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

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ABSTRACT

OBJECTIVE
To assess whether severe psychiatric reactions to trauma and other adversities are associated with subsequent risk of life threatening infections.

DESIGN
Population and sibling matched cohort study.

SETTING
Swedish population.

PARTICIPANTS
144 919 individuals with stress related disorders (post-traumatic stress disorder (PTSD), acute stress reaction, adjustment disorder, and other stress reactions) identified from 1987 to 2013 compared with 184 612 full siblings of individuals with a diagnosed stress related disorder and 1 449 190 matched individuals without such a diagnosis from the general population.

MAIN OUTCOME MEASURES
A first inpatient or outpatient visit with a primary diagnosis of severe infections with high mortality rates (ie, sepsis, endocarditis, and meningitis or other central nervous system infections) from the Swedish National Patient Register, and deaths from these infections or infections of any origin from the Cause of Death Register. After controlling for multiple confounders, Cox models were used to estimate hazard ratios of these life threatening infections.

RESULTS
The average age at diagnosis of a stress related disorder was 37 years (55 541, 38.3% men). During a mean follow-up of eight years, the incidence of life threatening infections per 1000 person years was 2.9 in individuals with a stress related disorder, 1.7 in siblings without a diagnosis, and 1.3 in matched individuals without a diagnosis. Compared with full siblings without a diagnosis of a stress related disorder, individuals with such a diagnosis were at increased risk of life threatening infections (hazard ratio for any stress related disorder was 1.47 (95% confidence intervals1.37 to 1.58) and for PTSD was 1.92 (1.46 to 2.52)). Corresponding estimates in the population based analysis were similar (1.58 (1.51 to 1.65) for any stress related disorder, P=0.09 for difference between sibling and population based comparison, and 1.95 (1.66 to 2.28) for PTSD, P=0.92 for difference). Stress related disorders were associated with all studied life threatening infections, with the highest relative risk observed for meningitis (sibling based analysis 1.63 (1.23 to 2.16)) and endocarditis (1.57 (1.08 to 2.30)). Younger age at diagnosis of a stress related disorder and the presence of psychiatric comorbidity, especially substance use disorders, were associated with higher hazard ratios, whereas use of selective serotonin reuptake inhibitors in the first year after diagnosis of a stress related disorder was associated with attenuated hazard ratios.

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

WHAT IS ALREADY KNOWN ON THIS TOPIC

Psychological stress might increase susceptibility to infections through compromised immunity

A series of experimental studies on humans and other animals suggests a link between psychological stress and acute respiratory tract infections

Data are, however, limited on more severe life threatening infections such as meningitis and sepsis

WHAT THIS STUDY ADDS

This study found an association between stress related disorders and risk of life threatening infections, including sepsis, endocarditis, central nervous system infections, and fatal infections of any other origin

The association was more pronounced among people with a diagnosed stress related disorder at a younger age and those with psychiatric comorbidities

The long term use of selective serotonin reuptake inhibitors was associated with an attenuated risk of life threatening infections after diagnosis of a stress related disorder

Introduction

Excessive or prolonged psychological stress compromises several physiological systems, which might increase 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 (eg, impaired humoral and cell mediated immunity)[1] and increased inflammatory reactivity.[1] Correspondingly, people exposed to psychological stress have been reported to have a higher risk of respiratory virus infections[4-6] paralleled with reduced immune responses to several antiviral and antibacterial vaccines.[7-10]

Stress related disorders, including post-traumatic 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, people with stress related disorders might represent a population with the most severe physiological dysregulation as a result of severe stress.[1] Indeed, disrupted immune profiles have been reported in populations with PTSD and other stress related disorders[1 12-14] as well as an increased risk of various autoimmune diseases.[15] Recent data suggest an association between PTSD and a number of infectious diseases,[16] although data are as yet scarce on the role of stress-related disorder in major life threatening infections. Taking advantage of nationwide registers in Sweden, with 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 risk of life threatening infections.

Methods

Study design

From the Swedish National Patient Register we identified all Sweden born residents with a first diagnosis of a stress related disorder between 1 January 1987 and 31 December 2013 (n=156 537). This register contains nationwide data on inpatient care from 1987 and specialist outpatient care from 2001. Utilising the national identification numbers that are uniquely assigned to all Swedish residents, we linked the cohort with stress related disorders to other health registers in Sweden.

We excluded those with a diagnosis of a stress related disorder at age 5 or younger (n=139),[17] a history of any life threatening infection before the diagnosis of a stress related disorder (n=4311), conflicting information (died or emigrated before the diagnosis, n=24), or missing information on county of birth (n=21). To ensure complete family links from the Swedish Multi-Generation Register,[18] we further excluded 7123 people born before 1932, leaving 144 919 people for analysis. The date of diagnosis was the index date.

Sibling cohort

To control for familial confounding,[17] we constructed a sibling cohort to compare individuals with a stress related disorder with their unaffected full siblings. Through the Multi-Generation Register, we identified 184 612 full siblings (of 103 072 (71.1%) individuals with a stress related disorder) without a diagnosis of a stress related disorder or life threatening infection at the diagnosis date of the affected sibling (ie, index date).

Population matched cohort

A matched cohort design was used to compare individuals with a stress related disorder with the general population. For each individual with a stress related disorder diagnosis, we then randomly selected 10 people from the Total Population Register with no diagnosis of a stress related disorder or life threatening infection at the diagnosis date of the affected individual (ie, index date). We individually matched individuals without a diagnosis of stress related disorder to individuals with such a diagnosis by sex, birth year, and county of birth.

Follow-up

Follow-up of the study cohorts 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 (31 December 2013), whichever occurred first. The follow-up for unaffected full siblings or individuals without a diagnosis of stress related disorder was additionally censored if a stress related disorder was diagnosed after the index date.

Stress related disorders

We defined stress related disorders as any first inpatient or outpatient visit with the main diagnosis of a stress related disorder registered in the National Patient Register according to ICD-9 (international classification of diseases, ninth revision) codes 308 or 309 and ICD-10 (10th revision) code 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, see supplementary table 1). Because PTSD might initially be diagnosed as other stress related disorders (eg, acute stress reaction[19]), we considered individuals with a PTSD diagnosis within one year after their first stress related disorder diagnosis to have had a PTSD diagnosis from the date of first diagnosed stress related disorder.

From the Swedish Prescribed Drug Register (July 2005 onwards) we obtained information on prescribing of selective serotonin reuptake inhibitors (Anatomical Therapeutic Chemical code N06AB) within the first year after the diagnosis of a stress related disorder. Although the use of selective serotonin reuptake inhibitors in children and young people is debatable,[20] this drug class has been widely used[21] and recommended as the first line pharmacotherapy for adults with stress related disorders (for example, in Sweden,[22] United Kingdom,[23] and United States[24]). We defined users of selective serotonin reuptake inhibitors as those with two or more dispensations of this drug. We calculated the average dosage by dividing the cumulative defined daily dose by the interval (days) from the first to the last dispensation; and this interval was also considered as the length of selective serotonin reuptake inhibitors treatment.

Life threatening infections

We identified incident cases of severe infections characterised by high fatality (sepsis, endocarditis, and meningitis or other central nervous system infections) as any first inpatient or outpatient visit with these infections as the main diagnosis, 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 (see supplementary table 1).

Covariates

Data on education level, family income, and marital status were obtained from the Longitudinal Integration Database for Health Insurance and Labour Market study database. Other psychiatric disorders are commonly diagnosed around the same time as diagnosis of stress related disorders.[25][26] Given that co-occurring psychiatric disorders might 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 three months before to one year after the diagnosis of stress related disorder as psychiatric comorbidity. In contrast, we considered other psychiatric disorders documented more than three months before the diagnosis of a stress related disorder as indicating a history of other psychiatric disorders. We further obtained information on history of severe somatic diseases (myocardial infarction, congestive heart failure, cerebrovascular disease, chronic pulmonary disease, connective tissue disease, diabetes, renal diseases, liver diseases, ulcer diseases, and HIV infection/AIDS),[27] and history of inpatient visit because of any infectious disease (as an indicator of baseline susceptibility to infectious diseases). The diagnoses were obtained from the National Patient Register, with corresponding ICD codes (see supplementary table 1). Family history of major life threatening infections was defined as any diagnosis of or death due to sepsis, endocarditis, and meningitis or other central nervous system infections among biological parents and full siblings of the study individuals, according to the National Patient Register or the Cause of Death Register. Except for the categories of history of other psychiatric disorder and of psychiatric comorbidity, we updated information until the index date (baseline) for all other covariates. For sensitivity analyses on somatic comorbidities and behaviour related factors, data on the presence of severe somatic diseases and substance use or sleep related diseases (see supplementary table 1) after the index date were also extracted from the National Patient Register. Anatomical defects (congenital diseases of heart and nervous system) are risk factors for severe infections,[28] 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 adjusted for sex, birth year, education level (<9 years, 9-12 years, >12 years,

unknown), family income (top 20%, middle, lowest 20%, unknown), marital status (single, married or cohabiting, divorced or widowed), history of severe somatic diseases (yes or no), history of other psychiatric disorders (yes or no), and history of inpatient visit because of 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, and meningitis or, other central nervous system infections, and deaths due to infections of any other origin.

In subgroup analyses, we calculated the hazard ratios by sex (men or women), time since index date (<1 year, 1-4 years, 5-9 years, or ≥10 years), history of severe somatic diseases (yes or no), calendar period at the index date (1987-2000, 2001-05, or 2006-13), history of other psychiatric disorders (yes or no), family history of major life threatening infections (yes or no), and history of inpatient visit because of any infectious diseases (yes or no). The differences of subgroup 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 these to the Cox models by adding an interaction term.[29] Age varying hazard ratios were estimated and visualised thereafter.

To study the potential impact of severity and complexity of stress related disorders 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 care). 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 other covariates. We compared hazard ratios between sibling and population based analyses using a z test.[30] Furthermore, we restricted analyses to individuals with a diagnosis of a stress related disorder after July 2005 and with more than one year of follow-up, and compared the risk of life threatening infections beyond one year between subgroups 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

supplementary table 1) within one year before the index date. In addition, to alleviate concerns that the observed associations were accounted for by the poorer health conditions or suboptimal behaviours of individuals with stress related disorders than those without, we restricted our analyses to individuals 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 or sleep related diagnoses (as a binary variable) during follow-up. Lastly, to account for increased risk of infection from anatomical defects, we repeated our analyses after excluding those with congenital heart or nervous system diseases. Analyses were conducted in SAS statistical software, version 9.4 (Cary, NC) and STATA 15 (StataCorp).

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 disseminate the results of the research directly to study participants or the relevant patient community. Dissemination to the Swedish population (which constitutes the study population) will be through media outreach (eg, press release and communication) on publication of this study.

Results

Fig 1 shows the flow chart of identifying study cohorts through the study. The sibling cohort accrued 2 370 354 person years, with on average eight years of follow-up. The mean age at entry to the study was 37 years (table 1), and 38.3% (39 513/103 072) of the individuals with a diagnosed stress related disorder were men. A history of other psychiatric disorders, severe somatic diseases, and inpatient stay for infectious diseases were more common among individuals with a diagnosis of a stress related disorder than among unaffected full siblings (34.8% v 12.6%, 16.5% v 12.8%, and 30.9% v 23.8%, respectively). In addition, individuals with a diagnosis tended to have lower family income and were more likely to be divorced or widowed (table 1).

During follow-up, 4843 individuals with incident life threatening infections were identified (2197 among individuals with a diagnosis of a stress related disorder and 2646 among unaffected full siblings, with a crude incidence rate of 2.7 and 1.7 per 1000 person years, respectively). After controlling for all covariates, an association was observed between stress related disorders and life threatening infections: hazard ratios were 1.47 (95% confidence interval 1.37 to 1.58) for any stress related disorder, 1.92 (1.46 to 2.52) for PTSD (fig 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 (see supplementary fig 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 these associations (fig 2 and supplementary fig 1) as differences between the estimates in the sibling based and population based analyses were not significant: hazard ratio for any stress related disorder was 1.58 (1.51 to 1.65), P=0.09 for difference between within sibling and population based comparison; hazard ratio for PTSD was 1.95 (1.66 to 2.28), P=0.92 for difference.

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 for infectious disease (table 2 and supplementary table 2). Associations seemed stronger, however, among individuals without a history of severe somatic diseases or of other psychiatric disorders both (P<0.001 for interaction in population based analysis) and within the first year after the diagnosis of a stress related disorder (P<0.001 for difference in population based analysis). Moreover, an age dependent risk pattern suggested a linear decline in hazard ratios with increased age at diagnosis (fig 3).

Additionally, hazard ratios were higher for any stress related disorder diagnosed through inpatient hospital care than through outpatient specialist care (supplementary table 3, P=0.009 for difference in 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 a further increased relative risk of life threatening infections in both sibling and population based analyses (supplementary fig 2).

Among individuals with a diagnosis of a stress related disorder after July 2005 (n=74 691), the use of selective serotonin reuptake inhibitors after diagnosis was associated with a lower risk of life threatening infections beyond one year (users compared with non-users: hazard ratio 0.81 (0.66 to 0.98), P=0.03). Persistent use of selective serotonin reuptake inhibitors in the first year after diagnosis of a stress related disorder 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 or less, 180-319, and 320 days or more of use, respectively, P=0.01 for trend; supplementary table 4).

Restricting the analyses to individuals without a diagnosis of severe somatic diseases, injury, or infectious diseases within one year before the index date, or those without anatomical defects, yielded largely identical results as the main analyses (supplementary tables 5 and 6). Moreover, although additional adjustments for severe somatic diseases during follow-up did not substantially modify the estimates, the hazard ratios, especially those from the population based analyses, were attenuated after additionally adjusting for the presence of substance use or sleep related diagnoses during follow-up (supplementary table 7).
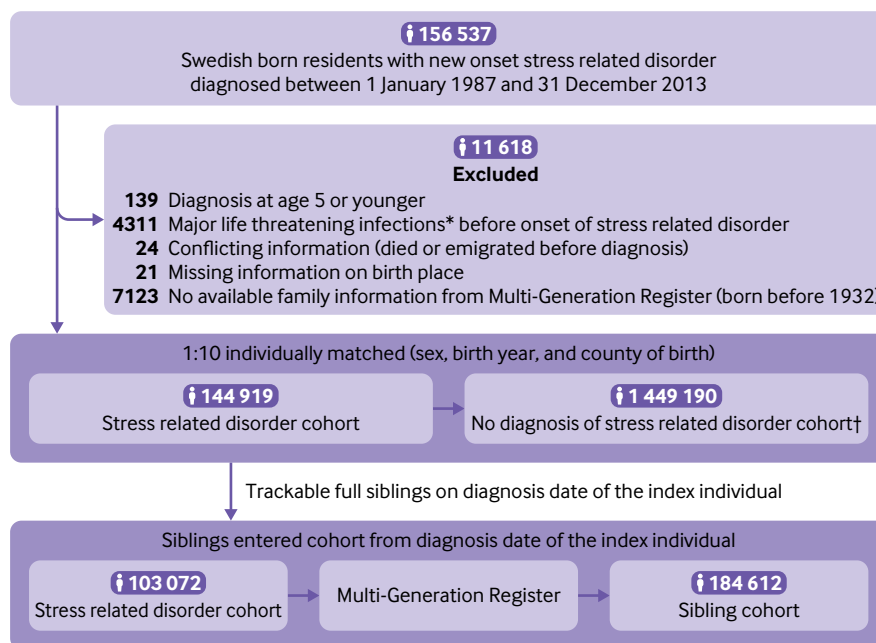
Fig 1 | Study design. *Sepsis, endocarditis, and meningitis or other central nervous system infections. †Randomly selected from general population: individuals without a diagnosis of stress related disorder or major life threatening infection at diagnosis date of the index individual

Discussion

In this study, individuals with stress related disorders, particularly when young at diagnosis, were at increased risk of life threatening infections, after taking into account sex, familial background, and baseline physical or psychiatric conditions. Psychiatric comorbidities, especially substance use disorders, were associated with further risk increases, whereas the long term (>1 year) risk of life threatening infections seemed attenuated by persistent use of selective serotonin reuptake inhibitors in the first year after diagnosis of a stress related disorder.

Strengths and weaknesses of this study

The major strength of our study was the use of a large population based cohort with complete follow-up for up to 27 years and the comparison within full siblings to tackle the a priori concern about familial confounding.[17] Information bias was minimised because the diagnosis and registration of diagnosis and outcome were compiled prospectively and independently. Also, because most of the outcomes of interest (eg, sepsis, meningitis) are aggressive diseases, characterised by sudden onset and severe symptoms, the influence of any surveillance bias or delayed diagnosis should be minor. Furthermore, the large sample size provided enough statistical power for detailed subgroup analyses; and the availability of rich sociodemographic and medical information enabled consideration of a wide range of important confounding and mediating factors.

This study has several limitations. Firstly, the late establishment of the Swedish Outpatient Register (2001) could potentially lead to underestimation of people with stress related disorders, especially milder forms. Also, changes in the definition and diagnostic criteria of stress related disorders over the study period could have influenced the observed associations. For instance, in 2005 exhaustion disorder was introduced to the Swedish ICD-10 system, which resulted in a small difference between the Swedish and international ICD-10 code category F43. Similar results were, however, obtained from a subanalysis of different calendar periods, suggesting a minor influence of these factors. Secondly, we had limited information on some important behaviour related factors (eg, smoking, drug and alcohol use), and our sensitivity analyses showed a considerable mediating effect of these factors on the observed associations. Further research with detailed data on lifestyle is warranted. Thirdly, although trauma focused psychotherapy has been given the highest priority for PTSD treatment in many countries, including Sweden,[22] we have no such data available for analyses. Future well designed studies are needed for exploring the influence of psychotherapy, alone or with drug treatment, on the association between stress related disorder and risk of severe infections. Fourthly, although the association between stress related disorders and risk of fatal infections seems robust, the observational nature of our analysis limits inference of causality or exploration of potential mediating pathways. For instance, despite efforts to control for susceptibility to diseases (eg, history of severe somatic diseases, other psychiatric disorders, or inpatient visit for any infectious diseases) that differ between individuals with a diagnosis of a stress related disorder and reference groups at baseline, we cannot refute the possibility that unmeasured factors contribute to the

Table 1 | Characteristics of study cohorts. Values are numbers (percentages) unless stated otherwise

Characteristics	Sibling cohort		Population based cohort	
	Stress related disorder (n=103 072)	Sibling (n=184 612)	Stress related disorder (n=144 919)	Matched* (n=1 449 190)
Mean (SD) age at index date (years)	37.0 (13.9)	38.0 (15.1)	37.2 (14.3)	37.2 (14.3)
Mean (SD) follow-up (years)	7.8 (6.4)	8.5 (6.8)	7.9 (6.5)	8.1 (6.6)
Men	39 513 (38.3)	94 163 (51.0)	55 541 (38.3)	555 410 (38.3)
Education level (years):				
<9	4191 (4.1)	11 919 (6.5)	6453 (4.4)	58 565 (4.0)
9-12	73 505 (71.3)	126 305 (68.4)	103 252 (71.3)	941 393 (65.0)
>12	23 839 (23.1)	41 569 (22.5)	32 625 (22.5)	426 442 (29.4)
Unknown	1537 (1.5)	4819 (2.6)	2589 (1.8)	22 790 (1.6)
Yearly family income level:				
Lowest 20%	22 941 (22.3)	33 782 (18.3)	32 847 (22.7)	247 467 (17.1)
Middle	56 877 (55.2)	95 927 (52.0)	79 051 (54.6)	799 409 (55.2)
Top 20%	13 160 (12.8)	29 946 (16.2)	18 292 (12.6)	254 009 (17.5)
Unknown	10 094 (9.8)	24 957 (13.5)	14 729 (10.2)	148 305 (10.2)
Marital status:				
Single	58 791 (57.0)	100 525 (54.5)	82 425 (56.9)	823 667 (56.8)
Married or cohabiting	30 730 (29.8)	66 694 (36.1)	42 868 (29.6)	514 251 (35.5)
Divorced or widowed	13 551 (13.2)	17 393 (9.4)	19 626 (13.5)	111 272 (7.7)
History of severe somatic diseases†:				
Yes	17 020 (16.5)	23 534 (12.8)	24 004 (16.6)	145 619 (10.1)
No	86 052 (83.5)	161 078 (87.3)	120 915 (83.4)	1 303 571 (90.0)
History of other psychiatric disorders‡:				
Yes	36 202 (34.8)	23 466 (12.6)	51 905 (35.8)	118 910 (8.2)
No	67 860 (65.2)	162 605 (87.4)	93 014 (64.2)	1 330 280 (91.8)
Family history of major life threatening infections:				
Yes	10 992 (10.7)	20 455 (11.1)	15 548 (10.7)	134 214 (9.3)
No	92 080 (89.3)	164 157 (88.9)	129 371 (89.3)	1 314 976 (90.7)
History of inpatient visit for infectious diseases:				
Yes	31 836 (30.9)	43 956 (23.8)	46 269 (31.9)	307 370 (21.2)
No	71 236 (69.1)	140 656 (76.2)	98 750 (68.1)	1 141 820 (78.8)
Type of stress related disorders:				
Post-traumatic stress disorder	8105 (7.8)	-	11 541 (7.9)	-
Acute stress reaction	47 195 (45.8)	-	66 758 (46.1)	-
Adjustment disorder and other stress reaction	47 772 (46.4)	-	66 620 (46.0)	-
Type of psychiatric care received at diagnosis:				
Inpatient	37 352 (36.2)	-	52 817 (36.5)	-
Outpatient	65 720 (63.8)	-	92 102 (63.5)	-
Psychiatric comorbidity§:				
Any				
Yes	22 619 (21.9)	-	31 415 (21.7)	-
No	80 453 (78.1)	-	113 504 (78.3)	-
Depression:				
Yes	10 581 (10.3)	-	14 500 (10.0)	-
No	92 491 (89.7)	-	130 419 (90.0)	-
Anxiety:				
Yes	6683 (6.5)	-	9222 (6.4)	-
No	96 389 (93.5)	-	135 697 (93.6)	-
Substance use disorder:				
Yes	4567 (4.4)	-	6514 (4.5)	-
No	98 505 (95.6)	-	138 405 (95.5)	-

*Matched individuals without a diagnosis of stress related disorder.
†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.
‡First diagnosis of a psychiatric disorder, other than stress related disorders, occurring more than three months before index date (ie, diagnosis date for individuals with stress related disorder, or diagnosis date of index patient for matched individuals and siblings without a diagnosis of stress related disorder).
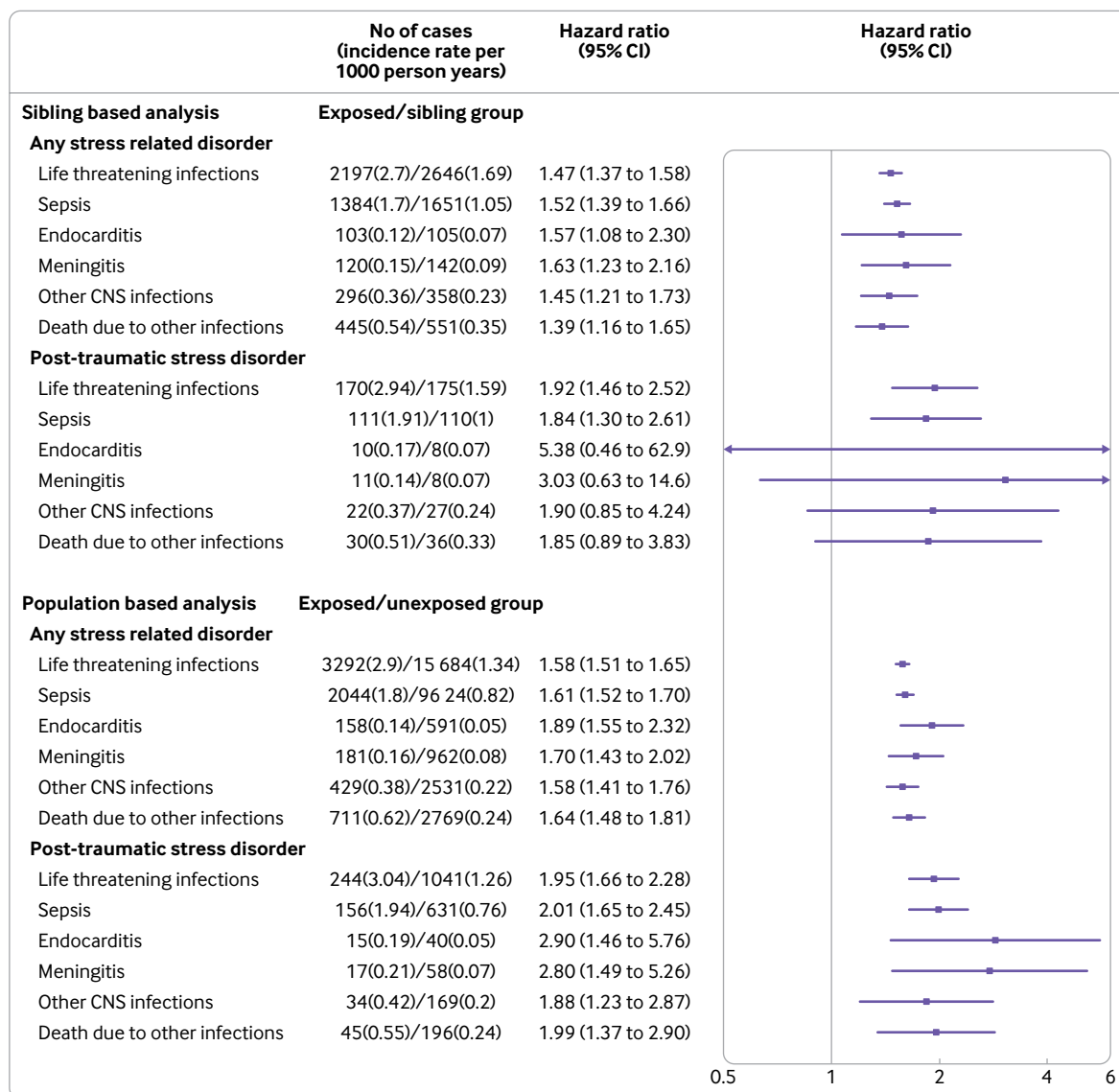§New onset psychiatric disorder, other than stress related disorders, diagnosed from three months before to one year after diagnosis of stress related disorder.

reported association. Fifthly, this study only involved individuals with a clinical diagnosis of stress related disorders through a hospital or specialist visit, thus the generalisability of our findings to those with less severe stress reaction or daily stress needs further assessment.

Comparison with other studies

With few comparable data, our results reinforce the link between stress and infection shown in experimental studies.[4] [5] [31] [32] In the early 1990s, a prospective, although non-randomised, study of 394 healthy volunteers who received a viral challenge (nasal drops containing a low dose of respiratory viruses) after questionnaire based psychological stress assessment found that psychological stress was associated with an increased risk of acute respiratory tract infections in a dose-response manner[4]; and similar conclusions were also made in subsequent research.[5] [31] [32] As common

	No of cases (incidence rate per 1000 person years)	Hazard ratio (95% CI)	Hazard ratio (95% CI)
Sibling based analysis	**Exposed/sibling group**		
Any stress related disorder			
Life threatening infections	2197(2.7)/2646(1.69)	1.47 (1.37 to 1.58)	
Sepsis	1384(1.7)/1651(1.05)	1.52 (1.39 to 1.66)	
Endocarditis	103(0.12)/105(0.07)	1.57 (1.08 to 2.30)	
Meningitis	120(0.15)/142(0.09)	1.63 (1.23 to 2.16)	
Other CNS infections	296(0.36)/358(0.23)	1.45 (1.21 to 1.73)	
Death due to other infections	445(0.54)/551(0.35)	1.39 (1.16 to 1.65)	
Post-traumatic stress disorder			
Life threatening infections	170(2.94)/175(1.59)	1.92 (1.46 to 2.52)	
Sepsis	111(1.91)/110(1)	1.84 (1.30 to 2.61)	
Endocarditis	10(0.17)/8(0.07)	5.38 (0.46 to 62.9)	
Meningitis	11(0.14)/8(0.07)	3.03 (0.63 to 14.6)	
Other CNS infections	22(0.37)/27(0.24)	1.90 (0.85 to 4.24)	
Death due to other infections	30(0.51)/36(0.33)	1.85 (0.89 to 3.83)	
Population based analysis	**Exposed/unexposed group**		
Any stress related disorder			
Life threatening infections	3292(2.9)/15 684(1.34)	1.58 (1.51 to 1.65)	
Sepsis	2044(1.8)/96 24(0.82)	1.61 (1.52 to 1.70)	
Endocarditis	158(0.14)/591(0.05)	1.89 (1.55 to 2.32)	
Meningitis	181(0.16)/962(0.08)	1.70 (1.43 to 2.02)	
Other CNS infections	429(0.38)/2531(0.22)	1.58 (1.41 to 1.76)	
Death due to other infections	711(0.62)/2769(0.24)	1.64 (1.48 to 1.81)	
Post-traumatic stress disorder			
Life threatening infections	244(3.04)/1041(1.26)	1.95 (1.66 to 2.28)	
Sepsis	156(1.94)/631(0.76)	2.01 (1.65 to 2.45)	
Endocarditis	15(0.19)/40(0.05)	2.90 (1.46 to 5.76)	
Meningitis	17(0.21)/58(0.07)	2.80 (1.49 to 5.26)	
Other CNS infections	34(0.42)/169(0.2)	1.88 (1.23 to 2.87)	
Death due to other infections	45(0.55)/196(0.24)	1.99 (1.37 to 2.90)	

0.5   1   2   4   6

Fig 2 | Crude incidence and hazard ratios (95% confidence intervals) for life threatening infections among individuals with any stress related disorder and post-traumatic stress disorder (exposed) compared with full siblings or matched individuals without such a diagnosis (unexposed). *Cox models were stratified by family identifiers and adjusted for sex, birth year, education level, family income, marital status, and history of severe somatic diseases, other psychiatric disorder, and inpatient visit for infectious diseases. †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, other psychiatric disorder, and inpatient visit for infectious diseases; and family history of major life threatening infections. CNS=central nervous system

respiratory viral infections were the predominant disease models in the investigations, however, it remains unclear whether the stress induced immune modulation leads to more severe infection related consequences.

Consistent with our findings, one recent Danish register based study, involving 4984 patients with PTSD diagnosed between 1995 and 2011, reported an association between PTSD and 34 types of infectious diseases, including infections of central nervous system.[16] Also, one cohort study[33] indicated that a higher perceived stress level was moderately associated with one year and 10 year risk of sepsis in a sample of 30 183 community dwelling adults aged 45 years or older in the United States. Although these results

were suggestive, these studies were either focused on PTSD only or based on one time measurement of psychological stress in an older population, with limited observed incident cases of severe infections and little control of familial and comorbidity factors.

Meaning of the study

With a specific focus on clinically diagnosed stress related disorders, we show that severe stress reactions, even transient ones (eg, acute stress reaction), were associated with an increased risk of life threatening infections, both in the short and in the long term. Importantly, the observed excess risks remained after controlling for most of the known risk factors of the studied infections,[34-36] such as socioeconomic factors,

Table 2 | Hazard ratios (95% confidence intervals) for life threatening infections among individuals with any stress related disorder compared with full siblings or matched unexposed individuals, by characteristics

Characteristics	No of cases (incidence per 1000 person years): sibling based analysis			No of cases (incidence per 1000 person years): population based analysis		
	Stress related disorder cohort	Sibling cohort	Hazard ratio (95% CI)*	Stress related disorder cohort	No stress related disorder cohort	Hazard ratio (95% CI)†
Sex:						
Men	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)
Women	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)
Time since index date (years):						
<1	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	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	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	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)	12 232 (1.14)	1.65 (1.57 to 1.73)
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)
2001-05	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)
2006-13	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)
History of other 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)	13 376 (1.21)	1.79 (1.70 to 1.88)
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)	14 425 (1.32)	1.60 (1.53 to 1.67)
History of inpatient stay for infectious diseases:						
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)	11 363 (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, and history of severe somatic diseases, other psychiatric disorder, and inpatient visit for 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, other psychiatric disorder, and inpatient visit for infectious diseases; and family history of major life threatening infections.
‡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.
§First diagnosis of a psychiatric disorder, other than stress related disorders, occurring more than three months before index date.

familial background, physical conditions at baseline (including baseline susceptibility to infection), and the occurrence of other severe somatic diseases during follow-up. Although relatively rare, severe infections contribute substantially to the global burden of disease because of high fatality, risk of long term complications, and high healthcare costs.[37 38] In contrast, stress related disorders are common in the general population. The reported lifetime prevalence of PTSD in Sweden was 5.6% in 2005,[39] and our data suggest at least a 10 times higher prevalence for other stress related disorders, underscoring the considerable clinical significance and public health implications of our findings.

Initial attempts at explaining the documented association between stress and infection were concentrated on altered circulating glucocorticoid levels and the role these played in suppression of cell mediated and humoral immunity,[40 41] which could potentially increase vulnerability to infections among stressed individuals. Yet studies testing the association between glucocorticoid levels and risk of infections produced mixed results.[42-45] A recent hypothesis places focus on the underlying inflammation, where glucocorticoid receptor resistance results in over-production of inflammatory cytokines.[6 46] This notion gains support from several studies, including the

present one, implying that traumatic stress may exacerbate the severity of future infections.[4 47]

Alternative explanations for the impact of severe stress reactions on life threatening infection include behaviour related changes after the diagnosis of a stress related disorder. In the present study we observed a further increased relative risk among individuals with a diagnosis of stress related disorders and with comorbid substance use disorders, as well as attenuated excess risk after additionally adjusting for substance use and sleep related diagnoses during follow-up. It is therefore possible that behavioural factors (eg, smoking, alcohol or drug use, and sleep disturbance) at least partially mediate the observed association, through increased possibility of exposure to pathogens (eg, needle sharing among drug users[48]) or inducing immune dysfunction, or both.[49] Nevertheless, it is unlikely that such behavioural factors can fully explain the increase in fatal infection related consequences, especially those that appear shortly after a diagnosis of stress related disorder.

Our finding suggesting that a diagnosis of stress related disorders in early life is associated with the largest relative risk increase in life threatening infections is in line with findings showing that childhood exposure to trauma might have a lifelong impact on susceptibility to disease, through pro-
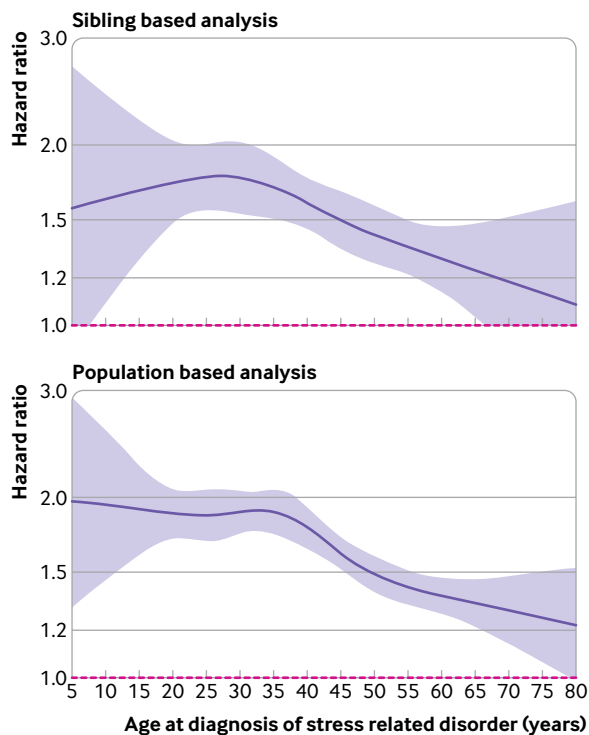
Fig 3 | Association between stress related disorders and life threatening infections by age at index date. *Restricted cubic splines were applied on age at index date, with five knots placed at 5, 27.5, 50, 72.5, and 95 quantiles of the distribution of outcome events. Age varying hazard ratios were then predicted based on fully adjusted Cox models where interaction terms between stress related disorders 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, and history of severe somatic diseases, inpatient visit for infectious diseases, and other psychiatric disorder. In population based analysis, the cox models were stratified by matching identifiers—that is, sex, birth year, and county of birth, and adjusted for education level; family income; marital status; history of severe somatic diseases, inpatient visit for infectious diseases, and other psychiatric disorders; and family history of major life threatening infections. Shaded area represents 95% confidence intervals

moting inflammatory reactions,[50] [51] interrupting neuropsychological and cognitive development,[52] [53] or an interplay between genes and the environment.[54] Indeed, the extent of epigenetic modifications, measured as frequency of DNA methylation changes, were up to 12 times higher in participants with PTSD who were exposed to trauma in childhood compared with participants with PTSD who were trauma-free in childhood.[54] These results constitute a molecular basis implying potentially more extensive biological disruptions and thereby potentially worse health outcomes for younger, rather than older, people with stress related disorders.

Conclusions

In this study, clinically diagnosed stress related disorders were associated with an increased risk of life threatening infections in the Swedish population. Despite a relatively low absolute risk, the high mortality from life threatening infections calls for increased clinical awareness among health professionals caring for patients with stress related disorders, especially those diagnosed at younger age. In addition, our findings, subject to replication, suggest an attenuation in the relative risk of life threatening infections with use of selective serotonin reuptake inhibitors. Further studies are needed to understand the potential mediating role of behaviour related factors in the observed association as well as potential mitigating role of various treatments for stress related disorders in reducing the excess risk of life threatening infections.

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Supplementary information: Supplementary tables 1-7 and figures 1 and 2