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Associations Between Adjustment Disorder and Hospital-Based Infections in the Danish Population

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INTRODUCTION

Psychological stress is associated with susceptibility to infections [1,2], possibly due to both immune dysregulation [3–5] and the initiation of unhealthy behaviors [6,7]. Consistent with this observation, a quintessential stress-related mental disorder, posttraumatic stress disorder (PTSD), is associated with increased risk of infections [8,9]. Adjustment disorder is another commonly-diagnosed stress-related mental disorder, typically triggered by an acute stressor that is not immediately life threatening and is less traumatic than events that trigger PTSD [10,11]. While there are no specific criteria for adjustment disorder diagnosis, symptoms must follow a stressful event and not fulfill criteria for another condition [10]. Some symptoms, such as intrusion, avoidance, and failure to adapt, may overlap with PTSD. Despite some similarities between adjustment disorder and PTSD, no study has examined whether adjustment disorder is associated with risk of infections.

Several possible biological and behavioral mechanisms could explain the association between PTSD and infections [8,9], and these mechanisms may or may not be applicable to adjustment disorder [12]. For example, changes in immune functioning have been linked to both stress [4,5] and PTSD [13–18]. In addition, adverse health outcomes could be due to worse health maintenance, unsafe drug use, alcohol intake, smoking, risky sexual practices, and/or other unhealthy behaviors triggered by stress [7]. An association between adjustment disorder and subsequent infections could

contribute to evidence that a variety of stress-related psychopathologies (e.g., PTSD, adjustment disorder), lead to similar biological and behavioral responses due to the common presence of severe stress.

In addition, it is plausible that stress disorders could affect risk of infections differently in men and women. Sex-based differences have been documented with respect to biological responses to stress [19], immune responses [20,21], and behaviors that could result from stress and affect health [22]. However, few studies [8] have attempted assess sex differences in the somatic consequences of stress disorders.

Aiming to address these gaps in the stress disorder literature, we examined the associations between adjustment disorder diagnosis and 32 types of infections in a nationwide registry-based cohort of Danish residents. We also assessed additive interaction between adjustment disorder and sex with respect to risk of infections.

METHODS

Data Sources

Adjustment disorder cohort. As described elsewhere [23], we obtained hospital-based adjustment disorder diagnoses from a registry of Danish-born citizens of Denmark with incident severe stress diagnoses, diagnosed at a psychiatric facility between January 1, 1995, and December 31, 2011. We excluded emergency room diagnoses due to their low positive predictive value [24,25]. Adjustment disorder was defined as an International

Classification of Diseases, 10th edition (ICD-10) diagnosis of F43.2 and initially identified from the Danish Psychiatric Central Research Registry (DPCRR; n = 66,288) [26]. The DPCRR maintains information on all inpatient psychiatric stays and outpatient psychiatric visits that have occurred since 1995. Patients could receive up to 20 diagnoses on the same day, and we included persons in the cohort if any of these diagnoses were for adjustment disorder. Adjustment disorder diagnosis in the DPCRR has high positive predictive value (94%) [27] when compared with independent symptom reassessment. We augmented the initial adjustment disorder cohort with persons diagnosed only at non-psychiatric treatment facilities (n = 3,564), using diagnoses in the Danish National Patient Registry (DNPR) [28]. The DNPR maintains data on all inpatient hospitalizations in non-psychiatric hospitals and hospital outpatient and emergency room visits that occurred since 1995. Adjustment disorder cohort members did not have a previous diagnosis of any stress disorder (i.e., PTSD, acute stress reaction, or unspecified/other reactions to severe stress). In total, the adjustment disorder cohort contained 69,852 individuals.

Comparison cohort. We created a matched general population comparison cohort of Danish-born residents of Denmark without a diagnosis of adjustment disorder. The comparison cohort was obtained from the Danish Civil Registration System (CRS), which maintains demographic data and unique individual-level identifiers assigned to all Danish residents that have occurred since 1968 [29–31]. The CRS is updated daily with data on the vital

status of each resident and can be used to link data across all Danish administrative and medical registries. Comparison cohort members were individually matched to counterparts in the adjustment disorder cohort by sex, age, and patient's adjustment disorder diagnosis date, at a ratio of 5 to 1 (n = 349,260). Persons in the CRS who met matching criteria were randomly selected. If a comparison cohort member was later diagnosed with adjustment disorder, that individual was moved to the adjustment disorder cohort (without replacement). Person-time before adjustment disorder diagnosis was analyzed as unexposed person-time.

Infections. We used the DNPR to identify patients diagnosed with any of 32 infection types following their adjustment disorder diagnosis. Only infections that were treated in hospital (inpatient or outpatient) could be included. We organized infections by body system (see **Appendix 1** for a list of infections and associated ICD-10 codes): circulatory system infections (heart infections), digestive system infections (viral hepatitis, gastrointestinal infections, intra-abdominal infections), immune system disorders (HIV), integumentary infections (cellulitis, skin infections), nervous system infections (meningitis, central nervous system infections, eye infections, ear infections), reproductive system infections (urinary tract infections, female pelvic infections, male genital infections, obstetrical infections), respiratory system infections (tuberculosis, pneumonia, influenza, other lower respiratory tract infections, upper respiratory infections), complications or sequelae of infections (bacteremia, infectious complications of medical

procedures, sepsis, atypical mycobacteria, abscesses, septic arthritis/osteomyelitis/myositis), and other infections (fungal infections, sexually transmitted infections, miscellaneous bacterial infections, parasitic infections, miscellaneous viral infections, other infections and their sequelae). Each infection was analyzed separately, meaning that a person who had multiple infections during the follow-up period was included in analyses for each individual infection.

Confounders. We collected information on factors known to be associated with both stress disorders and infections, which may confound the relation of interest. This included physical and psychiatric comorbidities, and marital status. As a measure of overall physical health at baseline, we used data from the DNPR to compute Charlson Comorbidity Index (CCI) scores [32]. The diagnoses used to construct these scores were 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 AIDS (see **Appendix 1** for a list of ICD-10 and ICD-8 codes that defined these conditions). These diagnoses have individually been shown to have excellent positive predictive value in the DNPR [33]. We also obtained information on substance abuse/dependence, depression, and anxiety diagnoses from the DPCRR and

DNPR, and on marital status from the CRS. All confounder information was based on status prior to the adjustment disorder diagnosis or the match date (as applicable).

Analyses

Participants were followed from the date of their adjustment disorder diagnosis (or match date for the comparison cohort), until their first infection during the follow-up period (for each individual infection type), emigration from Denmark, death, or the end of the study period (December 31, 2011), whichever came first. We used Cox proportional hazards regression to compute adjusted hazard ratios (aHR) and 95% confidence intervals (CI) for the association of adjustment disorder with each infection type. Cox models were adjusted for baseline marital status, prior physical comorbidities (CCI score ≥1 versus 0), and prior diagnosis of depression, anxiety disorder, alcohol abuse/dependence disorder, and other drug abuse/dependence disorder (see Appendix for ICD-10 codes). We controlled for age and sex in the design phase via matching. To assess the robustness of our findings, we calculated e-values [34], which indicate the degree (on a multiplicative scale) to which a hypothetical unmeasured confounder would need to increase the risk of both adjustment disorder and a given infection in order to fully explain the association between adjustment disorder and that infection.

Using interaction contrasts (IC) [35], we assessed potential additive interaction between adjustment disorder and sex. Positive interaction contrasts indicate positive interdependence between adjustment disorder and male sex, such that the risk of infections among men with adjustment disorder is greater than that based on the independent effects of adjustment disorder and male sex. Negative interaction contrasts indicate that the risk of infections among men with adjustment disorder is less than that expected based on the independent effects of adjustment disorder and male sex.

We conducted two sub-analyses. First, infections are often triggered by physical trauma or surgery, and the causes of such infections may differ from the causes of community-acquired infections. Thus, we stratified results for five infection types (intra-abdominal infections, skin infections, urinary tract infection, pneumonia, and sepsis) according to whether or not they occurred within 30 days of a trauma or surgery, given the fact that these infections are common sequelae of trauma. Trauma was defined based on ICD-10 codes, and surgery was defined based on Nordic Medico-Statistical Committee (NOMESCO) classification codes (see Appendix 1). Second, since the validity of adjustment disorder diagnosis in the DNPR is unknown, we repeated the analyses including in the adjustment disorder cohort only individuals who received their diagnosis in a psychiatric hospital (i.e. recorded in the DPCRR but not the DNPR).

Finally, it is plausible that persons with adjustment disorder could have had infections diagnosed more accurately, given that they are under the

care of a physician for their adjustment disorder. Thus, we conducted a bias analysis in which we adjusted HR estimates by multiplying the observed estimate by a bias-adjustment factor. This factor was Se_0/Se_1, where Se_0 represented sensitivity of infection diagnosis among the comparison cohort and Se_1 represented sensitivity of infection diagnosis among the adjustment disorder cohort [36]. We assumed perfect specificity of infection diagnoses. We set Se_0 at 0.80, based on a validation study of Danish patients with community-acquired infections [37]. We assessed the impact of three possible values of Se_1: 0.85, 0.90, and 0.95.

All analyses were performed 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

At the time of adjustment disorder diagnosis, 54% of persons with adjustment disorder were 16-39 years old, 33% were 40-59 years old, and 13% were greater than 60 years old (**Table 1**). The age distribution in the comparison cohort was similar due to age-matching. Persons with adjustment disorder were less likely to be married or in a registered partnership than members of the comparison cohort (31% vs. 43%). They were also more likely to be diagnosed with anxiety disorder (4.5% vs. 0.6%), depression (15% vs. 1.1%), alcohol abuse/dependence (12% vs. 1.9%), and drug abuse/dependence (4.8% vs. 0.6%), more likely to have at least one

physical health comorbidity as indicated by the CCI (21% vs. 12%), and more likely to have chronic pulmonary disease (a marker of smoking status, 6.7% vs. 3.5%). Persons with adjustment disorder had a greater frequency of death during the study period (13% vs. 6.2%), and had a similar prevalence of emigration from Denmark (0.6% vs. 0.9%).

The rate of any infection was almost two times higher in the adjustment disorder cohort compared to the comparison cohort (aHR = 1.8, 95% CI: 1.8, 1.9). The strength of the association between adjustment disorder and most infections was consistent, generally falling in the range of 1.5 and 2.3 (**Table 2**). Exceptions that were stronger in magnitude were viral hepatitis (aHR = 3.6, 95% CI: 3.1, 4.1) and HIV (aHR = 2.8, 95% CI: 2.3, 3.6). The e-value for any infection was 3.0, (**Table 2**), meaning that a hypothetical unmeasured confounder would need to increase the risk of both adjustment disorder and infections by a factor of at least 3.0 to explain away the association between these variables. E-values for individual infections averaged approximately 3, and ranged from 2.4 for obstetrical infections and miscellaneous viral infections to 6.7 for viral hepatitis.

There was evidence of additive interaction between adjustment disorder and male (versus female) sex for a number of infections (**Table 3**). In many cases, the infection rate among men with adjustment disorder was higher than what would have been expected based on the independent effects of adjustment disorder and male sex. The infections for which we found the greatest evidence of this type of interaction were skin infections

(IC = 199 per 100,000 person-years, 95% CI: 155, 243), pneumonia (IC = 172 per 100,000 person-years, 95% CI: 111, 234), and abscesses (IC = 156 per 100,000 person-years, 95% CI: 104, 207). On the contrary, for urinary tract infections (IC = -345, per 100,000 person-years, 95% CI: -394, -295) and sexually transmitted infections (IC = -64.1 per 100,000 person-years, 95% CI: -88.1, -40.1), the infection rate among men with adjustment disorder was lower than what would have been expected based on the independent effects of adjustment disorder and male sex, indicating weaker effects among men than women.

In the first subanalysis, hazard ratios did not differ meaningfully according to whether infections were trauma- and/or surgery-related versus not (**Table S1**). However, the degree of additive interaction between adjustment disorder and sex was greater for infections that were not related to trauma or surgery compared to infections that were (**Table S2**). In the second subanalysis, we found that when restricting to individuals those who received their diagnosis only in a psychiatric hospital, and their matched counterparts, the HR for any infection was still 1.8 (95% CI: 1.8, 1.8), and all HRs for individual infections types were similar to those in the primary analysis (±0.1). The demographic characteristics of individuals in this subanalysis did not differ from those in the main analysis.

Finally, assuming a valid bias model, HRs did not change substantially in the bias analysis addressing possible differential misclassification. In this analysis, the aHR for any infection was 1.7 (95% CI: 1.7, 1.8) when $Se_1 =$

0.85, 1.6 (95% CI: 1.6, 1.7) when $Se_1 = 0.90$, and 1.5 (95% CI: 1.5, 1.6) when $Se_1 = 0.95$. Associations for individual infections were similarly slightly decreased, but all estimates and 95% CI remained above 1.0.

DISCUSSION

Building on a body of work linking stress [1–7] and PTSD [8,9] to infections, this study is the first to assess the link between adjustment disorder and infections. In a cohort of Danish-born residents of Denmark, we found that persons with adjustment disorder had a 1.8-fold increased rate of any infection during the follow-up period, compared to the general population without adjustment disorder. While the adjusted hazard ratio was around 1.8 for most individual infections (range = 1.5 to 2.3 for 30 infection types), persons with adjustment disorder had almost three times or greater the rate of viral hepatitis and HIV compared to persons without. In some cases, adjustment disorder interacted with sex; for many infection types, the increase in infection rate due to adjustment disorder was greater for men compared to women. For urinary tract infections and sexually transmitted infections, the increase in infection rate due to adjustment disorder was greater in women compared to men.

Persons with adjustment disorder have similar long-term health outcomes—including risk of cardiovascular disease [38], autoimmune disorders [39,40], all-cause mortality [41], and hospital use [42]—compared to persons with PTSD. Adjustment disorder has been described as a

subclinical or mild disorder compared with other psychiatric disorders like PTSD [43,44] and depression [45]. However, our finding that adjustment disorder is associated with similarly increased rates of infections suggests that PTSD and adjustment disorder may work through similar biological and behavioral pathways.

There are several potential explanations for the association between stress disorders and infections. A large body of work has linked PTSD to immune dysregulation [16]. For example, persons with PTSD have increased levels of inflammation-related biomarkers such as C-reactive protein and interleukin-6 [14–17], and there is evidence of changes in hypothalamic pituitary adrenal axis activity in response to stress [5,16]. While immune dysregulation is a possible explanation for our findings, behavioral factors may also be explanatory. For example, following severe stress, persons may decrease their health maintenance, use drugs and alcohol more frequently, and/or engage in risky sexual practices, thereby increasing risk of exposure to infectious agents [6,7]. Behavioral explanations are particularly likely for the infections with the largest associations – namely viral hepatitis and HIV. Nevertheless, given existing literature, a combination of biological and behavioral mechanisms is plausible.

Our finding that rate differences for the majority of infections were greater in magnitude among men than women is consistent with previous research on PTSD and infections [8]. Potentially explaining these findings, limited evidence suggests that men have greater increases in cortisol

production in response to stress compared to women [19,46,47]. The consequences of behavioral responses to stress may also differ in men and women [22]. Additional work in this area is needed to better explain interactions with sex. In addition, additional work should expand this work to explore other potential interacting factors (such as psychiatric, somatic, and/or drug use comorbidities).

Our findings must be considered in light of several limitations. First, beyond the covariates adjusted for, there is a possibility of unmeasured confounding by factors that can cause both stress disorders and infections, such as socioeconomic status and risky behavior, but the use of registry data did not allow us to account for these variables. Nevertheless, the results of our e-value analysis indicate that a hypothetical unmeasured confounder would need to approximately triple the risk of both adjustment disorder and infections in order to fully explain away the observed associations. There is little evidence that the unmeasured potential confounders listed above cause adjustment disorder or other stress disorders to this degree, particularly conditional on the variables for which we did adjust. In addition, stress disorders have been linked to other health conditions like diabetes, even when adjusting for behavioral risk factors [48]. Second, we were not able to adjust for comorbid psychiatric disorders diagnosed prior to 1995 due to use of ICD-8 in Denmark prior to this time and inconsistencies in psychiatric diagnostic criteria between the two ICD versions. Third, because there may be delays in diagnosing psychiatric disorders, we may have adjusted for

variables on the causal pathway between adjustment disorder and infections if they were diagnosed first, thereby attenuating observed HRs.

Fourth, there may have been imperfect sensitivity of adjustment disorder due to misdiagnosis as depression or another disorder with overlapping symptomology; the stigma of mental illness, which can preclude help seeking; and/or avoidance of thinking about the event, which is a hallmark symptom of stress disorders. However, given the rarity of adjustment disorder in this population (about 2%), the magnitude of bias would be driven by specificity rather than sensitivity, and would thus be small. Given the prospective nature of the data, any misclassification was likely non-differential by infection status, and bias is expected to be towards the null. Fifth, detection bias was possible. Although the DNPR is considered suitable for monitoring infections requiring hospitalization [37,49], infections that were not treated in a hospital would not have been recorded in the DNPR. Infection diagnosis may have been more likely among persons with adjustment disorder, as they may be in greater contact with the healthcare system. However, our bias analysis to address imperfect and differential sensitivity of infection classification indicated that, assuming a valid bias model, this could not explain the observed associations.

Despite these limitations, this work highlights important physical health consequences faced by individuals with adjustment disorder, and documents that these consequences are relatively comparable to those faced by persons with PTSD [38,50,51]. Adjustment disorder is a relatively

common mental health diagnosis, with over half of psychiatrists worldwide reporting using this diagnosis once a week or more [52], yet adjustment disorder is vastly understudied [10,11]. Extending this work to better understand the specific pathways that explain the associations between stress disorders and infections, as well as the effects of stressful and traumatic experiences themselves, will be important areas for future research.

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564 Table 1: Baseline characteristics of members of the study cohorts, Denmark, 1995-
565 2011 (n=419,112)

	% of adjustment disorder cohort (n=69,852)	**% of comparison cohort (n=349,260)**
Female	61	61
Age group		
16-39 years	54	54
40-59 years	33	33
60+ years	13	13
Marital status		
Married/registered partnership	31	43
Single	36	32
Divorced	16	7.6
Widowed	5.9	4.1
Unknown	12	14
Anxiety disorder	4.5	0.6
Depression	15	1.1
Alcohol abuse/dependence	12	1.9
Drug abuse/dependence	4.8	0.6
Somatic comorbidities (comprising Charlson Comorbidity Index)		
Myocardial infarction	1.7	0.9
Congestive heart failure	1.3	0.6
Peripheral vascular disease	1.5	0.8
Cerebrovascular disease	3.3	1.6
Dementia	0.4	0.2
Chronic pulmonary disease	6.7	3.5
Connective tissue disease	1.8	1.2
Ulcer disease	2.9	1.1
Mild liver disease	1.2	0.3
Diabetes	2.6	1.4
Hemiplegia	0.2	0.1
Moderate to severe renal disease	0.9	0.4
Diabetes with end organ damage	1.2	0.5
Any tumor	3.3	2.4
Leukemia	0.1	0.1
Lymphoma	0.2	0.2
Moderate to severe liver disease	0.3	0.1
Metastatic solid tumor	0.4	0.2
AIDS	0	0
Charlson Comorbidity Index 1+	21	12

Table 2: Hazard ratios for episodes of infections by type from Cox regression models, by organ system, Denmark, 1995-2011 (n=419,112)

Infection type	Events in adjustment disorder cohort (n=69,852)	Events in comparison cohort (n=349,260)	Adjusted HR[1] (95% CI)	e-value (lower bound of 95% CI)
Any infection	19,838	57,353	1.8 (1.8, 1.9)	3.0 (3.0)
Circulatory system				
Heart infections[2]	127	320	1.8 (1.5, 2.4)	3.0 (2.4)
Digestive system				
Viral hepatitis	624	644	3.6 (3.1, 4.1)	6.7 (5.7)
Gastrointestinal infections	1,906	4,143	2.2 (2.1, 2.3)	3.8 (3.6)
Intra-abdominal infections	2,498	7,219	1.6 (1.6, 1.7)	2.6 (2.6)
Immune system				
HIV	169	244	2.9 (2.3, 3.6)	5.2 (4.0)
Integumentary system				
Cellulitis	652	1,521	1.9 (1.7, 2.1)	3.2 (2.8)
Skin infections	3,964	9,919	1.8 (1.8, 1.9)	3.0 (3.0)
Nervous system				
Meningitis	137	323	2.2 (1.8, 2.8)	3.8 (3.0)
Central nervous system infections, excluding meningococcal disease	168	503	1.6 (1.3, 2.0)	2.6 (1.9)
Eye infections	1,055	3,286	1.6 (1.5, 1.7)	2.6 (2.4)
Ear infections	486	1,456	1.6 (1.4, 1.8)	2.6 (2.1)
Reproductive system				
Urinary tract infections	4,034	9,910	2.1 (2.0, 2.2)	3.6 (3.4)
Female pelvic infections[3]	1,508	3,703	2.0 (1.8, 2.1)	3.4 (3.0)
Male genital infections[4]	404	1,120	1.9 (1.7, 2.2)	3.2 (2.8)
Obstetrical infections	973	3,466	1.5 (1.3, 1.6)	2.4 (1.9)
Respiratory system				
Tuberculosis	112	175	2.3 (1.7, 3.0)	4.0 (2.8)
Pneumonia	4,862	11,547	2.0 (1.9, 2.1)	3.4 (3.2)
Influenza	211	508	1.8 (1.5, 2.2)	3.0 (2.4)
Other lower respiratory tract infections	1,755	4,163	1.9 (1.8, 2.0)	3.2 (3.0)
Upper respiratory tract infections	1,111	2,997	1.8 (1.7, 2.0)	3.0 (2.8)
Complications and sequelae of infections				
Bacteremia	399	850	2.1 (1.8, 2.4)	3.6 (3.0)
Infectious complications of procedures, catheters, etc.	867	2,083	1.9 (1.8, 2.1)	3.2 (3.0)
Sepsis	1,264	3,026	1.9 (1.7, 2.1)	3.2 (2.8)
Atypical mycobacteria	8	24	2.1 (0.8, 5.4)	3.6 (1.0)
Abscesses	3,292	8,682	1.8 (1.7, 1.8)	3.0 (2.8)

Septic arthritis, osteomyelitis, myositis	218	571	1.8 (1.5, 2.2)	3.0 (2.4)
Other infections				
Candidiasis and other fungal infections	504	1,032	2.1 (1.9, 2.4)	3.2 (3.0)
Sexually transmitted infections	961	2,364	1.9 (1.7, 2.0)	3.2 (2.8)
Miscellaneous bacterial infections	655	1,605	1.9 (1.7, 2.1)	3.2 (2.8)
Parasitic infections	108	309	1.6 (1.3, 2.1)	2.6 (1.9)
Miscellaneous viral infections	502	1,563	1.5 (1.4, 1.7)	2.4 (2.1)
Other infections or sequelae of infections	231	646	1.7 (1.4, 2.0)	2.8 (2.1)

CI = confidence interval, HR = hazard ratio

[1] Adjusted for age group, sex, baseline marital status, physical comorbidities (CCI score ≥1 versus 0), prior depression diagnosis, prior anxiety disorder diagnosis, prior alcohol abuse/dependence diagnosis, and prior diagnosis of other drug abuse/ dependence disorder.

[2] Heart infections include acute rheumatic fever, infectious pericarditis or myocarditis, and endocarditis.

[3] Female pelvic infections include salpingo-oophritis, uterine infections, and vulovaginitis.

[4] Male genital infections include prostatitis, orchitis, and epididymitis.

580 Table 3: Rates and interaction contrasts for sex differences in the association between adjustment disorder
581 infections, Denmark, 1995-2011 (n=419,112)

	Males (n=163,680) Rate/100,000 PY		Females (n=255,432) Rate/100,000 PY		
	Adjustment disorder cohort	**Comparison cohort**	**Adjustment disorder cohort**	**Comparison cohort**	**IC/100,000 PY (95% CI)[1]**
Circulatory system					
Heart infections[2]	33	17	20	8.9	5.0 (-5.0, 15)
Digestive system					
Viral hepatitis	193	33	82	19	97 (74, 119)
Gastrointestinal infections	331	126	409	171	-32 (-68, 3.4)
Intra-abdominal infections	537	282	481	263	36 (-7.2, 80)
Immune system					
HIV	70	19	12	3.2	43 (30, 56)
Integumentary system					
Cellulitis	188	73	94	47	68 (45, 91)
Skin infections	1,094	467	647	317	297 (239, 356)
Nervous system					
Meningitis	25	9.4	28	14	0.4 (-9.1, 9.9)
Central nervous system infections, excluding meningococcal disease	33	18	33	19	1.2 (-9.6, 12)
Eye infections	282	143	167	110	81 (52, 111)
Ear infections	88	55	100	53	-14 (-32, 4.5)
Reproductive system					
Urinary tract infections	465	236	1,027	453	-345 (-394, -295)
Female pelvic infections[3] (salpingo-oophritis, uterine infections, vulovaginitis)	-	-	481	222	-
Male genital infections[4] (prostatitis, orchitis,	217	111	-	-	-

epididymitis)					
Obstetrical infections	-	-	306	207	-
Respiratory system and lungs					
Tuberculosis	31	9.4	17	4.7	9.6 (0.2, 19)
Pneumonia	1,139	478	894	405	172 (111, 234)
Influenza	43	18	41	19	2.8 (-9.4, 15)
Other lower respiratory tract infections	307	127	373	172	-21 (-55, 13)
Upper respiratory tract infections	202	105	230	115	-18.6 (-46.2, 9.0)
Complications and sequelae of infections					
Abscesses	808	367	587	302	156 (104, 207)
Sepsis	305	133	216	100	56 (25, 87)
Bacteremia	104	36	63	28	33 (15, 51)
Septic arthritis, osteomyelitis, myositis	62	32	32	15	13 (-0.1, 27)
Infectious complications of procedures, catheters, etc.	175	74	169	79	11 (-14, 35)
Atypical mycobacteria	2.1	1.1	1.2	0.8	0.6 (-2.0, 3.1)
Other infections					
Candidiasis and other fungal infections	89	35	105	40	-10 (-28, 8.0)
Sexually transmitted infections	123	62	229	103	-64 (-88, -40)
Miscellaneous bacterial infections	161	68	110	54	37 (15, 59)
Parasitic infections	21	12	21	11	-1.3 (-9.9, 7.4)
Miscellaneous viral infections	103	56	96	59	10 (-9.0, 29)
Other infections or sequelae of	44	24	46	24	-3.1 (-16, 9.6)

infections

CI = confidence interval, IC = interaction contract, PY = person-years

[1] Female is the reference category, such that a positive IC indicates positive interdependence between male (versus female) sex and adjustment disorder (versus general population) and a negative IC indicates negative interdependence between male (versus female) sex and adjustment disorder (versus general population).

[2] Heart infections include acute rheumatic fever, infectious pericarditis or myocarditis, and endocarditis.

[3] Female pelvic infections include salpingo-oophritis, uterine infections, and vulovaginitis.

[4] Male genital infections include prostatitis, orchitis, and epididymitis.