowed	13551 (13.2)	17393 (9.4)	19626 (13.5)	111272 (7.7)
History of severe somatic diseases[*], n (%)				
Yes	17020 (16.5)	23534 (12.8)	24004 (16.6)	145619 (10.1)
No	86052 (83.5)	161078 (87.3)	120915 (83.4)	1303571 (90.0)
History of other psychiatric disorders[†], n (%)				
Yes	36202 (34.8)	23466 (12.6)	51905 (35.8)	118910 (8.2)
No	67860 (65.2)	162605 (87.4)	93014 (64.2)	1330280 (91.8)
Family history of major life-threatening infections, n (%)				
Yes	10992 (10.7)	20455 (11.1)	15548 (10.7)	134214 (9.3)
No	92080 (89.3)	164157 (88.9)	129371 (89.3)	1314976 (90.7)
History of inpatient visit due to any infectious disease, n (%)				
Yes	31836 (30.9)	43956(23.8)	46269(31.9)	307370(21.2)
No	71236(69.1)	140656(76.2)	98750(68.1)	1141820(78.8)
Type of stress-related disorders, n (%)				
Diagnosis type				
Posttraumatic stress disorder	8105 (7.8)	-	11541 (7.9)	-
Acute stress reaction	47195 (45.8)	-	66758 (46.1)	-
Adjustment disorder and other stress reaction	47772 (46.4)	-	66620 (46.0)	-
Type of psychiatric care received at diagnosis				
Inpatient	37352 (36.2)	-	52817 (36.5)	-
Outpatient	65720 (63.8)	-	92102 (63.5)	-
Psychiatric comorbidity[€]				
Any				
Yes	22619 (21.9)	-	31415 (21.7)	-
No	80453 (78.1)	-	113504 (78.3)	-
Depression				
Yes	10581(10.3)	-	14500 (10.0)	-
No	92491(89.7)	-	130419 (90.0)	-

Anxiety					
Yes	6683(6.5)	-		9222 (6.4)	-
No	96389(93.5)	-		135697 (93.6)	-
Substance use disorder					
Yes	4567(4.4)	-		6514(4.5)	-
No	98505(95.6)	-		138405 (95.5)	-

* Involved somatic diseases included myocardial infarction, congestive heart failure, cerebrovascular disease, chronic pulmonary disease, connective tissue disease, dementia, diabetes, renal diseases, liver diseases, ulcer diseases, and HIV infection/AIDS.

†The first diagnosis of a psychiatric disorder, other than stress-related disorders, occurred *more than* 3 months prior to the index date (i.e., the diagnosis date of exposed patients, or the diagnosis date of the index patient for matched unexposed individuals and siblings).

€ A new-onset psychiatric disorder, other than stress-related disorders, diagnosed *from* 3 months before *to* 1 year after the diagnosis of a stress-related disorder.

Table 2 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 different characteristics

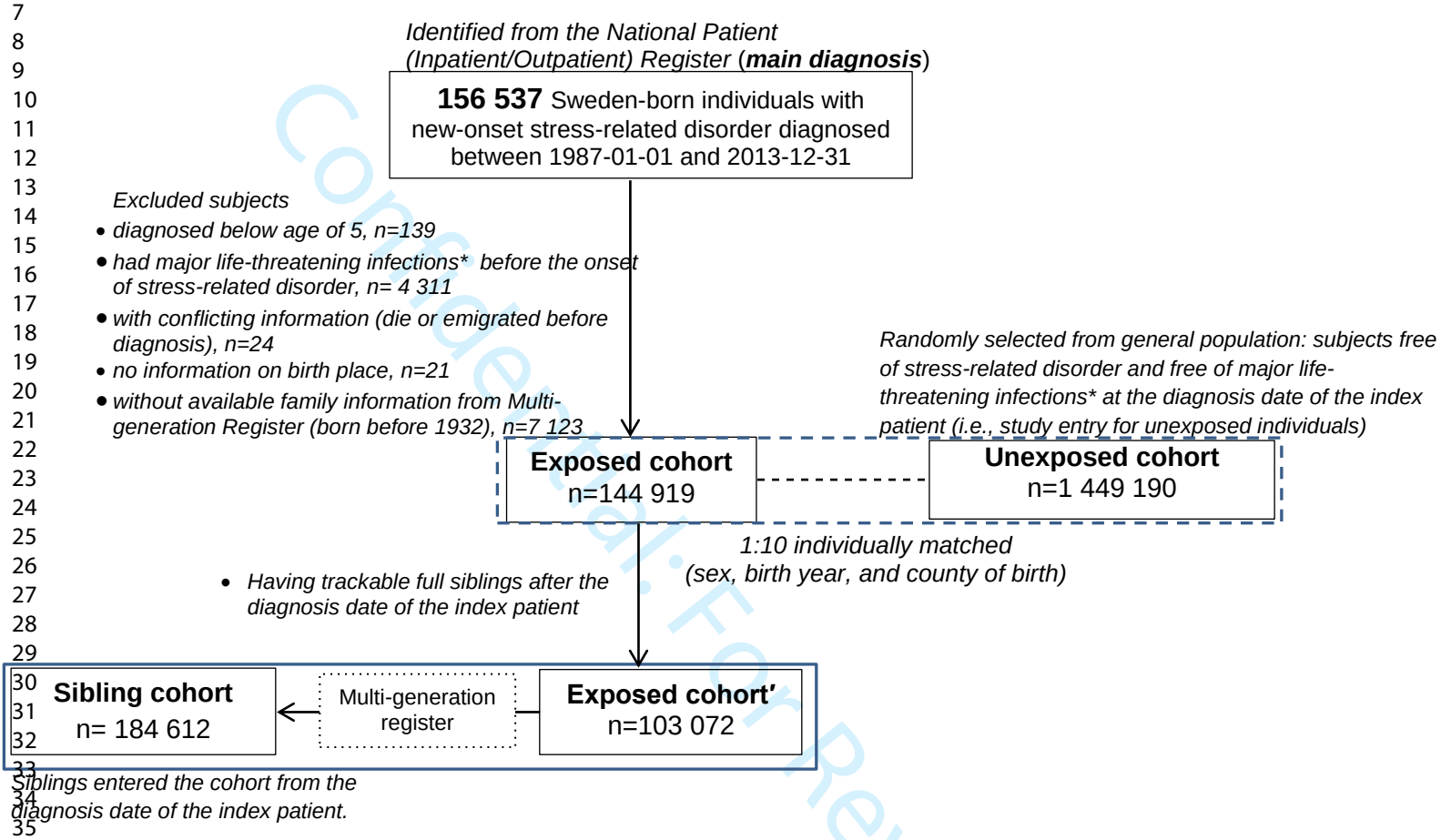
	Sibling-based analysis		Population-based analysis	
	Number of cases (IR, per 1 000 person-years), exposed/siblings	HR (95% CI)*	Number of cases (IR, per 1 000 person-years), exposed/unexposed	HR (95% CI)†
By gender				
Male	983(3.11)/1500(1.89)	1.44 (1.26 to 1.64)	1444(3.29)/7034(1.52)	1.57 (1.47 to 1.67)
Female	1214(2.44)/1146(1.48)	1.41 (1.24 to 1.59)	1848(2.66)/8650(1.22)	1.59 (1.50 to 1.68)
By time since index date				
< 1 year	266(2.71)/230(1.30)	1.61 (1.30 to 2.00)	410(2.98)/1438(1.04)	2.04 (1.81 to 2.30)
1-4 years	723(2.34)/805(1.42)	1.53 (1.36 to 1.73)	1045(2.43)/5053(1.16)	1.45 (1.35 to 1.56)
5-9 years	543(2.45)/694(1.64)	1.35 (1.18 to 1.54)	811(2.64)/3941(1.25)	1.51 (1.39 to 1.65)
≥10 years	665(3.59)/917(2.30)	1.50 (1.32 to 1.70)	1026(3.99)/5252(1.88)	1.65 (1.53 to 1.78)
History of severe somatic diseases€				
Yes	676(5.66)/663(3.92)	1.37 (1.06 to 1.76)	1044(6.09)/3452(3.40)	1.38 (1.23 to 1.56)
No	1521(2.19)/1983(1.42)	1.49 (1.37 to 1.62)	2248(2.34)/12232(1.14)	1.65 (1.57 to 1.73)
By calendar year at index date				
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)
By previous history of psychiatric disorders‡				
Yes	967(4.09)/576(3.86)	1.25 (1.01 to 1.56)	1465(4.33)/2308(3.44)	1.26 (1.12 to 1.41)
No	1230(2.13)/2070(1.46)	1.58 (1.45 to 1.73)	1827(2.30)/13376(1.21)	1.79 (1.70 to 1.88)
By family history of major life-threatening infections				
Yes	219(3.47)/248(1.99)	1.51 (1.20 to 1.89)	300(3.43)/1259(1.64)	1.81 (1.39 to 2.37)
No	1978(2.64)/2398(1.66)	1.38 (1.28 to 1.48)	2992(2.86)/14425(1.32)	1.60 (1.53 to 1.67)
By history of inpatient stay due to infectious disease				
Yes	931(3.94)/812(2.50)	1.25 (1.03 to 1.50)	1405(4.14)/4321(2.04)	1.52 (1.39 to 1.66)
No	1266(2.19)/1834(1.48)	1.58 (1.44 to 1.74)	1887(2.38)/11363(1.19)	1.69 (1.60 to 1.78)

*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.

€ Involved somatic diseases included myocardial infarction, congestive heart failure, cerebrovascular disease, chronic pulmonary disease, connective tissue disease, dementia, diabetes, renal diseases, liver diseases, ulcer diseases, and HIV infection/AIDS.

‡The first diagnosis of a psychiatric disorder, other than stress-related disorders, occurred more than 3 months prior to the index date.



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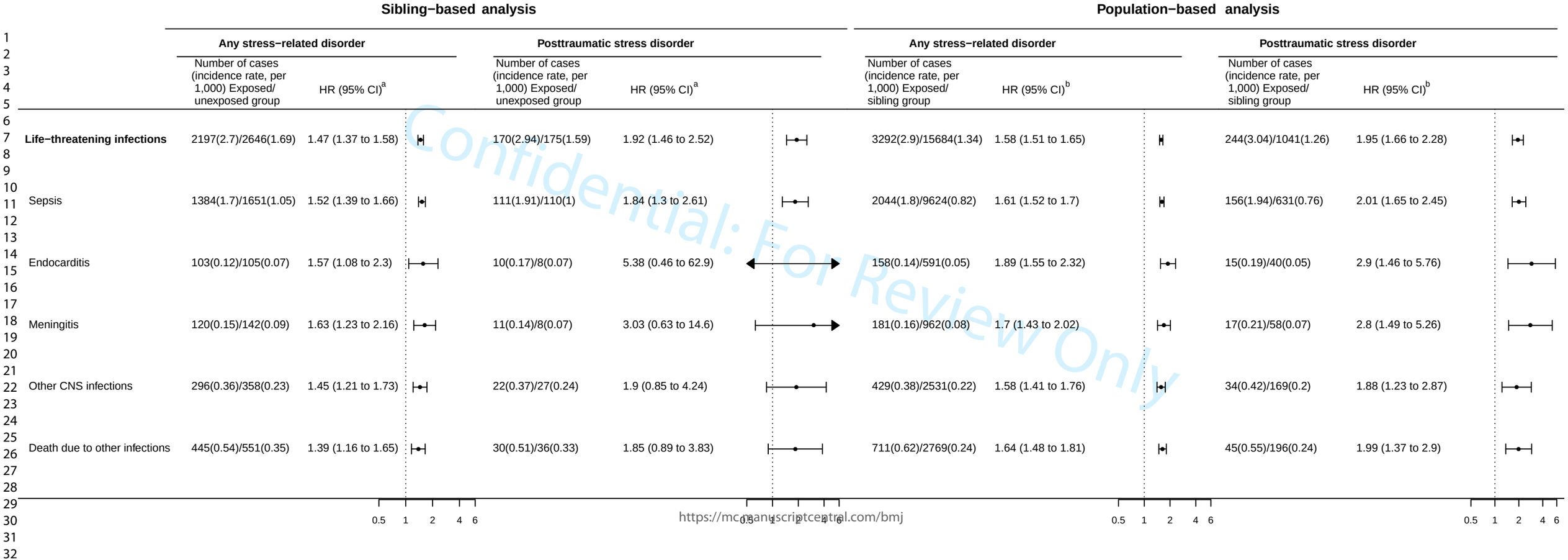
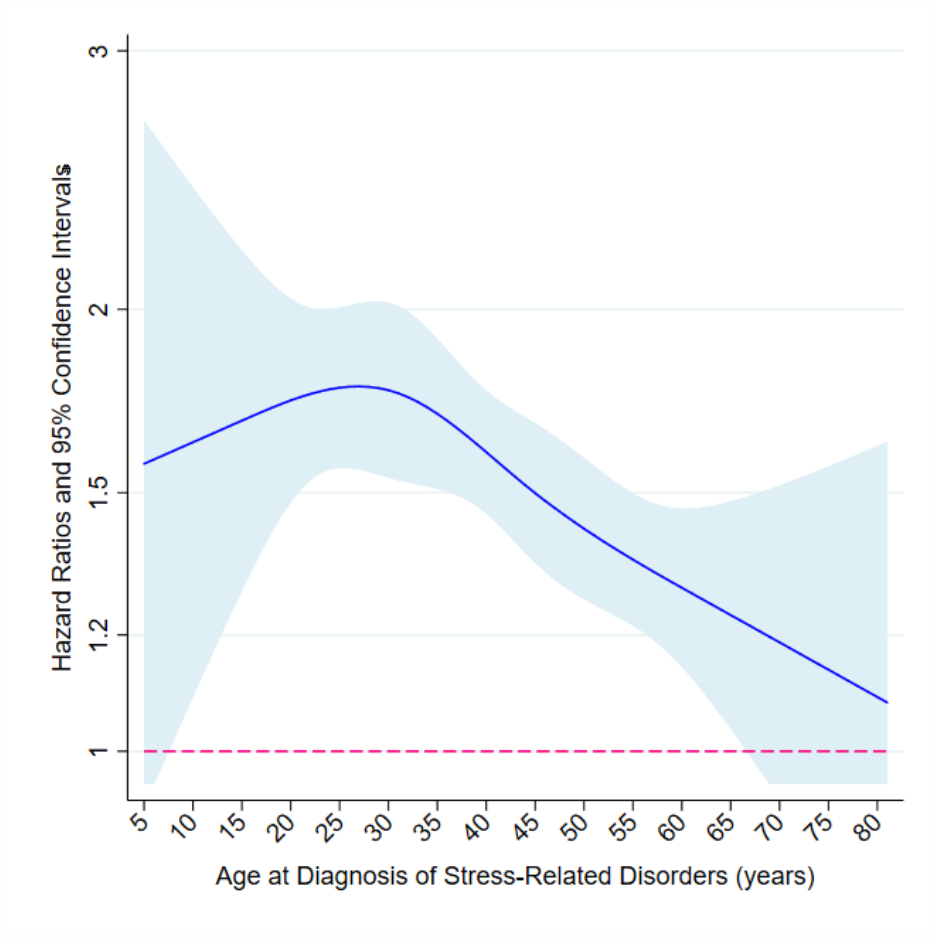
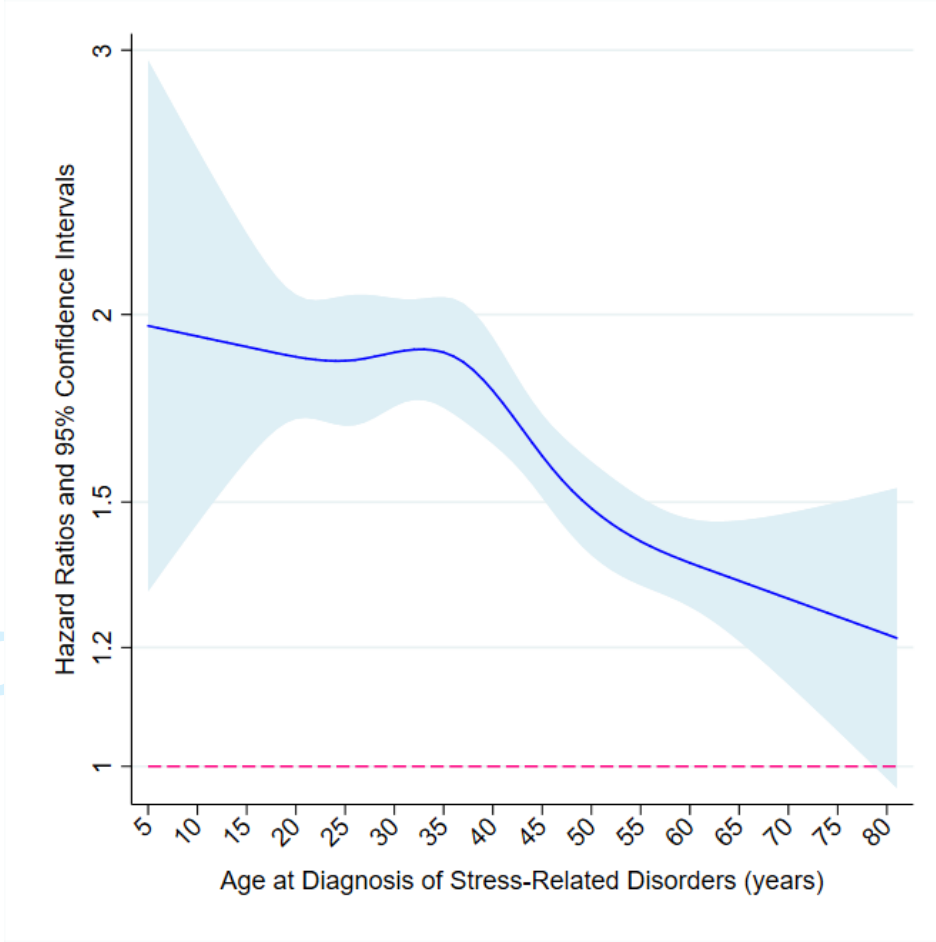


Sibling-based analysis



Population-based analysis



Supplementary Table 1 International Classification of Diseases (ICD) codes for exposure, outcome and covariate identification

Major category	Subgroup	ICD-10 codes	ICD-9 codes (Swedish version)
Stress related disorder		F43	308, 309
Posttraumatic stress disorder		F43.1	309B
Acute stress reaction		F43.0	308, 309A
Adjustment disorder		F43.2	309X
Other stress reactions	Other specified reactions to severe stress, including exhaustion disorder	F43.8	309X
	Reactions to severe stress, unspecified	F43.9	309X
Other psychiatric disorders			
Any other psychiatric disorder		F00-F99 (excl. F43)	209-315 (excl. 308, 309)
Depression		F32, F33	296B
Anxiety		F40, F41	300A, 300C
Substance use disorders		F10-F19	291, 303, 304, 305A, 305X
Major life-threatening infections			
Sepsis		A02.1, A04.0–A04.3, A39 (excl. A39.0, A39.1, A39.81,A39.9), A40–A41, A42.7, A48, A90–A99, B37.7, B38.7, B39.3, B40.7, B41.7, B42.7, B44.7, B45.7, B46.4, B95–B99	036C–036E, 038, 084, 112F, 117D
Endocarditis		I33, I38, I39	421, 424X
Meningitis		A17, A39.0, A39.9, G00-G03	013, 036A, 036X, 320-322
Other central nervous system infections		A06.6, A39.81, A80–A89, B00.3, B00.4, B01.0, B01.1,B02.0, B02.1, B05.0, B05.1, B06.0, B22.0, B26.1, B26.2, B37.5, B38.4, B43.1, B50.0, B58.2, B60.2, G04–G08	006F, 036B, 045–049, 052B, 053A, 053B, 054D, 054H, 055A, 056A, 062–064, 072B, 072C, 094, 136C, 323–325
Infection-related death (from the Cause of Death Register)			
Death due to major life-threatening infections	(Sepsis/endocarditis/meningitis/other CNS infections)	See above	See above
Death due to other infections			
Infection of respiratory tract	Upper respiratory infections and infections of the ear	J00-J06, J32, J35.0, J37.0, J37.1, H60, H65-H67, H70	380-383, 460-465, 473, 474
	Lower respiratory infections	J09-J18, J20-J22, J40-J42	466, 480-487, 490, 491B
Sexually transmitted, reproductive, and urinary tract infections		A50-A60, A63.0, A63.8, A64, B20-B24(excl. B22.0), B37.3, B37.4, N10-12, N13.6, N15.1, N15.9, N30, N34.0, N39.0, N41.0-N41.3, N43.1, N45, N48.1, N48.2, N49, N61, N70-N76, N77.1	042-044, 054B, 078J, 090-093,095-098 (excl.098E), 099A, 099C, 099D,099E, 112B, 112C, 131A, 590, 595, 599A, 601A-601D, 603B, 604A, 604X, 607B, 607C, 608A, 608E, 614-616

Infections of gastrointestinal tract	Intestinal infections	A00-A09 (excl. A02.1, A04.0–A04.3, A06.6)	001-009 (excl.006F)
	Hepatitis	B15-B19	070
	Gastritis and duodenitis	K29	535
	Appendicitis	K35-K37	540-542
Other infections	Skin	A46, L01-L08	035,680-686
	Eye infections	A54.3, B30, H00.0, H01.0, H04.0, H04.3, H05.0, H05.1, H10, H16, H32	077, 098E, 360A, 360B, 370, 372A-372D, 373, 375A, 376A, 376B
	Infections of the circulatory system (excl. endocarditis)	I30.0, I30.1, I40.0	420, 422
	Infections of the musculoskeletal system and connective tissue	M00, M01, M46, M60.0, M65, M71.0, M71.1, M86	711, 727A, 728A, 729E, 730
	Other bacterial infections	A15-A19, A20-A28, A30-A38, A39 (excl.A39.0, A39.81, A39.9), A42 (excl. A42.7), A43-A45, A47, A49, A65-A69, A70-A79	010-012, 014-018, 020-027,030-034, 035, 036 (excl. 036A,036B, 036X), 037,039-041(excl.040W), 080-083, 100-104
	Other viral infections	B00-B09 (excl. B00.3, B00.4, B01.0, B01.1, B02.0, B02.1, B05.0, B05.1, B06.0), B25, B26 (excl. B26.1, B26.2), B27-B29,B31-B34	050-059 (excl. 052B, 053A, 053B, 054D, 054H, 055A, 056A), 060, 061, 065, 066, 071-076 (excl. 072B, 072C), 078, 079
	Other infectious and parasitic diseases	B35, B36, B37(excl. B37.3-B37.5, B37.7), B38 (excl. B38.4, B38.7), B39-B89 (excl. B43.1, B44.7, B45.7, B46.4, B50.0, B58.2, B60.2)	084-088, 110-111,112A,112D,112E,112X, 113-118(excl. 117D), 120-139 (excl.131A, 136C)
Covariates: severe somatic conditions			
Myocardial infarction		I21, I22, I25.2	410,412
Congestive heart failure		I50	428
Cerebrovascular disease		G45, G46, I60-I69	430-438
Chronic pulmonary disease		J40-J47	490-496
Connective tissue disease		M05, M06, M32-M34, M35.1, M35.3	710A, 710B, 710E, 714A, 714B, 714C, 714W,714X, 725
Diabetes		E10-E14	250
Renal diseases		N01, N03, N05.2-N05.7	582,583
Liver diseases		K70.2-K70.4, K71.7, K72.1, K72.9, K73, K74, K76.6, K76.7	571C, 571E,571F, 571G, 572C, 572D, 572E, 572W, 456A, 456B, 456C
Ulcer diseases		K25-K28	531-534
HIV infection/AIDS		B20-B24 (excl. B22.0)	042-044
Covariates: any infectious disease (from National Patient Register)		A00- B99, G00–G08, H10, K29, K35-K37, L01-L08, M00, M01, M46, M60.0, M65, N10-12, N30, N41, N45, J00-J06, J09-J18, J20-J22, J32, J40-J42, I30, I33, I38-I40	001-139, 320–325, 372, 535, 540-542, 680-686, 711, 590, 595, 601, 604, 460-466, 472-474, 480-487, 490, 420-422, 424X

Covariates: for sensitivity analyses			
Injury and poisoning		S00-T98	800-995
	Alcohol use disorder and somatic diseases explicitly linked to alcohol misuse	F10, G31.2, G62.1, I42.6, K29.2, K70, K85.2	291,303,305A, 357F, 425F, 535D, 571A-D
Substance use/sleep-related diagnoses	Tobacco use disorder and somatic diseases highly relevant to tobacco use	F17, J41-J44	305B, 491,492
	Drug use disorder	F11-F16, F18, F19	304
	Sleep disorder	G47, F51, F90	780F,307E

Supplementary Table 2 Crude incidence rate (IR) and hazard ratios (HRs) with 95% confidence intervals (CIs) for life-threatening infections among patients with different types of stress-related infections, ***compared to matched unexposed individuals***, by different characteristics

	Posttraumatic stress disorder		Acute stress reaction		Adjustment disorder and other stress reactions	
	Number of cases (IR, per 1 000 person-years), exposed/unexposed	HR (95% CI)*	Number of cases (IR, per 1 000 person-years), exposed/unexposed	HR (95% CI)*	Number of cases (IR, per 1 000 person-years), exposed/unexposed	HR (95% CI)*
By gender						
Male	94(3.73)/405(1.54)	2.12 (1.65 to 2.73)	729(3.27)/3537(1.50)	1.55 (1.42 to 1.69)	621(3.25)/3092(1.54)	1.54 (1.40 to 1.70)
Female	150(2.72)/636(1.13)	1.87 (1.53 to 2.29)	841(2.69)/3964(1.24)	1.58 (1.45 to 1.71)	857(2.62)/4050(1.22)	1.56 (1.44 to 1.70)
By time since index date						
< 1 year	25(2.31)/104(0.96)	1.86 (1.12 to 3.10)	213(3.37)/677(1.06)	2.26 (1.91 to 2.68)	172(2.71)/657(1.03)	1.84 (1.53 to 2.22)
1-4 years	71(2.27)/313(1.00)	1.59 (1.19 to 2.13)	479(2.44)/2290(1.15)	1.45 (1.30 to 1.62)	495(2.44)/2450(1.19)	1.45 (1.30 to 1.61)
5-9 years	61(3.08)/206(1.02)	2.42 (1.74 to 3.37)	374(2.60)/1890(1.27)	1.46 (1.29 to 1.65)	376(2.62)/1845(1.25)	1.49 (1.32 to 1.69)
≥10 years	87(4.74)/418(2.11)	2.01 (1.56 to 2.60)	504(3.82)/2644(1.85)	1.57 (1.41 to 1.75)	435(4.07)/2190(1.89)	1.68 (1.49 to 1.88)
History of severe somatic diseases†						
Yes	77(6.15)/206(2.95)	1.45 (0.91 to 2.30)	496(6.18)/1642(3.46)	1.37 (1.14 to 1.64)	471(5.99)/1604(3.42)	1.39 (1.16 to 1.66)
No	167(2.46)/835(1.11)	1.86 (1.54 to 2.25)	1074(2.36)/5859(1.15)	1.65 (1.53 to 1.77)	1007(2.29)/5538(1.14)	1.63 (1.51 to 1.75)
By calendar year at index date						
1987-2000	114(3.38)/530(1.48)	2.07 (1.66 to 2.60)	757(3.03)/3624(1.37)	1.63 (1.49 to 1.78)	601(3.05)/2871(1.37)	1.65 (1.49 to 1.82)
2001-2013	130(2.79)/511(1.10)	1.84 (1.48 to 2.29)	813(2.85)/3877(1.34)	1.51 (1.39 to 1.64)	877(2.74)/4271(1.32)	1.51 (1.40 to 1.64)
By previous history of other psychiatric disorders€						
Yes	105(3.57)/125(2.58)	2.29 (1.47 to 3.56)	729(4.73)/1091(3.50)	1.24 (1.05 to 1.46)	631(4.07)/1092(3.53)	1.17 (0.98 to 1.39)
No	139(2.73)/916(1.18)	2.14 (1.76 to 2.59)	841(2.20)/6410(1.22)	1.70 (1.57 to 1.83)	847(2.34)/6050(1.21)	1.84 (1.70 to 1.98)
By family history of major life-threatening infections						
Yes	20(3.35)/83(1.63)	2.86 (0.88 to 9.31)	144(3.64)/611(1.77)	1.59 (1.06 to 2.38)	136(3.24)/565(1.53)	1.96 (1.33 to 2.89)
No	224(3.01)/958(1.24)	1.93 (1.64 to 2.28)	1426(2.87)/6890(1.32)	1.59 (1.49 to 1.69)	1342(2.82)/6577(1.33)	1.57 (1.47 to 1.68)

By history of inpatient visit due to infectious disease						
Yes	106(4.34)/256(1.73)	2.08 (1.47 to 2.96)	707(4.33)/2026(2.04)	1.69 (1.48 to 1.93)	592(3.90)/2039(2.09)	1.31 (1.14 to 1.50)
No	138(2.47)/785(1.16)	1.81 (1.48 to 2.22)	863(2.32)/5475(1.20)	1.61 (1.49 to 1.74)	886(2.42)/5103(1.17)	1.76 (1.63 to 1.91)

* 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.

† Involved somatic diseases included myocardial infarction, congestive heart failure, cerebrovascular disease, chronic pulmonary disease, connective tissue disease, dementia, diabetes, renal diseases, liver diseases, ulcer diseases, and HIV infection/AIDS.

€The first diagnosis of a psychiatric disorder, other than stress-related disorders, occurred more than 3 months prior to the index date

Supplementary Table 3 Relative risks of life-threatening infections among stress-related disorder patients, sub-grouped by the type of medical care received at diagnosis, ***compared to full siblings or matched unexposed individuals***

	Type of medical 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.

Supplementary Table 4 Relative risks for life-threatening infections among stress-related disorders patients[*] ***with difference status of serotonin selective reuptake inhibitors (SSRI) use***

Information on SSRI use during **the first year** after a stress-related disorder diagnosis	Number of cases (incidence rate, per 1 000 person-years) among exposed patients	Hazard ratios (95% confidence intervals)[†]
SSRI user[€]		
No	582(2.72)	Reference
Yes	133(2.63)	0.81 (0.66 to 0.98)
P for difference		0.032
Average dosage level of SSRI (by median)		
Not user	582(2.72)	Reference
≤ 1.2 DDD	62(2.32)	0.77 (0.63 to 0.93)
> 1.2 DDD	71(2.98)	0.86 (0.69 to 1.07)
P for trend[‡]		0.090
Duration of SSRI (by tertiles)		
Not user	582(2.72)	Reference
≤179 days	29(3.10)	0.96 (0.66 to 1.40)
180-319 days	54(2.74)	0.85 (0.64 to 1.13)
≥320 days	50(2.33)	0.70 (0.52 to 0.94)
P for trend[‡]		0.014

DDD, Defined Daily Dose

[*] 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 SSRI users as individuals with two or more dispensations of SSRIs within the first year after a stress-related disorder diagnosis.

[‡] *P* for trend was calculated using Wald test.

Supplementary Table 5 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 full siblings or matched unexposed individuals***, restricting to participants without any diagnosis of severe somatic diseases/injury/infectious diseases within 1 year prior to the 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)€
Any stress-related disorder	1425(2.28)/1617(1.45)	1.52 (1.39 to 1.65)	2146(2.46)/10034(1.19)	1.62 (1.54 to 1.71)
Posttraumatic stress disorder	113(2.64)/106(1.38)	2.10 (1.49 to 2.97)	160(2.67)/666(1.15)	1.91 (1.57 to 2.31)
Acute stress reaction	647(2.24)/755(1.44)	1.46 (1.28 to 1.66)	1016(2.51)/4742(1.20)	1.63 (1.51 to 1.76)
Adjustment disorder and other stress reactions	665(2.27)/756(1.47)	1.52 (1.34 to 1.72)	970(2.39)/4626(1.18)	1.58 (1.47 to 1.71)

* Sample size for analysis in the sibling cohort: 77,746 in exposed group and 126,379 in sibling group; in the population-matched cohort: 110,125 in exposed group and 1,019,447 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.

Supplementary Table 6 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 full siblings or matched unexposed individuals***, restricting to participants without any congenital malformations of heart and nerves system*

	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	1425(2.28)/1617(1.45)	1.52 (1.39 to 1.65)	2146(2.46)/10034(1.19)	1.62 (1.54 to 1.71)
Posttraumatic stress disorder	113(2.64)/106(1.38)	2.10 (1.49 to 2.97)	160(2.67)/666(1.15)	1.91 (1.57 to 2.31)
Acute stress reaction	647(2.24)/755(1.44)	1.46 (1.28 to 1.66)	1016(2.51)/4742(1.20)	1.63 (1.51 to 1.76)
Adjustment disorder and other stress reactions	665(2.27)/756(1.47)	1.52 (1.34 to 1.72)	970(2.39)/4626(1.18)	1.58 (1.47 to 1.71)

* Sample size for analysis in the sibling cohort: 101,314 in exposed group and 179,031 in sibling group; in the population-matched cohort: 142,378 in exposed group and 1,405,627 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.

Supplementary Table 7 Association of stress-related disorders with life-threatening infection, additionally adjusted for the presence of severe somatic diseases (as a time-varying variable) or substance use/sleep-related diagnoses (as a binary variable) during follow-up — analyses restricted to individuals without a history of severe somatic diseases*

	Sibling-based analysis				Population-based analysis			
	Number of cases (incidence rate, per 1 000 person-years), exposed/siblings	HR (95% CI)†	HR (95% CI)†, additionally adjusted for severe somatic diseases	HR (95% CI)†, additionally adjusted for substance use/sleep-related diagnoses	Number of cases (incidence rate, per 1 000 person-years), exposed/unexposed	HR (95% CI)€	HR (95% CI)€, additionally adjusted for severe somatic diseases	HR (95% CI)€, additionally adjusted for substance use/sleep related diagnoses
Any stress-related disorder	1521(2.19)/1613(1.35)	1.49 (1.37 to 1.62)	1.43 (1.30 to 1.56)	1.42 (1.30 to 1.55)	2248(2.34)/9930(1.10)	1.65 (1.57 to 1.73)	1.57 (1.49 to 1.66)	1.50 (1.43 to 1.58)
Posttraumatic stress disorder	115(2.35)/115(1.37)	1.95 (1.40 to 2.73)	1.90 (1.35 to 2.67)	1.83 (1.29 to 2.58)	167(2.46)/682(1.08)	1.86 (1.54 to 2.25)	1.72 (1.42 to 2.09)	1.70 (1.40 to 2.06)
Acute stress reaction	716(2.19)/754(1.32)	1.49 (1.31 to 1.69)	1.41 (1.23 to 1.60)	1.40 (1.23 to 1.60)	1074(2.36)/4741(1.10)	1.65 (1.53 to 1.77)	1.57 (1.45 to 1.69)	1.49 (1.38 to 1.60)
Adjustment disorder and other stress reactions	690(2.17)/744(1.38)	1.45 (1.28 to 1.64)	1.40 (1.23 to 1.59)	1.40 (1.23 to 1.59)	1007(2.29)/4507(1.10)	1.63 (1.51 to 1.75)	1.56 (1.44 to 1.68)	1.49 (1.38 to 1.61)

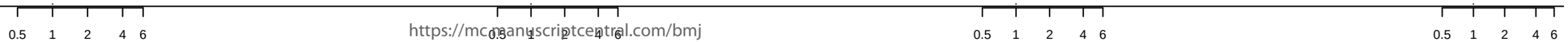
CI, confidence intervals; HR, Hazard ratios.

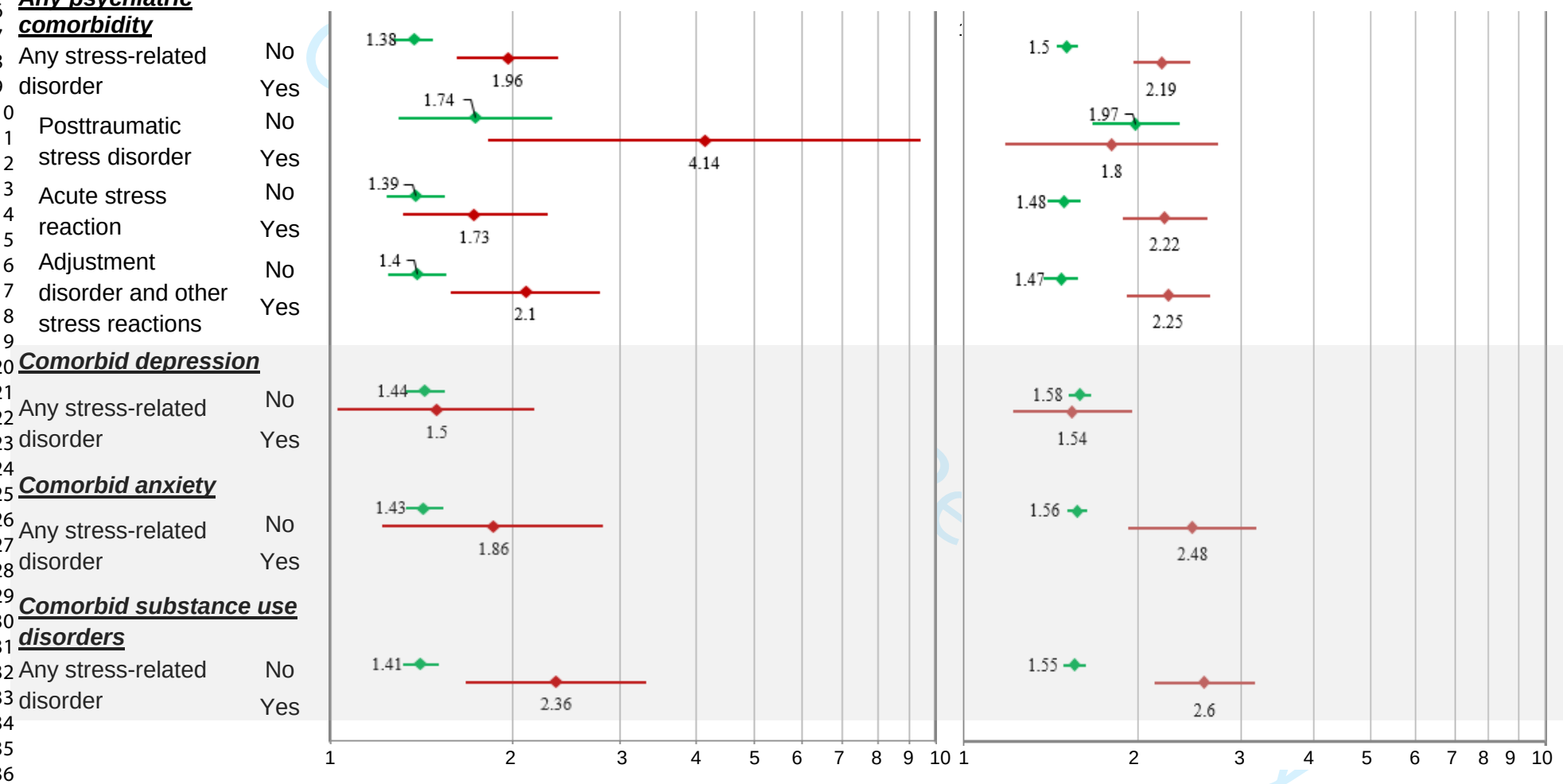
* Sample size for analysis in the sibling cohort: 86,052 in exposed group and 136,047 in sibling group; in the population-matched cohort: 120,915 in exposed group and 1,093,047 in unexposed group.

† 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.

	Sibling−based analysis				Population−based analysis			
	Acute stress reaction		Adjustment disorder and other stress reactions		Acute stress reaction		Adjustment disorder and other stress reactions	
	Number of cases (incidence rate, per 1,000) Exposed/ unexposed group	HR (95% CI)[a]	Number of cases (incidence rate, per 1,000) Exposed/ unexposed group	HR (95% CI)[a]	Number of cases (incidence rate, per 1,000) Exposed/ sibling group	HR (95% CI)[b]	Number of cases (incidence rate, per 1,000) Exposed/ sibling group	HR (95% CI)[b]
Life−threatening infections	1013(2.65)/1270(1.7)	1.43 (1.29 to 1.58)	1014(2.71)/1201(1.69)	1.48 (1.33 to 1.64)	1570(2.93)/7501(1.34)	1.56 (1.47 to 1.66)	1478(2.86)/7142(1.34)	1.55 (1.46 to 1.65)
Sepsis	621(1.62)/791(1.05)	1.44 (1.27 to 1.64)	652(1.74)/750(1.06)	1.6 (1.4 to 1.82)	970(1.8)/4630(0.83)	1.56 (1.45 to 1.69)	918(1.77)/4363(0.82)	1.61 (1.48 to 1.74)
Endocarditis	50(0.13)/51(0.07)	1.65 (0.93 to 2.92)	43(0.11)/46(0.06)	1.46 (0.8 to 2.66)	81(0.15)/297(0.05)	1.89 (1.42 to 2.51)	62(0.12)/254(0.05)	1.74 (1.27 to 2.39)
Meningitis	55(0.14)/62(0.08)	1.65 (1.08 to 2.53)	54(0.14)/72(0.1)	1.36 (0.88 to 2.11)	81(0.15)/467(0.08)	1.65 (1.28 to 2.13)	83(0.16)/437(0.08)	1.65 (1.28 to 2.13)
Other CNS infections	144(0.37)/164(0.22)	1.6 (1.24 to 2.06)	130(0.35)/167(0.23)	1.24 (0.95 to 1.63)	206(0.38)/1177(0.21)	1.7 (1.45 to 2)	189(0.36)/1185(0.22)	1.44 (1.22 to 1.7)
Death due to other infections	205(0.53)/272(0.36)	1.13 (0.87 to 1.46)	210(0.56)/243(0.34)	1.64 (1.27 to 2.13)	330(0.61)/1316(0.24)	1.53 (1.32 to 1.77)	336(0.64)/1257(0.23)	1.71 (1.48 to 1.98)




Psychological comorbidity*
Hazard ratio (95% confidence interval)
Sibling-based analysis†
Population-based analysis€
Any psychiatric comorbidity
Any stress-related disorder
No
Yes
Posttraumatic stress disorder
No
Yes
Acute stress reaction
No
Yes
Adjustment disorder and other stress reactions
No
Yes
Comorbid depression
Any stress-related disorder
No
Yes
Comorbid anxiety
Any stress-related disorder
No
Yes
Comorbid substance use disorders
Any stress-related disorder
No
Yes
1.38
1.96
1.74
4.14
1.39
1.73
1.4
2.1
1.44
1.5
1.43
1.86
1.41
2.36
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2.19
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Supplementary Figure 2 Relative risks of life-threatening infections among stress-related disorder patients, sub-grouped by the occurrence of psychiatric comorbidity, *compared to full siblings or matched unexposed individuals*

* Psychiatric comorbidity was defined as a new-onset psychiatric disorder, any (excluding stress-related disorder) or specific type (depression, anxiety, and substance use disorders), diagnosed from 3 months before to 1 year after the diagnosis of a stress-related disorder.

† 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.