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Stress-related disorders and subsequent risk of life-threatening infections: a population-based sibling-controlled cohort study

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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 11,449,190 matched unexposed individuals and 184,612 full siblings of these exposed patients.

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 (HRs) with 95% confidence intervals (CIs) of these life-threatening infections.

Results The average age at diagnosis was 37 years and 39% of exposed patients were male. During a mean follow-up of 8 years, the incidence rate of life-threatening infections was 2.9, 1.3, and 1.7 per 1,000 person-years among the exposed, matched unexposed- and sibling- cohorts, respectively. Compared to the unexposed population, patients with stress-related disorders were at increased risk of life-threatening infections (HR=1.58 [95% CI 1.51-1.65] for any stress related disorder and 1.95 [95% CI 1.66-2.28] for PTSD). Stress-related disorders were associated with all studied life-threatening infections with the highest magnitude observed for endocarditis (HR=1.89, 95%CI 1.55-2.32). Younger age at diagnosis of stress-related disorders and the presence of psychiatric comorbidity, especially substance use disorders,

yielded greater HRs, while persistent use of selective serotonin reuptake inhibitors throughout the first year after a stress-related disorder diagnosis was associated with attenuated HRs. The sibling-controlled analysis confirmed the observed associations, as did several sensitivity analyses.

Conclusion Stress-related disorders are associated with a subsequent increased risk of life-threatening infections, independent of familial background and physical or psychological 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 (1-3 sentences)

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 (1-2 sentences)

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 developing psychiatric comorbidities. Particularly, the long-term risk of life-threatening infections after diagnosis of stress-related disorders seems attenuated by early persistent use of selective serotonin reuptake inhibitors.

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 dysregulation of the hypothalamic-pituitary-adrenal axis in response to stress with varying indices of immunosuppression (e.g., impaired humoral and cell-mediated immunity)[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 (ASR, also known as acute stress disorder), adjustment disorder (AD), 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[1,12,13] and increased risk of various autoimmune diseases[14]. 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 and sibling-controlled cohort study to explore the association between stress-related disorders and subsequent risk of life-threatening infections.

Methods

Study Design

Population-matched cohort

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 (NPR). The NPR 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. The study was approved by the Regional Ethics Review Board in Stockholm.

We excluded patients diagnosed below age of 5 (n=139)[15], 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[16], 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).

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.

Sibling cohort

To control for familial confounding[15], we constructed a sibling cohort where we compared exposed patients with their unaffected full siblings. Through the Multi-Generation Register, we recruited 184,612 full siblings (of 71.6% [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).

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 unexposed individuals or unaffected full siblings 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 NPR 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), ASR (ICD-9: 308, 309A; ICD-10: F43.0), and AD and other stress reactions (ICD-9: 309X; ICD-10: F43.8, F43.9). Because PTSD might initially be diagnosed as other stress-related disorders (e.g., ASR[17]), 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 (SSRIs, Anatomical Therapeutic Chemical [ATC] code 'N06AB'), the recommended first-line pharmacotherapy for stress-related disorders[18], within the first year after the diagnosis of a stress-related disorder, from the Swedish Prescribed Drug Register (July 2005-). We defined SSRI users as patients with two or more dispensations of SSRIs. We calculated the average dosage by dividing cumulative Defined Daily Dose (DDD) by the time interval (days) from the first to the last dispensation; and this time interval was also considered as the length of SSRIs 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 NPR), 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[19,20]. We therefore considered other psychiatric disorders diagnosed more than 3 months before the diagnosis of a stress-related disorder as 'history of other psychiatric disorders' whereas psychiatric diagnoses from 3 months before to 1 year after the stress-related disorder diagnosis as 'psychiatric comorbidity'. 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)[21] 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 NPR, 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 NPR 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 a sensitivity analysis on somatic comorbidities, data on the presence of severe somatic diseases (as defined above) after the index date were also extracted from the NPR.

Statistical analysis

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

In the population-matched cohort, all models were stratified by matching identifiers (sex, birth year, and county of birth), and adjusted for education level (<9 years, 9-12 years, >12 years, unknown), family income (top 20%, middle, lowest 20%), marital status (single, married or cohabiting, divorced or widow), history of severe somatic diseases (yes/no), family history of major life-threatening infections (yes/no), history of other psychiatric disorders (yes/no), and history of inpatient visit due to any infectious diseases (yes/no). We first considered stress-related disorders as one group, and then by diagnostic categories of of PTSD, ASR, and AD 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 HRs by sex (male/female), time since index date (<1 year, 1-5 years, 6-9 years, ≥10 years), calendar period at the index date (1987-2000/2001-2013), history of severe somatic diseases (yes/no), family history of major life-threatening infection (yes/no), history of other psychiatric disorders (yes/no), and history of inpatient visit due to any infectious diseases (yes/no). The differences of sub-grouped HRs 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[22]. Age-varying HRs were estimated and visualized thereafter.

To study the potential impact of psychiatric comorbidity, we assessed HRs by any psychiatric comorbidities as well as by specific type, including depression, anxiety, and substance use disorders. Within one year after the diagnosis of a stress-related disorder, we considered the psychiatric comorbidity as a time-varying variable. Further, restricting to patients diagnosed 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 SSRI use.

We repeated the main analyses in the sibling cohort, where we used conditional Cox models stratified by family identifier, adjusting for sex, birth year, county of birth, as well as all abovementioned covariates. We compared HRs between population and sibling-based analyses using a z-test[23].

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 mainly due to the poorer health conditions of exposed patients than unexposed individuals both before and 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 during follow-up (as time-varying variables). 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 setting 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 population-matched cohort accrued 12,832,632 person-years, with an approximately 8-year average duration of follow-up. The mean age at entry was 37 years (Table 1), and 30.3% of the exposed patients were males. Prior histories of other psychiatric disorders, severe somatic diseases, and inpatient stay due to infectious diseases were more common among exposed patients than among matched unexposed individuals (35.8% vs 8.2%, 16.6% vs 10.1%, and 31.9% vs 21.2%, 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, 18,976 individuals with incident life-threatening infections were identified —3,292 among exposed patients and 15,684 among matched unexposed individuals, with a crude incidence rate (IR) of 2.9 and 1.3 per 1,000 person-years, respectively. After controlling for all covariates, we observed an association between stress-related disorders and life-threatening infections: HR was 1.58 (95% CI 1.51-1.65) for any stress-related disorder, 1.95 (95% CI 1.66-2.28) for PTSD (Figure 2), 1.56 (95% CI 1.47-1.66) for ASR, and 1.55 (95% CI 1.46-1.65) for AD and other stress reactions (Supplementary Figure 1). Stress-related disorders were associated with all studied life-threatening infections, with HRs varying from 1.58 (95% CI 1.41-1.76) for CNS infection other than meningitis to 1.89 (95% CI 1.55-2.32) for endocarditis. The within-sibling comparisons corroborated the abovementioned associations (Figure 2 and Supplementary Figure 1) as differences between the estimates in the population-based and sibling-based analysis were non-significant (HR for any stress-related disorder: 1.47 [95% CI 1.37-1.58], *P* for difference between population-based and within-sibling comparison=0.09; for PTSD: 1.92 [95% CI 1.46-2.52], *P* for difference=0.92).

Based on the 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 were considerably stronger among participants without a history of severe somatic diseases (*P* for interaction<.001), without history of other psychiatric disorders

(*P* for interaction<.001), and within the first year after the diagnosis of a stress-related disorder (*P* for difference<.001). Moreover, an age-dependent risk pattern suggested a linear decline in HR with increased age at diagnosis (Figure 3). Subgroup analyses of the sibling cohort revealed largely identical risk patterns, but with less statistical precision (Table 2 and Figure 3).

For patients with stress-related disorders other than PTSD, the presence of psychiatric comorbidity, especially comorbid substance use disorders, was linked to further elevated HRs of life-threatening infections in both population and sibling-based analyses (Supplementary Figure 2). Additionally, we found that use of SSRIs after the diagnosis of a stress-related disorder was associated with lower risk of life-threatening infections (SSRI user compared to non-user: HR=0.81 [95% CI 0.66-0.98], *P*= 0.03). Indeed, persistence in use of SSRIs 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 (HR=0.96 [95% CI 0.66-1.40], 0.85 [95% CI 0.64-1.13], and 0.70 [95% CI 0.52-0.94] for ⩽179, 180-319, and ⩾ 320 days of use, respectively, *P* for trend=0.01; Supplementary Table 3).

Neither restricting the analyses to individuals without any diagnosis of severe somatic diseases, injury, or infectious diseases within 1 year prior to the index date, nor additionally adjusting for severe medical conditions during follow-up modified the estimates (Supplementary Table 4 and 5).

Discussion

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 psychological 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 SSRIs during the first year after the diagnosis of stress-related disorders.

A series of experimental studies in humans and other animals suggest that psychological stress is associated with acute infectious respiratory illness in a dose-dependent manner[4,5,24,25]. Initial attempts of explaining the documented association were concentrated on altered circulating glucocorticoids and their role in suppression of cell-mediated and humoral immunity[26,27]. Yet, studies testing the link between glucocorticoid levels and risk of infections yielded mixed results[28-31]. A recent hypothesis places focus on the underlying inflammation, induced by glucocorticoid receptor resistance ensuing overproduction of inflammatory cytokines[6,32]. However, since common respiratory viral infections are the predominant disease models in all aforementioned investigations, it remains unclear whether the stress-induced immune modulation can lead to more severe infection-related consequences.

With few comparable data, our findings are consistent with a recent cohort study[33] indicating 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. With a specific focus on clinically diagnosed stress-related disorders, we show that severe stress reactions, even in transient form (e.g., ASR), 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[34-36], , 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. However, the further elevated HRs among exposed patients with comorbid substance use disorders suggest that behavioral factors (e.g., smoking, alcohol, or drug use) may partially mediate the observed association, through increased possibility of pathogen exposure (e.g. needle sharing among drug users[37]) and/or inducing immune dysfunction[38]. Yet, 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[39], interrupting neuropsychological/cognitive development[40,41], or gene-environment interplay[42]. 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[42].

The major merit of our study was the use of large population-based cohort with a complete follow-up up to 27 years and a comparison within full siblings to address the a priori concern for familial confounding[15]. 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 the late establishment of Swedish Outpatient Register (2001-) potentially leading to the underestimated number of stress-related disorder cases, especially the milder forms. However, similar results were obtained from a sub-analysis of different calendar periods, suggesting a minor influence of this factor. In addition, we have limited information on behavior-related factors (e.g., smoking, drug and alcohol use). Further research with detailed data on lifestyle is warranted to clarify a potential mediating role of behavioral and other factors on the reported association.

In conclusion, in the Swedish population, we found that individuals diagnosed with stress-related disorders were subsequently at elevated risk of major life-threatening infections.

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Disclosure of Potential Conflict of Interest

No potential conflicts of interest were disclosed.

Authors' contributions

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.

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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 matched unexposed individuals or full siblings***

CNS, central nervous system.
[a] 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.
[b] Cox models were stratified by family identifiers, and adjusted for sex, birth year, county of birth, 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.

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 HRs were predicted based on fully adjusted Cox models where interaction terms between stress-related disorder and splined age profiles were added. 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.

† In sibling-based analysis, the cox models were stratified by family identifiers, and adjusted for sex, birth year, county of birth, 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

	Population-matched cohort		Sibling cohort	
	Exposed cohort	Matched unexposed cohort	Exposed cohort'	Sibling cohort
Number of participants	144,919	1,449,190	103072	184612
Age at index date, mean±SD, year	37.2±14.3	37.2±14.3	37.0±13.9	38.0±15.1
Follow-up time, mean±SD, year	7.9±6.5	8.1±6.6	7.8±6.4	8.5±6.8
% of male	38.3%	38.3%	38.3%	51.0%
Education level, n (%)				
<9 years	6453 (4.4)	58565 (4.0)	4191 (4.07)	11919 (6.5)
9-12 years	103252 (71.3)	941393 (65.0)	73505 (71.3)	126305 (68.4)
>12 years	32625 (22.5)	426442 (29.4)	23839 (23.1)	41569 (22.5)
Unknown	2589 (1.8)	22790 (1.6)	1537 (1.5)	4819 (2.6)
Yearly family income level, n (%)				
Lowest 20%	32847 (22.7)	247467 (17.1)	22941 (22.3)	33782 (18.3)
Middle	79051 (54.6)	799409 (55.2)	56877 (55.2)	95927 (52.0)
Top 20%	18292 (12.6)	254009 (17.5)	13160 (12.8)	29946 (16.2)
Unknown	14729 (10.2)	148305 (10.2)	10094 (9.79)	24957 (13.5)
Marital status, n (%)				
Single	82425 (56.9)	823667 (56.8)	58791 (57.0)	100525 (54.5)
Married or cohabiting	42868 (29.6)	514251 (35.5)	30730 (29.8)	66694 (36.1)
Divorced or widowed	19626 (13.5)	111272 (7.68)	13551 (13.2)	17393 (9.42)
History of severe somatic diseases[*], n (%)				
Yes	24004 (16.6)	145619 (10.1)	17020 (16.5)	23534 (12.8)
No	120915 (83.4)	1303571 (90.0)	86052 (83.5)	161078 (87.3)
History of other psychiatric disorders[†], n (%)				
Yes	51905 (35.8)	118910 (8.2)	36202 (34.8)	23466 (12.6)
No	93014 (64.2)	1330280 (91.8)	67860 (65.2)	162605 (87.4)
Family history of major life-threatening infections, n (%)				
Yes	15548 (10.7)	134214 (9.3)	10992 (10.7)	20455 (11.1)
No	129371 (89.3)	1314976 (90.7)	92080 (89.3)	164157 (88.9)
History of inpatient visit due to any infectious disease, n (%)				
Yes	46269(31.9)	307370(21.2)	31836 (30.9)	43956(23.8)
No	98750(68.1)	1141820(78.8)	71236(69.1)	140656(76.2)
Type of stress-related disorders, n (%)				
Diagnosis type				
Posttraumatic stress disorder	11541 (7.9)	-	8105 (7.8)	-
Acute stress reaction	66758 (46.1)	-	47195 (45.8)	-
Adjustment disorder and other stress reaction	66620 (46.0)	-	47772 (46.4)	-
Psychiatric comorbidity[€]				
Any				
Yes	31415 (21.7)	-	22619 (21.9)	-
No	113504 (78.3)	-	80453 (78.1)	-
Depression				
Yes	14500 (10.0)	-	10581(10.3)	-
No	130419 (90.0)	-	92491(89.7)	-
Anxiety				
Yes	9222 (6.4)	-	6683(6.5)	-
No	135697 (93.6)	-	96389(93.5)	-
Substance use disorder				
Yes	6514(4.5)	-	4567(4.4)	-
No	138405 (95.5)	-	98505(95.6)	-

* 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

Table 2 Hazard ratios (HRs) with 95% confidence intervals (CIs) for life-threatening infections among patients with any stress-related disorder, ***compared to matched unexposed individuals or full siblings***, by different characteristics

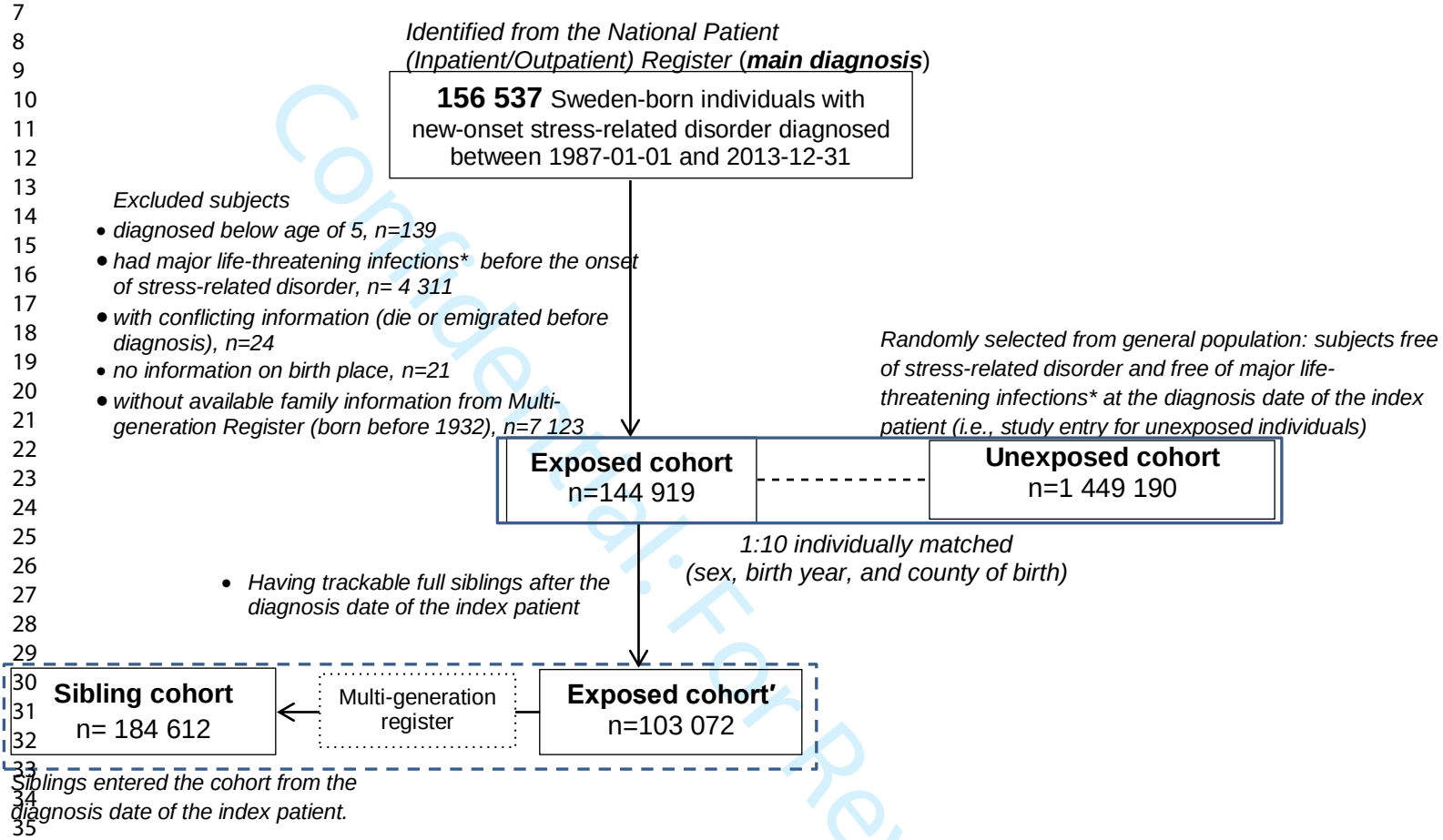
	Population-based analysis		Sibling-based analysis	
	Number of cases (IR, per 1 000 person-years), exposed/unexposed	HR (95% CI)*	Number of cases (IR, per 1 000 person-years), exposed/siblings	HR (95% CI)†
By gender				
Male	1444(3.29)/7034(1.52)	1.57 (1.47-1.67)	983(3.11)/1500(1.89)	1.44 (1.26-1.64)
Female	1848(2.66)/8650(1.22)	1.59 (1.50-1.68)	1214(2.44)/1146(1.48)	1.41 (1.24-1.59)
By time since index date				
< 1 year	410(2.98)/1438(1.04)	2.04 (1.81-2.30)	266(2.71)/230(1.30)	1.61 (1.30-2.00)
1-4 years	1045(2.43)/5053(1.16)	1.45 (1.35-1.56)	723(2.34)/805(1.42)	1.53 (1.36-1.73)
5-9 years	811(2.64)/3941(1.25)	1.51 (1.39-1.65)	543(2.45)/694(1.64)	1.35 (1.18-1.54)
≥10 years	1026(3.99)/5252(1.88)	1.65 (1.53-1.78)	665(3.59)/917(2.30)	1.50 (1.32-1.70)
History of severe somatic diseases€				
Yes	1044(6.09)/3452(3.40)	1.38 (1.23-1.56)	676(5.66)/663(3.92)	1.37 (1.06-1.76)
No	2248(2.34)/12232(1.14)	1.65 (1.57-1.73)	1521(2.19)/1983(1.42)	1.49 (1.37-1.62)
By calendar year at index date				
1987-2000	1472(3.06)/7025(1.38)	1.66 (1.56-1.77)	963(2.79)/1274(1.72)	1.51 (1.36-1.67)
2001-2013	1820(2.79)/8659(1.31)	1.53 (1.44-1.61)	1234(2.63)/1372(1.66)	1.44 (1.31-1.59)
By previous history of psychiatric disorders‡				
Yes	1465(4.33)/2308(3.44)	1.26 (1.12-1.41)	967(4.09)/576(3.86)	1.25 (1.01-1.56)
No	1827(2.30)/13376(1.21)	1.79 (1.70-1.88)	1230(2.13)/2070(1.46)	1.58 (1.45-1.73)
By family history of major life-threatening infections				
Yes	300(3.43)/1259(1.64)	1.81 (1.39-2.37)	219(3.47)/248(1.99)	1.51 (1.20-1.89)
No	2992(2.86)/14425(1.32)	1.60 (1.53-1.67)	1978(2.64)/2398(1.66)	1.38 (1.28-1.48)
By history of inpatient stay due to infectious disease				
Yes	1405(4.14)/4321(2.04)	1.52 (1.39-1.66)	931(3.94)/812(2.50)	1.25 (1.03-1.50)
No	1887(2.38)/11363(1.19)	1.69 (1.60-1.78)	1266(2.19)/1834(1.48)	1.58 (1.44-1.74)

* 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.

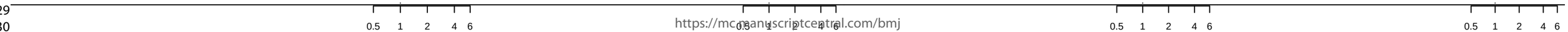
† Cox models were stratified by family identifiers, and adjusted for sex, birth year, county of birth, education level, family income, marital status, history of severe somatic diseases, history of other psychiatric disorder, and history of inpatient visit due to infectious disease.

€ 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.

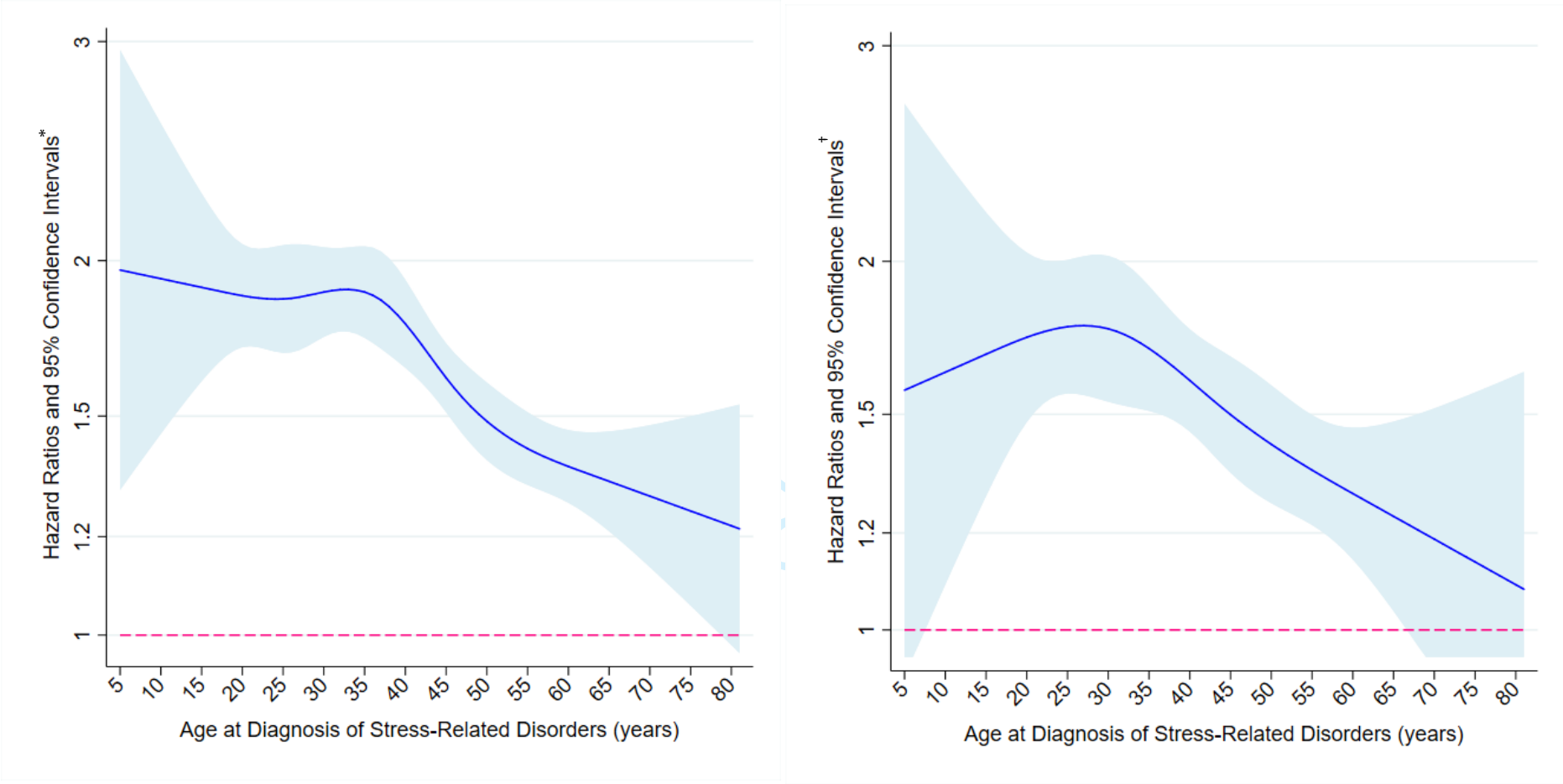
‡The first diagnosis of a psychiatric disorder, other than stress-related disorders, occurred more than 3 months prior to the index date.



	Population−based analysis				Sibling−based analysis			
	Any stress−related disorder		Posttraumatic stress disorder		Any stress−related disorder		Posttraumatic stress disorder	
	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	3292(2.9)/15684(1.34)	1.58 (1.51−1.65)	244(3.04)/1041(1.26)	1.95 (1.66−2.28)	2197(2.7)/2646(1.69)	1.47 (1.37−1.58)	170(2.94)/175(1.59)	1.92 (1.46−2.52)
Sepsis	2044(1.8)/9624(0.82)	1.61 (1.52−1.7)	156(1.94)/631(0.76)	2.01 (1.65−2.45)	1384(1.7)/1651(1.05)	1.52 (1.39−1.66)	111(1.91)/110(1)	1.84 (1.3−2.61)
Endocarditis	158(0.14)/591(0.05)	1.89 (1.55−2.32)	15(0.19)/40(0.05)	2.9 (1.46−5.76)	103(0.12)/105(0.07)	1.57 (1.08−2.3)	10(0.17)/8(0.07)	5.38 (0.46−62.9)
Meningitis	181(0.16)/962(0.08)	1.7 (1.43−2.02)	17(0.21)/58(0.07)	2.8 (1.49−5.26)	120(0.15)/142(0.09)	1.63 (1.23−2.16)	11(0.14)/8(0.07)	3.03 (0.63−14.6)
Other CNS infections	429(0.38)/2531(0.22)	1.58 (1.41−1.76)	34(0.42)/169(0.2)	1.88 (1.23−2.87)	296(0.36)/358(0.23)	1.45 (1.21−1.73)	22(0.37)/27(0.24)	1.9 (0.85−4.24)
Death due to other infections	711(0.62)/2769(0.24)	1.64 (1.48−1.81)	45(0.55)/196(0.24)	1.99 (1.37−2.9)	445(0.54)/551(0.35)	1.39 (1.16−1.65)	30(0.51)/36(0.33)	1.85 (0.89−3.83)



Population-based analysis	Sibling-based analysis



Supplementary Table 1 International Classification of Diseases (ICD) codes for 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 reaction		F43.8, 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

Other infections	Gastritis and duodenitis	K29	535
	Appendicitis	K35-K37	540-542
	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

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 (1.65-2.73)	729(3.27)/3537(1.50)	1.55 (1.42-1.69)	621(3.25)/3092(1.54)	1.54 (1.40-1.70)
Female	150(2.72)/636(1.13)	1.87 (1.53-2.29)	841(2.69)/3964(1.24)	1.58 (1.45-1.71)	857(2.62)/4050(1.22)	1.56 (1.44-1.70)
By time since index date						
< 1 year	25(2.31)/104(0.96)	1.86 (1.12-3.10)	213(3.37)/677(1.06)	2.26 (1.91-2.68)	172(2.71)/657(1.03)	1.84 (1.53-2.22)
1-4 years	71(2.27)/313(1.00)	1.59 (1.19-2.13)	479(2.44)/2290(1.15)	1.45 (1.30-1.62)	495(2.44)/2450(1.19)	1.45 (1.30-1.61)
5-9 years	61(3.08)/206(1.02)	2.42 (1.74-3.37)	374(2.60)/1890(1.27)	1.46 (1.29-1.65)	376(2.62)/1845(1.25)	1.49 (1.32-1.69)
≥10 years	87(4.74)/418(2.11)	2.01 (1.56-2.60)	504(3.82)/2644(1.85)	1.57 (1.41-1.75)	435(4.07)/2190(1.89)	1.68 (1.49-1.88)
History of severe somatic diseases†						
Yes	77(6.15)/206(2.95)	1.45 (0.91-2.30)	496(6.18)/1642(3.46)	1.37 (1.14-1.64)	471(5.99)/1604(3.42)	1.39 (1.16-1.66)
No	167(2.46)/835(1.11)	1.86 (1.54-2.25)	1074(2.36)/5859(1.15)	1.65 (1.53-1.77)	1007(2.29)/5538(1.14)	1.63 (1.51-1.75)
By calendar year at index date						
1987-2000	114(3.38)/530(1.48)	2.07 (1.66-2.60)	757(3.03)/3624(1.37)	1.63 (1.49-1.78)	601(3.05)/2871(1.37)	1.65 (1.49-1.82)
2001-2013	130(2.79)/511(1.10)	1.84 (1.48-2.29)	813(2.85)/3877(1.34)	1.51 (1.39-1.64)	877(2.74)/4271(1.32)	1.51 (1.40-1.64)
By previous history of other psychiatric disorders€						
Yes	105(3.57)/125(2.58)	2.29 (1.47-3.56)	729(4.73)/1091(3.50)	1.24 (1.05-1.46)	631(4.07)/1092(3.53)	1.17 (0.98-1.39)
No	139(2.73)/916(1.18)	2.14 (1.76-2.59)	841(2.20)/6410(1.22)	1.70 (1.57-1.83)	847(2.34)/6050(1.21)	1.84 (1.70-1.98)
By family history of major life-threatening infections						
Yes	20(3.35)/83(1.63)	2.86 (0.88-9.31)	144(3.64)/611(1.77)	1.59 (1.06-2.38)	136(3.24)/565(1.53)	1.96 (1.33-2.89)
No	224(3.01)/958(1.24)	1.93 (1.64-2.28)	1426(2.87)/6890(1.32)	1.59 (1.49-1.69)	1342(2.82)/6577(1.33)	1.57 (1.47-1.68)
By history of inpatient visit due to infectious disease						
Yes	106(4.34)/256(1.73)	2.08 (1.47-2.96)	707(4.33)/2026(2.04)	1.69 (1.48-1.93)	592(3.90)/2039(2.09)	1.31 (1.14-1.50)

No	138(2.47)/785(1.16)	1.81 (1.48-2.22)	863(2.32)/5475(1.20)	1.61 (1.49-1.74)	886(2.42)/5103(1.17)	1.76 (1.63-1.91)

[*] 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 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 (0.66-0.98)
P for difference		0.0318
Average dosage level of SSRI (by median)		
Not user	582(2.72)	Reference
≤ 1.2 DDD	62(2.32)	0.77 (0.63-0.93)
> 1.2 DDD	71(2.98)	0.86 (0.69-1.07)
P for trend[‡]		0.0896
Duration of SSRI (by tertiles)		
Not user	582(2.72)	Reference
≤179 days	29(3.10)	0.96 (0.66-1.40)
180-319 days	54(2.74)	0.85 (0.64-1.13)
≥320 days	50(2.33)	0.70 (0.52-0.94)
P for trend[‡]		0.0137

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 4 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***, restricting to participants without any diagnosis of severe somatic diseases/injury/infectious diseases within 1 year prior to the index date*

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

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

† 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.

€ Cox models were stratified by family identifiers, and adjusted for sex, birth year, county of birth, 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.

Supplementary Table 5 Association of stress-related disorders with life-threatening infection, additionally adjusted for the presence of severe somatic diseases during follow-up (as a time-varying variable) — analyses restricted to individuals without a history of severe somatic diseases*

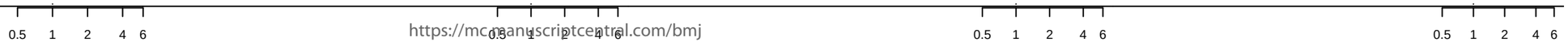
	Population-based analysis		Sibling-based analysis	
	Number of cases (IR, per 1 000 person-years), exposed/unexposed	HR (95% CI)†	Number of cases (IR, per 1 000 person-years), exposed/sibling	HR (95% CI)‡
Any stress-related disorder	2248(2.34)/9930(1.10)	1.57 (1.49-1.66)	1521(2.19)/1613(1.35)	1.43 (1.30-1.56)
Posttraumatic stress disorder	167(2.46)/682(1.08)	1.72 (1.42-2.09)	115(2.35)/115(1.37)	1.90 (1.35-2.67)
Acute stress reaction	1074(2.36)/4741(1.10)	1.57 (1.45-1.69)	716(2.19)/754(1.32)	1.41 (1.23-1.60)
Adjustment disorder and other stress reactions	1007(2.29)/4507(1.10)	1.56 (1.44-1.68)	690(2.17)/744(1.38)	1.40 (1.23-1.59)

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

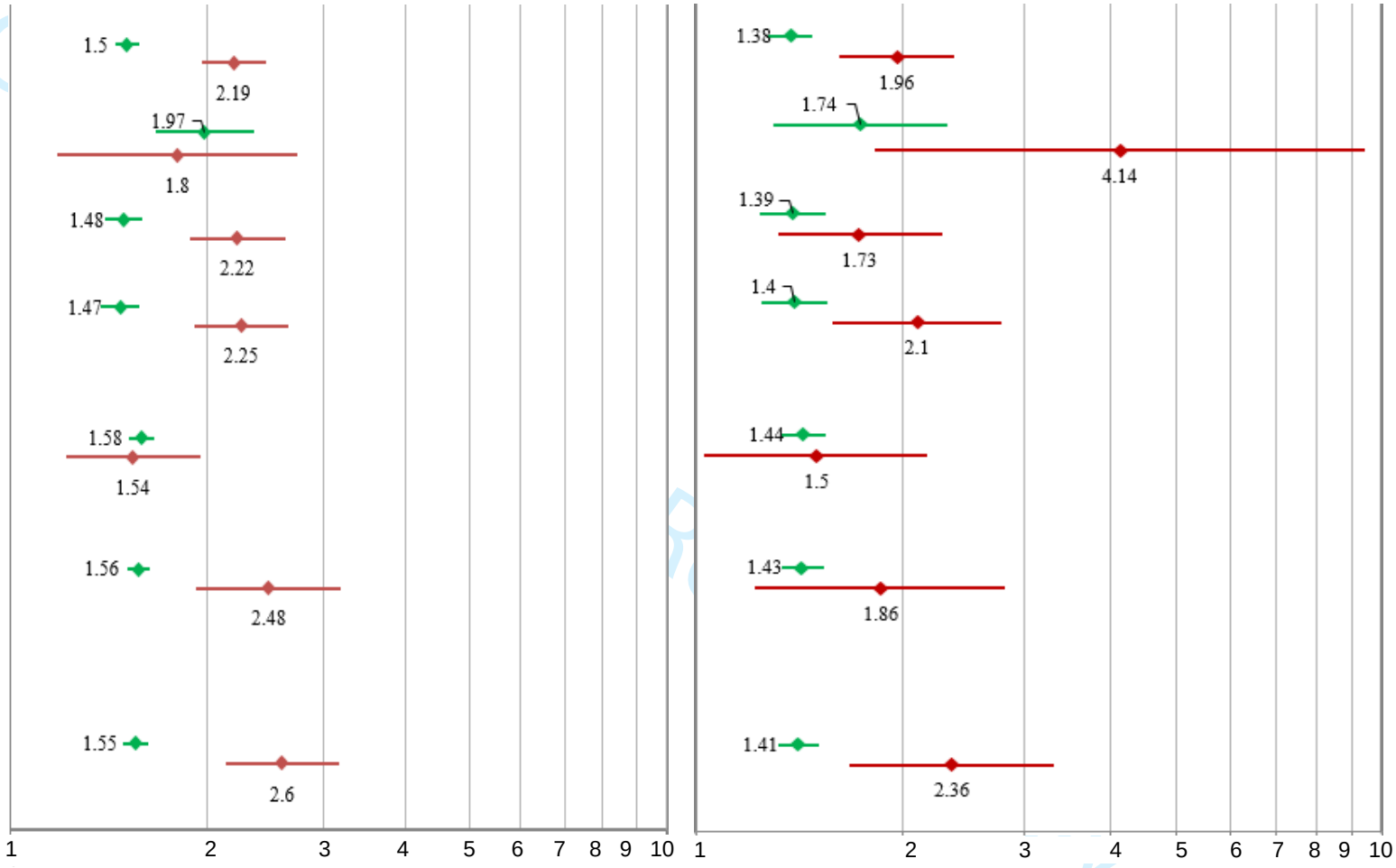
†Cox models were stratified by matching identifiers (sex, birth year, and county of birth), and adjusted for education level, family income, marital status, history of severe somatic diseases, history of other psychiatric disorder, history of inpatient visit due to infectious disease, and family history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

‡ Cox models were stratified by family identifiers, and adjusted for sex, birth year, county of birth, 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.

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



Psychological comorbidity*		Hazard ratio (95% confidence interval)	
		Population-based analysis†	Sibling-based analysis€
Any psychiatric comorbidity			
Any stress-related disorder	No	1.5	1.38
	Yes	2.19	1.96
Posttraumatic stress disorder	No	1.97	1.74
	Yes	1.8	4.14
Acute stress reaction	No	1.48	1.39
	Yes	2.22	1.73
Adjustment disorder and other stress reactions	No	1.47	1.4
	Yes	2.25	2.1
Comorbid depression			
Any stress-related disorder	No	1.58	1.44
	Yes	1.54	1.5
Comorbid anxiety			
Any stress-related disorder	No	1.56	1.43
	Yes	2.48	1.86
Comorbid substance use disorders			
Any stress-related disorder	No	1.55	1.41
	Yes	2.6	2.36



Supplementary Figure 2 Relative risks of life-threatening infections among stress-related disorder patients, sub-grouped by the occurrence of psychiatric comorbidity, *compared to matched unexposed individuals or full siblings*

* 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 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.

€ Cox models were stratified by family identifiers, and adjusted for sex, birth year, county of birth, 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.