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Posttraumatic stress disorder and incident infections: A nationwide cohort study

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Abstract

Background—It is unknown whether posttraumatic stress disorder (PTSD) is associated with incident infections. This study's objectives were to examine (1) the association between PTSD diagnosis and 28 types of infections and (2) the interaction between PTSD diagnosis and sex on the rate of infections.

Methods—The study population consisted of a longitudinal nationwide cohort of all residents of Denmark who received a PTSD diagnosis between 1995 and 2011, and an age- and sex-matched general population comparison cohort. We fit Cox proportional hazards regression models to examine associations between PTSD diagnosis and infections. To account for multiple estimation, we adjusted the hazard ratios using semi-Bayes shrinkage. We calculated interaction contrasts to assess the presence of interaction between PTSD diagnosis and sex.

Results—After semi-Bayes shrinkage, the hazard ratio (HR) for any type of infection was 1.8 [95% confidence interval (CI: 1.6, 2.0)], adjusting for marital status, non-psychiatric comorbidity, and diagnoses of substance abuse, substance dependence, and depression. The association between PTSD diagnosis and some infections (*e.g.,* urinary tract infections) were stronger among women whereas other associations were stronger among men (*e.g.,* skin infections).

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Conflicts of interest

None declared.

Data and computing code

For access to data, please contact the Department of Clinical Epidemiology at Aarhus University Hospital. The analytic code used for the analyses contained in this article is presented in the appendix.

Conclusions—This study's findings suggest that PTSD diagnosis is a risk factor for numerous infection types and that the associations between PTSD diagnosis and infections are modified by sex.

Keywords

Posttraumatic stress disorder; stress; trauma; infection

INTRODUCTION

Posttraumatic stress disorder (PTSD) is a common psychiatric disorder which involves chronic severe stress occurring in response to a traumatic event and can have detrimental effects on physical health [1]. Epidemiologic and animal studies have found that stress may influence risk of infections [2–12]. A meta-analysis of prospective studies showed that psychological stress is associated with greater susceptibility to upper respiratory infections [3]. In two large nested case–control studies of Swedish women, loss of a family member was associated with increased risk of human papillomavirus infection [4]. Similarly, a nationwide cohort of women in Sweden found that loss of a family member was associated with increased risk of sexually transmitted infections (STIs) including condyloma, gonorrhea, chlamydia, syphilis, and genital herpes simplex [5]. This association was stronger among women who lost a spouse compared to women who lost a child, sibling, or parent, suggesting that loss of a spouse may be associated with a change in sex partners and increased risk of STIs. In two studies of men and women caring for a spouse with dementia, caregivers who were chronically stressed had deficits in their cellular and humoral immune responses to influenza vaccination compared with non-caregivers [6,7]. Furthermore, some clinical studies indicate that immune responses are delayed, weaker, and short-lived among distressed or anxious individuals compared to individuals who are less stressed [8–11]. Animal studies provide evidence that stress can dysregulate immune responses to pathogens and increase the risk of infections in mice [2,12].

Although the literature suggests that stress may be associated with infections, no study to date has examined the association between PTSD and a wide range of infections in a population-based sample. Thus a 2011 review of immune alterations among individuals with PTSD called for prospective studies to examine whether PTSD plays a role in the development of medical illnesses such as infections [13]. Furthermore, few previous studies have examined sex differences in the association between psychological stress and infections despite sex differences in biological responses to stress [14]. The current study fills these gaps in the literature by examining the associations of PTSD diagnosis with 28 different types of infections and the interaction between PTSD diagnosis and sex on the rate of infections, in a setting of universal healthcare with complete long-term follow-up.

METHODS

Danish-born residents of Denmark were the source population for this study. As described elsewhere, we obtained PTSD diagnoses from a stress disorder cohort [15]. In brief, we created a national cohort of Danes coded with incident *International Classification of*

Diseases, Tenth Revision (ICD-10) PTSD diagnoses at a psychiatric treatment facility between 1 January 1995 and 31 December 2011 (n = 3,784). For this study, persons with PTSD diagnoses from non-psychiatric treatment facilities were added to the cohort (n = 1,200). We then created a matched comparison cohort of Danish-born residents of Denmark without a PTSD diagnosis. Members of the comparison cohort were individually matched to PTSD cohort members by sex and age (year of birth) on the patient's PTSD diagnosis date at a ratio of 5 to 1 (n = 24,920). Any unexposed matched individuals who were later diagnosed with PTSD were moved to the PTSD cohort. Their person–time before PTSD diagnosis was analyzed as unexposed person–time, and their person–time after PTSD diagnosis was analyzed as exposed person–time.

Data Sources

The Danish Civil Registration System (CRS) maintains demographic data and unique individual-level identifiers (central personal registry [CPR] numbers) assigned to all Danish residents since 1968, which can be used to link data across all Danish administrative and medical registries [16]. The CRS is updated daily with data on the vital status of each resident. We used the CRS to randomly select comparison cohort members from persons who met the matching criteria described earlier.

Since 1995, the Danish Psychiatric Central Research Registry (DPCRR) has recorded up to 20 diagnoses per treatment episode and the dates of all inpatient psychiatric stays and outpatient psychiatric visits [17,18]. Stress disorder diagnoses in the DPCRR were shown to have high positive predictive value for PTSD diagnoses [19]. We used the DPCRR to create the initial cohort of Danes with incident ICD-10 PTSD diagnoses.

The Danish National Patient Registry (DNPR) contains data on all inpatient hospitalizations in non-psychiatric hospitals and hospital outpatient and emergency room visits since 1995 [20]. The DNPR was used to identify additional patients with PTSD diagnosed only at non-psychiatric hospitals, as well as patients diagnosed with various types of infections, including miscellaneous bacterial infections, miscellaneous viral infections, candidiasis and other fungal infections, parasitic infections, herpes simplex or zoster, human immunodeficiency virus (HIV), tuberculosis, atypical mycobacteria, bacteremia, sepsis, abscesses, skin infections, cellulitis, other skin infections (including carbuncle, furuncle, lymphadenitis, cutaneous abscesses, cysts, and dermatitis), eye infections, ear infections, central nervous system infections (except meningococcal disease), meningitis, gastrointestinal infections, intra-abdominal infections, viral hepatitis, heart infections (acute rheumatic fever, infectious pericarditis or myocarditis, and endocarditis), upper respiratory tract infections, influenza, pneumonia, other lower-respiratory tract infections, urinary tract infections, sexually transmitted diseases, male genital infections (prostatitis, orchitis, and epididymitis), female pelvic infections (salpingo-oophritis, uterine infections, and vulvovaginitis), obstetrical infections, septic arthritis, osteomyelitis, myositis, infectious complications of procedures (*e.g.*, urinary catheter placement), and other infections or sequelae. Although we examined 34 types of infections, we do not present results for instances in which there were fewer than five cases of infection in either the PTSD cohort or comparison cohort. We present the results for 28 infection types.

We also used data from the DNPR to compute Charlson Comorbidity Index (CCI) scores at baseline, as a measure of the overall physical health of each study participant. Charlson conditions have been shown to have excellent positive predictive values in the DNPR [21,22]. The diagnoses used to construct the CCI score include myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, ulcer disease, mild liver disease, diabetes types I and II, hemiplegia, moderate to severe renal disease, diabetes with end-organ damage, any tumor diagnosis, leukemia, lymphoma, moderate to severe liver disease, metastatic solid tumor, and acquired immune deficiency syndrome (AIDS). ICD codes for all analytic variables are provided in eTable1, eAppendix 1.

Analyses

Participants were followed from the PTSD diagnosis date (for the exposed) or the date of their matched exposed individual's PTSD diagnosis date (for the unexposed) until the first diagnosis of each infection type in the study period, date of emigration, date of death, or 31 December 2011, whichever came first. We restricted the analyses to persons aged 16 years or older. We fit Cox proportional hazards regression models to examine individual associations of PTSD diagnosis with different infections. All models adjusted for marital status, physical comorbidities (CCI score), substance abuse and dependence diagnoses, and presence of a depression diagnosis at the time of PTSD diagnosis. These variables are potential confounders because previous studies have found these factors to predict PTSD and to also increase the risk of infections [23,24]. We further adjusted the hazard ratios (HRs) for each infection type using semi-Bayes shrinkage. This adjustment was used to account for multiple estimation because we examined the associations between PTSD diagnosis and a large number of infection outcomes [25,26]. This technique attenuates individual associations toward the overall mean in proportion to their variance, thus de-emphasizing high-magnitude, imprecisely measured associations. This approach can help to improve statistical accuracy compared to conventional analyses when a large number of outcomes are under study and there is limited statistical precision of estimates [25]. It also can help avoid unproductive investigations of associations that are likely to be spurious. For semi-Bayes adjustment, the empirical mean of the natural logarithm of the hazard ratios derived from the data was 0.57 and we specified a true population variance of 0.281, implying a prior expectation that 95% of the HRs would lie between 0.62 and 4.98.

To the assess the presence of interaction between PTSD diagnosis and sex, we calculated the interaction contrast as a measure of the departure from additive effects [27]. Positive interaction contrasts describe the excess infection rate caused by positive interdependence (i.e., the synergy between PTSD diagnosis and sex that increases the infection rate). A negative interaction contrast indicates a protective or antagonistic interaction (i.e., the antagonism between PTSD diagnosis and sex that decreases the infection rate).

Infections that did not result in inpatient hospitalizations in non-psychiatric hospitals nor in hospital outpatient and emergency room visits would not have been recorded in the DNPR. Thus, we may have underestimated the true number of infections. Misclassification of infections may reduce the validity of the associations between PTSD diagnosis and

infections. We therefore conducted a bias analysis to assess the potential impact of differential misclassification of infections on the association between PTSD diagnosis and infections. Assuming no false positive diagnoses of infections, we used the formula IRR * (s_0/s_1), where IRR is the measured incidence rate ratio (as estimated by the HR), s_0 is the sensitivity of infection diagnoses among persons without a PTSD diagnosis, and s_1 is the sensitivity of infection diagnoses among persons with a PTSD diagnosis. The sensitivity of ICD-10 diagnoses of infections among patients with community-acquired infections in a Danish medical emergency department has been found to be 0.80 (s_0) [28]. We calculated corrected IRRs assuming a sensitivity of ascertainment of infections of 0.85, 0.90, and 0.95 among persons with a PTSD diagnosis (s_1).

We performed analyses using SAS, version 9.4. The study was approved by the Danish Data Protection Agency (record number 2012–41-0841) and by the Institutional Review Board at Boston University.

RESULTS

Median follow-up time for the first incident infection overall was 4.5 years (interquartile range: 1.8, 8.9 years) in the PTSD cohort and 5.4 years (interquartile range: 2.2, 10 years) in the comparison cohort. The proportion of the PTSD cohort whose follow-up ended in death was 8%, in emigration was 0.9%, and in administrative censoring was 91.1%. The proportion of the comparison cohort whose follow-up ended in death was 4.5%, in emigration was 0.8%, and in administrative censoring was 94.7%. Table 1 presents the baseline characteristics of the PTSD and comparison cohorts. The majority of PTSD cohort members were female and younger than 60 years of age. A higher proportion of comparison cohort members were married or in a registered partnership than in the PTSD cohort. The PTSD cohort had higher proportions of members with diagnoses of anxiety disorders, depression, substance use and dependence, and a CCI score of one or greater, compared with the matched general population cohort.

Table 2 presents the original hazard ratios (HRs) and the semi-Bayes shrinkage estimates for 28 types of infections. The infection types are arranged in rows representing the increasing magnitude of the original HRs. We found that persons with a PTSD diagnosis were at increased risk of all the infections under study compared with persons without a PTSD diagnosis. The original HR of any infection was 1.8 (95% CI, 1.6, 2.0). As expected, semi-Bayes shrinkage attenuated estimates that were high-magnitude and imprecise. For example, the original HR for viral hepatitis was 3.1 (95% CI: 1.8, 5.4); its corresponding semi-Bayes estimate was smaller and more precise (semi-Bayes HR: 2.7; 95% CI: 1.7, 4.5). In contrast, pneumonia, which affected 269 subjects in the PTSD cohort, showed a moderate association with PTSD, measured with good precision (original HR=1.8, 95% CI: 1.6, 2.1); its semi-Bayes estimate was similar to the original estimate (semi-Bayes HR=1.8, 95% CI: 1.5, 2.2). Most hazard ratios for each infection type did not change much after semi-Bayes adjustment, but their 95% confidence intervals became narrower because the estimates were borrowing strength from the prior.

We stratified the infection rates by PTSD diagnosis and sex, and then calculated the interaction contrasts describing the interaction between PTSD diagnosis and sex on the rate of each type of infection (Table 3). The strongest evidence of an interaction between PTSD diagnosis and sex was found for urinary tract infections. There were an additional 208.2 cases of urinary tract infections per 100,000 person–years among women with a PTSD diagnosis compared with men with a PTSD diagnosis. We also found strong evidence of an interaction for skin infections, with 185.1 additional skin infection cases per 100,000 person–years occurring among men with a PTSD diagnosis, compared with women with a PTSD diagnosis.

The results of the bias analysis showed that at all evaluated sensitivity levels (sensitivity of ascertainment of infections = 0.80 among persons without a PTSD diagnosis and sensitivity of ascertainment of infections = 0.85, 0.90, and 0.95 among persons with a PTSD diagnosis), associations remained between PTSD diagnosis and infections (corrected IRRs: 1.7, 1.6, and 1.5, respectively). This analysis suggests that our results remained robust against bias from differential misclassification of infections, assuming a valid bias model and accurate values assigned to the bias parameters.

Discussion

This nationwide study is, to our knowledge, the first to examine associations between PTSD diagnosis and various types of infections using clinical diagnoses tracked during a long follow-up period. We found that PTSD diagnosis was associated with increased risk of infections, consistent with previous research documenting associations between stress and infections in the general population [3–5].

Our findings support a previous meta-analysis that found that psychological stress was associated with increased susceptibility to upper respiratory tract infections [3]. In our study, the rate of upper respiratory tract infections among persons with a PTSD diagnosis was two times the rate of such infections among persons without a PTSD diagnosis. Previous studies also documented associations between bereavement and sexually transmitted infections among women [4,5]. In line with this finding, the current study found a higher rate of sexually transmitted infections among women with a PTSD diagnosis compared with women without a PTSD diagnosis. Our study also contributes further to the literature by identifying novel associations between PTSD diagnosis and a wide range of additional infection outcomes, such as viral hepatitis, eye infections, and gastrointestinal infections.

Another novel contribution of this study is its identification of interactions between PTSD diagnosis and sex on the rate of infections. A previous meta-analysis found that sex did not modify the association between stress and upper respiratory infections [3]. However, our study found that women with a PTSD diagnosis had an additional 35.2 cases of upper respiratory tract infection per 100,000 person–years compared with men with a PTSD diagnosis. Different analytic approaches for assessing interactions may explain discrepant results. The meta-analysis relied on a meta-regression using the percentage of females among participants as an independent predictor and examined the effect size of this predictor. Our study calculated interaction contrasts as a measure of the departure from

additive effects. Our results indicate that further examination of the interaction between stress and sex in the association with infections is warranted.

Biologic mechanisms proposed for the association between psychological stress and infections include activation of the hypothalamic pituitary adrenal axis and sympathetic adrenal medullary axis, leading to the release of pituitary adrenal hormones that may contribute to dysregulated immune function [13,29,30]. Trauma exposure and PTSD are also associated with epigenetic changes that may lead to a greater number of unmethylated genes related to immune and inflammatory function. These unmethylated genes may induce the expression of altered immune function and enhanced inflammatory activity [31]. In addition to these biologic pathways, psychological stress can lead to adverse behavioral changes. For example, individuals experiencing high levels of psychological stress may engage in unsafe sexual practices or have poor hygiene, which increases risk of infections [32].

Several limitations should be kept in mind when interpreting our results. Our sample contained few cases of some infections (*e.g.*, central nervous system infections and influenza), which limited our ability to conduct stratified analyses for these infection types. A validation study of infections among cancer patients found that the DNPR was suitable for monitoring infections requiring hospitalization among cancer patients [33]. However, detection bias may still be present in our study, *i.e.,* not all infections are recorded in the DNPR and infections might be more frequently diagnosed among individuals with a PTSD diagnosis compared to individuals without a PTSD diagnosis because PTSD patients may be in greater contact with medical care. Differential misclassification of the outcome may lead to overestimates of the association between PTSD diagnosis and infections. We conducted a bias analysis to examine this concern and found that differential infection misclassification would not substantially impact our results, assuming a valid bias model. In addition to potential misclassification of the outcome, there may also be non-differential misclassification of exposure. PTSD is a rare psychiatric disorder and thus the strength of bias from misclassification will be driven by specificity. In our previous validation study of stress diagnoses in the DPCRR, we investigated the occurrence of stress diagnoses among the comparison cohort and found that no one in the subsample of comparison cohort members included in the validation study had PTSD [19]. This suggests that the specificity of PTSD is 100%. Non-differential misclassification of exposure is likely to have a limited biasing effect since PTSD is rare and specificity is perfect. Another limitation of our study is that it is possible that depression and substance abuse/dependence measured at baseline may not truly precede the onset of PTSD. Thus, there may be some cases of depression and substance abuse/dependence which occurred after the onset of PTSD but before PTSD was diagnosed. Conditioning on a causal intermediate of the association between PTSD and infections is expected to bias the observed association toward the null [34]. The HR for the association between PTSD and all types of infections was 1.9 (95% CI: 1.8, 2.1) when we did not adjust for diagnoses of depression, substance use/dependence, and other potential confounders. After adjustment for confounders, the HR was 1.8 (95% CI: 1.6, 1.9). The HR estimates were similar before and after confounder-adjustment, which suggests that this potential limitation did not have a strong biasing effect. Another limitation of this study is the potential role of death as a competing risk. To assess the amount of bias that resulted from censoring due to death, we calculated the expected number of infections which were

missed because of censoring due to death. We first multiplied the total person–time that would have accrued if no one died with the infection rate to obtain the expected number of infections if no one died. We then subtracted the observed number of infections from the expected number of infections to obtain the expected number of infections that were missed because of censoring due to death. The expected number of overall infections which were missed because of censoring due to death was 68 infections in the PTSD cohort and 114 in the comparison cohort. The observed number of overall infections was 1239 in the PTSD cohort and 3715 in the comparison cohort. Censoring due to death may have resulted in fewer observed infections, but these missing infections would not have had a large biasing effect since there were relatively few missing infections due to censoring due to death compared to the observed number of infections in the PTSD and comparison cohorts.

A strength of our study is our access to a large cohort of individuals diagnosed with PTSD, which enabled us to examine many types of infections and to conduct stratified analyses. Another strength is that we reduced the potential for selection bias through the use of nationwide registries to identify subjects, with few exclusion criteria and little loss to follow-up. Classification of PTSD in the DPCRR, the registry from which we identified PTSD cohort members, proved accurate when validated against medical records, with a positive predictive value of 83% [19].

This study found that PTSD diagnosis is associated with an increased rate of infections in a nationwide cohort and that there are interactions between PTSD diagnosis and sex in the association with infections. Future studies should corroborate these findings and examine the mechanisms that underlie the observed associations between PTSD and infections. Another area for further investigation is the association of traumatic events that led to PTSD diagnoses with infections because outcomes might differ by trauma type.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

[1]. Pacella ML, Hruska B, Delahanty DL. The physical health consequences of PTSD and PTSD symptoms: a meta-analytic review. J Anxiety Disord 2013;27:33–46. doi:10.1016/j.janxdis.2012.08.004. [PubMed: 23247200]

[2]. Glaser R, Kiecolt-Glaser JK. Stress-induced immune dysfunction: implications for health. Nat Rev Immunol 2005;5:243–51. doi:10.1038/nri1571. [PubMed: 15738954]

[3]. Pedersen A, Zachariae R, Bovbjerg DH. Influence of Psychological Stress on Upper Respiratory Infection—A Meta-Analysis of Prospective Studies. Psychosom Med 2010;72:823–832. doi:10.1097/PSY.0b013e3181f1d003. [PubMed: 20716708]

[4]. Lu D, Sundström K, Sparén P, Fall K, Sjölander A, Dillner J, et al. Bereavement is associated with an increased risk of HPV infection and cervical cancer: an epidemiological study in Sweden. Cancer Res 2016;76:643–51. doi:10.1158/0008-5472.CAN-15-1788. [PubMed: 26634926]

[5]. Bond E, Lu D, Herweijer E, Sundström K, Valdimarsdóttir U, Fall K, et al. Sexually transmitted infections after bereavement - a population-based cohort study. BMC Infect Dis 2016;16:419. doi:10.1186/s12879-016-1705-x. [PubMed: 27528204]

[6]. Kiecolt-Glaser JK, Glaser R, Gravenstein S, Malarkey WB, Sheridan J. Chronic stress alters the immune response to influenza virus vaccine in older adults. Proc Natl Acad Sci U S A 1996;93:3043–7. [PubMed: 8610165]

[7]. Vedhara K, Cox NK, Wilcock GK, Perks P, Hunt M, Anderson S, et al. Chronic stress in elderly carers of dementia patients and antibody response to influenza vaccination. Lancet Lond Engl 1999;353:627–31. doi:10.1016/S0140-6736(98)06098-X.

[8]. Morag M, Morag A, Reichenberg A, Lerer B, Yirmiya R. Psychological variables as predictors of rubella antibody titers and fatigue--a prospective, double blind study. J Psychiatr Res 1999;33:389–95. [PubMed: 10504007]

[9]. Glaser R, Sheridan J, Malarkey WB, MacCallum RC, Kiecolt-Glaser JK. Chronic stress modulates the immune response to a pneumococcal pneumonia vaccine. Psychosom Med 2000;62:804–7. [PubMed: 11139000]

[10]. Burns VE, Drayson M, Ring C, Carroll D. Perceived stress and psychological well-being are associated with antibody status after meningitis C conjugate vaccination. Psychosom Med 2002;64:963–70. [PubMed: 12461201]

[11]. Glaser R, Kiecolt-Glaser JK, Bonneau RH, Malarkey W, Kennedy S, Hughes J. Stress-induced modulation of the immune response to recombinant hepatitis B vaccine. Psychosom Med 1992;54:22–9. [PubMed: 1553399]

[12]. Konstantinos AP, Sheridan JF. Stress and influenza viral infection: modulation of proinflammatory cytokine responses in the lung. Respir Physiol 2001;128:71–7. doi:10.1016/S0034-5687(01)00266-3. [PubMed: 11535264]

[13]. Pace TWW, Heim CM. A short review on the psychoneuroimmunology of posttraumatic stress disorder: from risk factors to medical comorbidities. Brain Behav Immun 2011;25:6–13. doi:10.1016/j.bbi.2010.10.003. [PubMed: 20934505]

[14]. Kudielka BM, Kirschbaum C. Sex differences in HPA axis responses to stress: a review. Biol Psychol 2005;69:113–32. doi:10.1016/j.biopsycho.2004.11.009. [PubMed: 15740829]

[15]. Gradus JL, Bozi I, Antonsen S, Svensson E, Lash TL, Resick PA, et al. Severe Stress and Adjustment Disorder Diagnoses in the Population of Denmark: Stress Diagnoses in Denmark. J Trauma Stress 2014;27:370–4. doi:10.1002/jts.21926. [PubMed: 24948539]

[16]. Schmidt M, Pedersen L, Sørensen HT. The Danish Civil Registration System as a tool in epidemiology. Eur J Epidemiol 2014;29:541–9. doi:10.1007/s10654-014-9930-3. [PubMed: 24965263]

[17]. Munk-Jørgensen P, Mortensen PB. The Danish Psychiatric Central Register. Dan Med Bull 1997;44:82–4. [PubMed: 9062767]

[18]. Mors O, Perto GP, Mortensen PB. The Danish Psychiatric Central Research Register. Scand J Public Health 2011;39:54–7. doi:10.1177/1403494810395825. [PubMed: 21775352]

[19]. Svensson E, Lash TL, Resick PA, Hansen JG, Gradus JL. Validity of reaction to severe stress and adjustment disorder diagnoses in the Danish Psychiatric Central Research Registry. Clin Epidemiol 2015;7:235–42. doi:10.2147/CLEP.S80514. [PubMed: 25870515]

[20]. Schmidt M, Schmidt SAJ, Sandegaard JL, Ehrenstein V, Pedersen L, Sørensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. Clin Epidemiol 2015;7:449–90. doi:10.2147/CLEP.S91125. [PubMed: 26604824]

[21]. Thygesen SK, Christiansen CF, Christensen S, Lash TL, Sørensen HT. The predictive value of ICD-10 diagnostic coding used to assess Charlson comorbidity index conditions in the population-based Danish National Registry of Patients. BMC Med Res Methodol 2011;11:83. [PubMed: 21619668]

[22]. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373–83. [PubMed: 3558716]

[23]. DiGangi JA, Gomez D, Mendoza L, Jason LA, Keys CB, Koenen KC. Pretrauma risk factors for posttraumatic stress disorder: A systematic review of the literature. Clin Psychol Rev 2013;33:728–44. doi:10.1016/j.cpr.2013.05.002. [PubMed: 23792469]

[24]. Segerstrom SC, Miller GE. Psychological Stress and the Human Immune System: A Meta-Analytic Study of 30 Years of Inquiry. Psychol Bull 2004;130:601–30. doi: 10.1037/0033-2909.130.4.601. [PubMed: 15250815]

[25]. Greenland S, Poole C. Empirical-Bayes and semi-Bayes approaches to occupational and environmental hazard surveillance. Arch Environ Health 1994;49:9–16. doi: 10.1080/00039896.1994.9934409. [PubMed: 8117153]

[26]. Steenland K, Bray I, Greenland S, Boffetta P. Empirical Bayes adjustments for multiple results in hypothesis-generating or surveillance studies. Cancer Epidemiol Biomark Prev Publ Am Assoc Cancer Res Cosponsored Am Soc Prev Oncol 2000;9:895–903.

[27]. Greenland S, Lash TL, Rothman KJ. Concepts of Interaction Mod. Epidemiol Third Edition, Philadelphia, PA: Lippincott Williams & Wilkins; 2008, p. 71–86.

[28]. Henriksen DP, Nielsen SL, Laursen CB, Hallas J, Pedersen C, Lassen AT. How Well Do Discharge Diagnoses Identify Hospitalised Patients with Community-Acquired Infections? – A Validation Study. PLOS ONE 2014;9:e92891. doi:10.1371/journal.pone.0092891. [PubMed: 24663388]

[29]. Wessa M, Rohleder N, Kirschbaum C, Flor H. Altered cortisol awakening response in posttraumatic stress disorder. Psychoneuroendocrinology 2006;31:209–15. [PubMed: 16154709]

[30]. Yehuda R Status of glucocorticoid alterations in post-traumatic stress disorder. Ann N Y Acad Sci 2009;1179:56–69. doi:10.1111/j.1749-6632.2009.04979.x. [PubMed: 19906232]

[31]. Uddin M, Aiello AE, Wildman DE, Koenen KC, Pawelec G, de los Santos R, et al. Epigenetic and immune function profiles associated with posttraumatic stress disorder. Proc Natl Acad Sci U S A 2010;107:9470–5. doi:10.1073/pnas.0910794107. [PubMed: 20439746]

[32]. Cohen S, Williamson GM. Stress and infectious disease in humans. Psychol Bull 1991;109:5–24. [PubMed: 2006229]

[33]. Holland-Bill L, Xu H, Sørensen HT, Acquavella J, Sværke C, Gammelager H, et al. Positive predictive value of primary inpatient discharge diagnoses of infection among cancer patients in the Danish National Registry of Patients. Ann Epidemiol 2014;24:593–7, 597.e1–18. doi: 10.1016/j.annepidem.2014.05.011. [PubMed: 25084702]

[34]. Rothman KJ, Greenland S, Lash TL. Modern Epidemiology. Lippincott Williams & Wilkins; 2008.

Table 1.

Baseline characteristics of members of the study cohorts, Denmark, 1995–2011.

Participant characteristics	PTSD cohort, % (n=4,984)	Comparison cohort, % (n=24,920)
Sex[a]		
Female	60	60
Male	40	40
Age group[a]		
16–39 years	49	49
40–59 years	43	43
60+ years	7.7	7.7
Marital status		
Married/registered partnership	38	47
Single	32	30
Divorced	15	8.5
Widowed	3.9	2.7
Unknown	11	13
Anxiety disorder diagnosis	1.6	0.2
Depression diagnosis	3.2	0.5
Alcohol abuse and dependence diagnosis	8.8	2.6
Drug abuse and dependence diagnosis	2.0	0.5
Somatic Comorbidity		
CCI score 0	82	89
CCI score 1+	18	11
Myocardial infarction	1.7	0.8
Congestive heart failure	0.8	0.5
Peripheral vascular disease	1.2	0.7
Cerebrovascular disease	2.4	1.3
Dementia	0.3	0.1
Chronic pulmonary disease	6.3	3.1
Connective tissue disease	1.6	1.1
Ulcer disease	2.4	1.1
Mild liver disease	0.8	0.3
Diabetes	2.0	1.4
Hemiplegia	0.1	0.2
Moderate to severe renal disease	0.6	0.4
Diabetes with end organ damage	0.7	0.5
Any tumor	2.6	2.1
Leukemia	0.1	0.1
Lymphoma	0.1	0.2
Moderate to severe liver disease	0.1	0.1
Metastatic solid tumor	0.3	0.2

Participant characteristics	PTSD cohort, % (n=4,984)	Comparison cohort, % (n=24,920)
AIDS	0.0	0.0

[a]Members of the comparison cohort were individually matched to PTSD cohort members by sex and age on the patient's PTSD diagnosis date at a ratio of 5 to 1.

Table 2.

Hazard ratios for episodes of infection by type, before and after semi-Bayes shrinkage, from Cox regression models, Denmark, 1995–2011.

Infection Type	Events in PTSD cohort	Events in comparison cohort	Original Hazard Ratio (95% CI)	Semi-Bayes Hazard Ratio (95% CI)
Infections overall	1239	3715	1.8 (1.6, 1.9)	1.8 (1.6, 2.0)
Meningitis	6	28	0.97 (0.38, 2.4)	1.3 (0.63, 2.5)
Misc. bacterial infections	32	115	1.3 (0.88, 2.0)	1.4 (0.93. 2.0)
Sexually transmitted diseases	43	154	1.4 (0.97, 1.9)	1.4 (1.0, 2.0)
Ear infections	30	104	1.4 (0.90, 2.1)	1.4 (0.95, 2.1)
Obstetrical infections	72	242	1.5 (1.1, 1.9)	1.5 (1.1, 1.9)
Sepsis	60	198	1.5 (1.1, 2.1)	1.6 (1.1, 2.1)
Central Nervous System infections (except meningococcal disease)	15	50	1.6 (0.86, 2.9)	1.6 (0.95, 2.7)
Infectious complications of procedures, catheters etc.	57	152	1.6 (1.2, 2.2)	1.6 (1.2, 2.2)
Cellulitis	37	105	1.6 (1.1, 2.4)	1.6 (1.1, 2.4)
Skin infections	134	384	1.6 (1.3, 2.0)	1.6 (1.3, 2.0)
Influenza	10	34	1.7 (0.81, 3.5)	1.7 (0.93, 3.1)
Intra-abdominal infections	166	475	1.7 (1.4, 2.0)	1.7 (1.4, 2.0)
Abscesses	226	623	1.7 (1.4, 2.0)	1.7 (1.4, 2.0)
Male genital infections	28	78	1.7 (1.1, 2.7)	1.7 (1.1, 2.6)
Other lower-respiratory tract infections	102	265	1.7 (1.4, 2.2)	1.7 (1.4, 2.2)
Septic arthritis, osteomyelitis, myositis	16	35	1.8 (0.88, 3.5)	1.8 (0.98, 3.1)
Miscellaneous viral infections	36	99	1.8 (1.2, 2.6)	1.8 (1.2, 2.6)
Other skin infections	130	347	1.8 (1.4, 2.2)	1.8 (1.4, 2.2)
Pneumonia	269	723	1.8 (1.6, 2.1)	1.8 (1.5, 2.2)
Female pelvic infections (salpingo-oophritis, uterine infections, vulvovaginitis)	103	257	1.9 (1.5, 2.4)	1.9 (1.5, 2.4)
Upper respiratory tract infections	73	174	2.1 (1.5, 2.7)	2.0 (1.5, 2.7)
Other infections or sequelae of infections	18	40	2.1 (1.1, 3.8)	2.0 (1.2, 3.4)
Urinary tract infections	234	569	2.1 (1.8, 2.5)	2.1 (1.7, 2.5)
Bacteremia	21	46	2.1 (1.2, 3.7)	2.0 (1.2, 3.3)
Gastrointestinal infections	124	267	2.2 (1.7, 2.8)	2.1 (1.7, 2.7)

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Infection Type	Events in PTSD cohort	Events in comparison cohort	Original Hazard Ratio (95% CI)	Semi-Bayes Hazard Ratio (95% CI)
Candidiasis and other fungal infections	33	76	2.3 (1.5, 3.6)	2.2 (1.4, 3.4)
Eye infections	85	188	2.3 (1.8, 3.1)	2.3 (1.7, 3.0)
Viral hepatitis	33	48	3.1 (1.8, 5.4)	2.7 (1.7, 4.5)

Abbreviations: CI, confidence interval; PTSD, posttraumatic stress disorder

The infection types are arranged in rows representing increasing magnitude of the original HRs.

Models were adjusted for marital status, comorbidity (CCI score), substance abuse and dependence diagnoses, and depression diagnosis. Limited to infections with at least 5 observed events in the PTSD cohort and comparison cohort.

Table 3.

Rates and interaction contrasts for sex differences in the association between PTSD and infections, Denmark, 1995–2011.

	Males		Females		
	Rate/100,000 PY		Rate/100,000 PY		IC/100,000 PY (95% CI)
Infection	**PTSD cohort**	**Comparison cohort**	**PTSD cohort**	**Comparison cohort**	
Meningitis	--	19.7	27.2	13.3	--
Misc. bacterial infections	161.4	71.4	54.4	60.4	96.0 (14.9, 177.1)
Sexually transmitted diseases	80.6	63.8	150.9	99.8	−34.4 (−110.9, 42.2)
Ear infections	56.3	59.3	104.8	57.8	−50.0 (−114.2, 14.2)
Obstetrical infections	--	--	331.0	216.7	--
Sepsis	217.4	127.7	150.2	101.3	40.8 (−61.4, 142.9)
Central Nervous System infections (except meningococcal disease)	40.1	38.0	45.4	22.2	−21.1 (−69.3, 27.2)
Infectious complications of procedures, catheters etc.	185.7	85.2	155.0	85.4	31.1 (−65.2, 127.3)
Cellulitis	104.7	74.6	109.5	49.8	−29.6 (−105.5, 46.3)
Skin infections	602.0	304.2	279.0	166.2	185.1 (22.8, 347.3)
Influenza	--	18.2	27.2	19.5	--
Intra-abdominal infections	575.3	309.0	443.3	245.9	69.0 (−100.5, 238.4)
Abscesses	721.9	414.6	649.3	320.4	−21.6 (−217.1, 173.9)
Male genital infections	226.8	119.0	--	--	--
Other lower-respiratory tract infections	307.5	126.4	293.3	162.6	50.4 (−76.1, 177.0)
Septic arthritis, osteomyelitis, myositis	80.4	31.9	27.2	12.4	33.8 (−22.7, 90.2)
Miscellaneous viral infections	40.2	56.2	141.5	55.1	−102.4 (−167.5, −37.4)
Other skin infections	508.6	259.6	312.9	159.2	95.4 (−58.4, 249.1)
Pneumonia	950.7	477.5	717.8	369.6	125.0 (−92.1, 342.0)
Female pelvic infections (salpingo-oophritis, uterine infections, vulvovaginitis)	--	--	479.0	230.8	--
Upper respiratory tract infections	178.1	85.2	233.3	105.3	−35.2 (−137.7, 67.3)
Other infections or sequelae of infections	56.3	21.2	49.9	23.1	8.2 (−44.8, 61.2)
Urinary tract infections	438.6	196.9	846.7	396.7	−208.2 (−385.8, −30.7)
Bacteremia	96.6	30.3	40.8	23.1	48.5 (−14.3, 111.3)
Gastrointestinal infections	340.6	95.9	378	182.4	49.1 (−86.8, 185.1)
Candidiasis and other fungal infections	72.4	41.0	109.1	43.5	−34.2 (−101.5, 33.1)

Infection	Males Rate/100,000 PY		Females Rate/100,000 PY		IC/100,000 PY (95% CI)
	PTSD cohort	Comparison cohort	PTSD cohort	Comparison cohort	
Eye infections	277.0	128.5	234.4	92.7	6.7 (−111.1, 124.5)
Viral hepatitis	153.3	41.0	63.5	18.6	67.4 (−11.1, 145.9)

Notes. CI = confidence interval; IC= interaction contrast; PTSD = posttraumatic stress disorder; PY = person-years.

Women were used as the reference for the interaction contrast calculation.

Analyses with fewer than 5 infection cases in either the PTSD or comparison cohort are not presented.