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Posttraumatic Stress Disorder and Gastrointestinal Disorders in the Danish Population

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Abstract

Background—Evidence for the association between posttraumatic stress disorder (PTSD) and gastrointestinal (GI) disorders is mixed, owing in part to methodologic differences across studies. Further, studies which have combined GI disorders or symptoms for examination as one overall category may potentially obscure associations between PTSD and individual GI diagnoses.

Methods—This nationwide cohort study examined the incidence of all major non-malignant GI disorders in patients with a prior PTSD diagnosis (n = 4,076), compared to the general population incidence from 1995–2013, using Danish medical registry data. We examined differences by sex, age, marital status, psychiatric and somatic comorbidity and follow-up time. Risks, standardized incidence rates (SIRs), and confidence intervals (95% CIs) were calculated.

Results—Risk of any GI disorder among PTSD patients was 25% (95% CI= 21%, 29%); the SIR for any GI disorder was 1.8 (95% CI = 1.7, 2.0). Risk and SIRs varied by disorder (*e.g.*, no association with diverticula of the intestines (SIR = 1.1, 95% CI = 0.83, 1.5); stronger association with peptic ulcer, site unspecified (SIR = 3.3, 95% CI = 1.8, 5.5)). Stratified analyses revealed that some associations were stronger for persons aged 16–39 or unmarried at PTSD diagnosis, persons with comorbid psychiatric diagnoses, and in the year following PTSD diagnosis.

Conclusions—This study documents associations between clinician-diagnosed PTSD and all major non-malignant GI disorders in an unselected nationwide cohort with long follow-up. Differences in associations across GI disorders and important modifiers may account for previous conflicting research findings.

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Conflicts of Interest: We have no conflicts of interest to disclose.

For access to data contact the Department of Clinical Epidemiology at Aarhus University Hospital. The analytic code used for the analyses contained herein is presented in eAppendix 3.

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Keywords

stress disorders; posttraumatic; gastrointestinal diseases; cohort studies

Posttraumatic stress disorder (PTSD) is a prevalent public health problem which has long has been implicated in the etiology of various somatic disorders.[1,2] Gastrointestinal (GI) disorders have been examined as a possible outcome of PTSD for over two decades.[3] Possible mechanisms through which the association between PTSD and GI disorders is proposed to occur include changes in autonomic nervous system function that impact the gut, hypothalamic-pituitary-adrenal axis dysregulation and accompanying changes in cortisol levels, and behavior risk factors such as smoking, alcohol use and medications.[4,5] Despite existence of these plausible mechanisms, clinical research examining the association between PTSD and GI disorders has yielded mixed evidence, owing in part to methodological differences across studies.[3]

In cross-sectional data from the US National Comorbidity Survey, PTSD was associated with self-reported ulcer and stomach/gallbladder issues.[6] In a Canadian cross-sectional self-report study, PTSD was associated with 1.9 times the odds of Crohn's disease and ulcerative colitis (95% confidence interval [CI] = 1.1, 3.2) and 1.9 times the odds of ulcers (95% CI = 1.2, 3.1).[7] PTSD was also associated with overall GI disorders in a cross-sectional self-report study of male US World War II veterans.[8] Two prospective studies of US veterans have corroborated these findings. Self-reported PTSD was associated with clinician-diagnosed upper and lower GI disorders in male combat veterans.[9] In a recent study using clinical data, PTSD was associated with irritable bowel syndrome (IBS), gastroesophageal reflux disorder (reflux), and dyspepsia among veterans who served in Iraq and Afghanistan.[10] In contrast, a self-report study in Israel found that the proportion of patients with IBS who met diagnostic criteria for PTSD was comparable to the general population prevalence of PTSD.[11] In a cross-sectional study of patients receiving health care from the US Department of Veterans Affairs, PTSD was not associated with overall GI diagnoses.[12] A larger prospective study of disaster survivors in the Netherlands found no association between self-reported PTSD and de-novo medically documented combined GI disorders.[13]

In addition to inconsistency in results which may result from study methodology,[3] examining combined GI disorders or symptoms as an outcome may potentially obscure differences in associations between PTSD and individual GI diagnoses. No prospective population-based study has examined clinician-diagnosed PTSD as a risk factor for all major individual non-malignant clinically-diagnosed GI disorders. The current study, conducted in a setting of universal healthcare with complete long-term follow up, fills this gap in the literature by comparing the incidence of all major individual non-malignant GI disorders in a nationwide cohort of patients with a prior diagnosis of PTSD with the incidence of these disorders in the general population during the same time period. Further, we examine whether these associations vary by sex, age, substance abuse, somatic comorbidity and follow-up time.

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METHODS

We used Danish national medical and social registries to compare the rate of GI disorders among patients with an incident PTSD diagnosis with the rate of diagnoses expected among the general population during the same period. The base population was Danish-born residents of Denmark.

Data Sources

The Danish Civil Registration System (CRS) contains date of birth, sex, other demographic data, and a unique identifier (the central personal registry [CPR] number) that can be used to link data across all Danish administrative and medical registries for all persons residing in Denmark since 1968.[14] The CRS contains data on vital status for each resident and is updated daily.

The Danish Psychiatric Central Research Registry (DPCRR) has, since 1995, recorded up to 20 diagnoses per treatment episode, as well as dates of all inpatient and outpatient psychiatric treatment.[15,16] We used the DPCRR to create a cohort of Danes with incident *International Classification of Diseases, Tenth Revision* (ICD-10) stress-related diagnoses from January 1, 1995 to December 31, 2011.[17] All patients with PTSD were included in the current study. Validation studies of diagnoses in the DPCRR (*e.g.*, schizophrenia and affective disorders) have shown high validity.[15,16] Our study of stress diagnoses in the DPCRR revealed similar validity for PTSD diagnoses.[18]

The Danish National Patient Registry (DNPR) covers all inpatient non-psychiatric hospital treatment and hospital outpatient and emergency room visits since 1995.[19] The DNPR was used to identify patients with GI disorders, including esophagitis, stomach ulcer, duodenal ulcer, peptic ulcer, gastritis and duodenitis, acute appendicitis, diverticula of the intestines, chronic enteritis and ulcerative colitis, irritable bowel syndrome, acute and subacute necrosis of the liver, cirrhosis of the liver, cholelithiasis, cholecystitis and cholangitis, and pancreatitis. A validation study that included a subset of these GI diagnoses (e.g., ulcer disease, liver disease) showed very high validity when compared with medical record review (positive predictive value = 98% and 100% respectively).[20] We also used data from the DNPR to compute a Charlson Comorbidity Index (CCI) score as a measure of overall physical health, which has been shown to have high validity.[20,21] Patients with PTSD and substance abuse registered in the DNPR during the study period were also included in the current study. The diagnostic codes for all variables included in the analysis are displayed in eAppendix 1.

Analyses

PTSD patients with no history of GI diagnoses were followed until a GI disorder diagnosis, date of emigration, date of death or 30 November 2013, whichever came first. We calculated risk and associated 95% CIs for overall GI disorders and each individual GI disorder among people with PTSD during the study period, treating death as a competing risk. We also calculated the expected number of incident GI disorder diagnoses after PTSD using Danish national incidence rates of GI diagnoses according to sex, 5-year age groups, and 5-year

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calendar periods. Multiplying person-years of follow-up and incidence rates yielded the number of GI diagnoses that would be expected if those with PTSD had the same GI disorder rate as the general population.[22] We calculated standardized incidence ratios (SIRs) to measure the association between PTSD and GI disorders as the ratio of observed to expected cases. Confidence intervals (CIs) were calculated assuming that the observed number of GI diagnoses followed a Poisson distribution. Exact confidence limits were calculated when there were fewer than 10 observed GI diagnoses. Otherwise Byar's approximation was used.[22]

Analyses were stratified by sex, age (16–39 years, 40–59 years, and 60+ years), marital status and psychiatric comorbidity at incident PTSD diagnosis, CCI score, and follow-up time between PTSD diagnosis and incident GI diagnosis (0–1 years, >1 years). Results of individual GI disorder analyses were presented for GI disorders with at least 5 incident cases in the PTSD cohort within each subgroup. All analyses were conducted using SAS version 9.2. 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

We identified a nationwide cohort of 4,076 persons with an incident diagnosis of PTSD with no prior GI diagnosis from 1995 – 2011. Table 1 shows descriptive characteristics of the PTSD cohort at the time of diagnosis. The majority of cohort members were female (n = 2,438; 60%) and aged 16–39 (n = 2,125; 52%), without a substance abuse diagnosis (n = 3,405; 84%) and with a CCI score of 0 (n = 3,503; 86%). Chronic pulmonary disease was the most common comorbid condition among the patients with PTSD at baseline (n = 220; 5.4%).

Overall associations and impact of demographic factors

Table 2 displays the observed and expected numbers of incident GI disorders among the PTSD cohort, with associated SIRs, risks, and 95% confidence intervals. Risk for any GI disorder among people with PTSD was 25% over the 18.9 year study period (95% CI= 21%, 29%). Risk estimates over the study period varied by GI disorder, with the lowest risk found for cirrhosis of the liver (0.44%, 95% CI = 0.18%, 0.96%) and the highest risk found for esophagitis (6.2%, 95% CI = 4.6%, 8.1%). The overall incidence rate of GI disorders was 1.8 times higher in the PTSD cohort than expected based on the rate in the general population (95% CI = 1.7, 2.0). No substantial association was found for PTSD and diverticula of the intestines (SIR = 1.1, 95% CI = 0.83, 1.5), and the magnitude of the remaining associations were variable. For example, more compelling evidence for a stronger association between PTSD and peptic ulcer, site unspecified (SIR = 3.3, 95% CI = 1.8, 5.5).

Results of the analysis exploring variation in associations between PTSD and GI disorders by sex and age are displayed in Table 3. The pattern of associations between PTSD and the GI disorders was similar for males and females. Associations were mostly consistent across the age groups and marital status, with a few exceptions, for which evidence of effect modification was found. For peptic ulcer site unspecified, those aged 16 –39 had an SIR of 7.4 (95% CI: 3.2, 15) while those aged 40 – 59 had an SIR of 2.3 (95% CI: 0.73, 5.3).

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Similarly, for married persons the SIR for this association was 2.5 (95% CI: 0.81, 5.9) but 7.2 (95% CI: 2.3, 17) for unmarried persons. We also found evidence of effect modification by age for acute appendicitis; among persons age 16 – 39 we found an SIR of 1.9 (95% CI: 1.4, 2.6), while among persons aged 40 – 59 the SIR was 0.93 (95% CI: 0.45, 1.7).

Follow-up time

We further examined differences in associations between PTSD and GI disorders by length of time between diagnoses (0–1 or 1+ years). We found some evidence for increases in the associations between PTSD and stomach ulcer (SIR = 3.5, 95% CI = 1.8, 6.1), acute appendicitis (SIR = 2.5, 95% CI = 1.3, 4.5), and acute and subacute necrosis of the liver (SIR = 4.4, 95% CI = 1.8, 9.1) within the year following PTSD diagnosis.

Impact of psychiatric and somatic comorbidity

Stratified analyses exploring modification of the association by somatic comorbidity (as measured by CCI score) are also displayed in Table 3. We also found limited evidence of modification in associations between PTSD and GI disorders due to physical health comorbidity as measured by the CCI. Some evidence of potential modification by CCI score was present for pancreatitis, where among those with a CCI score of 0 the SIR was 2.3 (95% CI: 1.5, 3.6) and among those with a CCI score of 1 or more the SIR was 5.1 (95% CI: 2.2, 10). Associations among those with a CCI score of 0 were generally comparable with overall associations.

We further examined the association between PTSD and GI disorders stratified by comorbid psychiatric diagnoses at the time of PTSD diagnosis (eAppendix 2). We found evidence of effect modification by depression, alcohol abuse and drug abuse diagnosis for almost all associations, such that the associations between PTSD and individual GI disorders were stronger among persons with comorbid psychiatric diagnoses. This modification was particularly strong for the alcohol and drug abuse diagnoses. Further, associations among persons without psychiatric comorbidity were consistent with overall associations, indicating that diagnosed psychiatric comorbidity specific to these disorders does not account for observed associations.

DISCUSSION

This nationwide study is the first to report risk and associations for PTSD and all individual major non-malignant GI disorders using clinical diagnoses over a long period of follow-up. We found that PTSD was associated with most individual GI disorders with varying strength, which is consistent with research documenting associations between PTSD and GI disorders in the general population and among US veterans.[6–10,23] Although we found no evidence of an association between PTSD and diverticula of the intestines, our findings are largely inconsistent with studies which have found no evidence of an association between PTSD and overall GI disorders. Differences between our results and the results of previous studies may be attributable in part to variation in study methodology.[3] However, one previous study that found no association also used prospective population-based medical registry data to identify GI disorders.[13] In that study GI disorders were grouped into one

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overall category for analysis, which may have obscured associations between PTSD and individual GI diagnoses, particularly if that sample experienced mostly GI diagnoses that have a null or weak associations with PTSD. We document here the variability in associations between PTSD and specific GI disorders, highlighting the importance of examining individual GI disorders as outcomes.

We found few differences in the strength of associations for men and women, consistent with research in veterans that found no compelling evidence of sex differences.[10] Further, we found limited evidence of effect modification by age group, marital status, or somatic comorbidity. We found some evidence of an increased rate of certain GI disorders in the year following PTSD diagnosis, although there was substantial overlap in the confidence intervals for the 0–1 year and 1+ year estimates so these results should be interpreted with this in mind. If corroborated in future studies, this finding may have important treatment implications. For numerous GI disorders, there was evidence that associations are strongest among persons with depression, alcohol abuse, and drug abuse diagnoses.

Strengths of the current study include a nationwide cohort sample with highly valid clinical diagnoses, a substantial follow-up period and no selection bias. In addition, the use of registry-based prospective data gleaned from clinical diagnoses ensures that biases related to recall and use of self-report data, present in some of the previous studies, did not influence our results.

Despite these strengths, some limitations must be kept in mind when interpreting our results. It is possible that detection bias is present for some of our results, such that GI disorders were more frequently diagnosed among people with PTSD who were receiving medical care, particularly for the stronger associations that were observed in the year following PTSD diagnoses (e.g., stomach ulcer). It is also possible that not all persons with GI disorders seek medical attention and these people would be misclassified in our analyses. However, we expect specificity of GI diagnoses in this population to be 100% (i.e., those without GI disease are correctly classified as such) and any imperfect sensitivity to be non-differential with respect to PTSD diagnosis. This form of misclassification would result in unbiased ratio measures.[24] Further, the sample for this study included only persons who received a PTSD diagnosis in a healthcare setting. A hallmark symptom of PTSD is avoidance of reminders of the trauma, which may discourage seeking care and potentially result in PTSD misclassification in studies that use treatment-seeking samples. However, our validation study of PTSD diagnoses among a random sample of the Danish general population without stress diagnoses coded in the DPCRR found no evidence of PTSD diagnosis in this group.[25] Further, data from Statistics Denmark indicate that over 90% of the Danish population seeks healthcare in a given year.[26] Therefore, almost all residents of Denmark come in contact with the healthcare system in a given year and have an opportunity to receive a PTSD diagnosis if a PTSD diagnosis is present. Finally, we believe we have perfect specificity of PTSD diagnoses (e.g., all those without PTSD are correctly classified as such) and it is specificity that would primarily influence the strength of bias of our estimates of association.[27] For all of these reasons, we do not think bias related to misclassification of PTSD diagnosis (as a result of treatment avoidance) substantially biased the estimates of association. Due to sparse sample sizes we were unable to examine

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precisely associations between PTSD and many GI disorders among persons aged 60+ years, and with some psychiatric comorbidities (i.e., drug abuse, generalized anxiety disorder, panic disorder, and phobias). Also, we were unable to adjust for behavioral risk factors for GI disorders (e.g., smoking, obesity), use of some medications (e.g., NSAIDs), body mass index, and socioeconomic status (SES), which may have an impact on observed associations. Of these, smoking is one important potential unmeasured confounder of on the observed associations, as tobacco has been shown to be associated with increased risk of PTSD in epidemiologic studies[28,29] and PTSD-like behavioral changes in animal studies[30] and is associated with GI disorders.[31] Thus we conducted a bias analysis to assess the impact of unmeasured confounding due to smoking on the association between PTSD and GI disorders (using the formula $RR*P_{z1}+1- P_{z1}/RR*P_{z0} +1 - P_{z0}$; where RR = the association between the unmeasured confounder and the outcome, P_{z1} = the prevalence of the unmeasured confounder among the exposed and P_{z0} = the prevalence of the unmeasured confounder among the unexposed).[32] The prevalence of smoking among people with and without PTSD is well documented (~58% and ~39%, respectively),[33] and an approximately 1.6-fold risk of GI disorders among smoker versus non-smokers has been documented as well.[31] Using these parameters, we were able to estimate the potential bias in the associations between PTSD diagnosis and GI disorders due to uncontrolled confounding by smoking. This analysis revealed a ratio of 1.1 for the unadjusted to adjusted PTSD and GI disorder rate ratios, which indicates that uncontrolled confounding due to smoking would not completely account for our observed associations between PTSD and GI disorders, assuming a valid bias model. Socioeconomic status (SES) is a second important potential unmeasured confounder of the association between PTSD and GI disorders in the current study, as an association exists between low SES and PTSD[34] and low SES has also been shown to be associated with GI symptoms in gender-stratified analyses.[35] The parameters needed to conduct a bias analysis with the formula above while adhering to reasonable assumptions are not available in the extant literature, however SES will be an important variable to consider in future analyses of these associations.

This study documents associations between PTSD and all major individual non-malignant GI disorders, both overall, and within important subgroups. Important directions for future research include examining the influence of trauma itself and clusters of PTSD symptomatology on GI disorders, as well as examining the influence of multiple co-occurring psychiatric disorders on GI disorder incidence. This study also serves as a call for future research that differentiates between GI disorders to further elucidate specific associations and mechanisms.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Characteristics of the posttraumatic stress disorder (PTSD) cohort at the time of diagnosis, Denmark, 1995 – 2011.

	PTSD (n, %) (N = 4,076)
Sex	
Male	1,638 (40%)
Female	2,438 (60%)
Age	
16–39	2,125 (52%)
40–59	1,705 (42%)
60+	246 (6.0%)
Marital Status	
Married	1537 (38%)
Unmarried	1306 (32%)
Divorced	570 (14%)
Widowed	137 (3.4%)
Unknown	526 (13%)
Depression Diagnoses	212 (5.2%)
Alcohol Abuse Diagnoses	330 (8.1%)
Drug Abuse Diagnoses	67 (1.6%)
Generalized Anxiety Disorder	15 (0.37%)
Panic Disorder Diagnoses	19 (0.47%)
Phobia Diagnoses	2 (0.05%)
Charlson Comorbidity Index Diagnoses[a]	
Myocardial Infarction	53 (1.3%)
Congestive Heart Failure	21 (0.52%)
Peripheral Vascular Disease	35 (0.86%)
Cerebrovascular Disease	91 (2.2%)
Dementia	12 (0.29%)
Chronic Pulmonary Disease	220 (5.4%)
Connective Tissue Diseases	55 (1.4%)
Mild Liver Disease	13 (0.32%)
Diabetes Without Organ Damage	58 (1.4%)
Diabetes With Organ Damage	22 (0.54%)
Hemiplegia	4 (0.10%)
Moderate to Severe Renal Disease	24 (0.59%)
Non-Metastatic Solid Tumor	86 (2.1%)
Leukemia	3 (0.07%)
Lymphoma	5 (0.12%)
Moderate to Severe Liver Disease	3 (0.07%)
Metastatic Cancer	11 (0.27%)

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	PTSD (n, %) (N = 4,076)
AIDS	–
Charlson Comorbidity Index Score	
0	3,503 (86%)
1+	573 (14%)

[a]Ulcer disease removed from Charlson Comorbidity Index calculation.

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Table 2

Standardized incidence rates (SIRs) for incident gastrointestinal disorders among patients with posttraumatic stress disorder (PTSD), Denmark, 1995 – 2013

		Association with PTSD		
	Risk (95% CI)	**Observed**	**Expected**	**SIR (95% CI)**
All gastrointestinal disorders	25% (21%, 29%)	531	294.3	1.8 (1.7, 2.0)
Esophagitis	6.2% (4.6%, 8.1%)	119	52.9	2.3 (1.9, 2.7)
Stomach ulcer	2.7% (1.7%, 4.1%)	49	19.3	2.5 (1.9, 3.4)
Duodenal ulcer	0.67% (0.37%, 1.1%)	17	12.3	1.4 (0.80, 2.2)
Peptic ulcer, site unspecified	1.5% (0.32%, 4.7%)	14	4.3	3.3 (1.8, 5.5)
Gastritis and duodenitis	5.4% (4.1%, 7.0%)	103	39.9	2.6 (2.1, 3.1)
Acute appendicitis	3.4% (1.5%, 6.8%)	58	36.6	1.6 (1.2, 2.1)
Diverticula of the intestines	3.4% (2.0%, 5.4%)	44	38.4	1.1 (0.83, 1.5)
Chronic enteritis and ulcerative colitis	1.5% (1.0%, 2.2%)	37	22.5	1.6 (1.2, 2.3)
Irritable bowel syndrome	3.2% (1.9%, 4.9%)	57	31.8	1.8 (1.4, 2.3)
Acute and subacute necrosis of the liver	2.4% (1.7%, 3.1%)	57	17.6	3.2 (2.5, 4.2)
Cirrhosis of the liver	0.44% (0.18%, 0.96%)	7	4.4	1.6 (0.64, 3.3)
Cholelithiasis	5.8% (4.7%, 7.1%)	130	88.8	1.5 (1.2, 1.7)
Cholecystitis and cholangitis	0.98% (0.57%, 1.6%)	20	10.6	1.9 (1.2, 2.9)
Pancreatitis	1.9% (1.1%, 3.0%)	35	11.9	2.9 (2.1, 4.1)

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Table 3

Standardized incidence ratios (SIR) for posttraumatic stress disorder (PTSD) and incident gastrointestinal disorders, stratified by sex, age at PTSD diagnosis, marital status, Charlson Comorbidity Index (CCI) score, and follow-up time

	Sex SIR (95% CI)		Age at PTSD Diagnosis, yrs SIR (95% CI)			Marital Status at PTSD Diagnosis SIR (95% CI)				CCI Score SIR (95% CI)		Follow-up Time, yrs SIR (95% CI)	
	Male	Female	16–39	40–59	60+	Married	Unmarried	Divorced	Widowed	0	1+	0–1	1+
All gastrointestinal disorders	2.0 (1.7, 2.3)	1.7 (1.6, 1.9)	1.9 (1.7, 2.2)	1.8 (1.5, 2.0)	1.4 (1.0, 1.9)	1.7 (1.4, 1.9)	2.0 (1.7, 2.4)	1.7 (1.3, 2.1)	1.7 (1.1, 2.5)	1.7 (1.6, 1.9)	2.3 (1.8, 2.8)	2.0 (1.6, 2.6)	1.8 (1.6, 1.9)
Esophagitis	2.1 (1.6, 2.9)	2.3 (1.8, 2.9)	2.3 (1.7, 3.1)	2.3 (1.8, 2.9)	1.8 (0.77, 3.5)	2.3 (1.8, 3.0)	2.5 (1.7, 3.6)	1.6 (0.85, 2.7)	2.5 (1.0, 5.1)	2.2 (1.8, 2.7)	2.3 (1.3, 3.7)	2.9 (1.7, 4.9)	2.2 (1.8, 2.6)
Stomach ulcer	2.8 (1.7, 4.3)	2.4 (1.6, 3.5)	4.0 (2.3, 6.5)	1.9 (1.1, 2.9)	2.9 (1.5, 4.9)	2.1 (1.3, 3.3)	4.7 (2.5, 8.0)	1.7 (0.64, 3.8)	3.0 (1.2, 6.2)	2.3 (1.6, 3.2)	3.5 (1.8, 6.1)	3.5 (1.8, 6.1)	2.5 (1.8, 3.3)
Duodenal ulcer	1.7 (0.82, 3.1)	1.1 (0.44, 2.2)	2.8 (1.0, 6.1)	1.3 (0.59, 2.4)	–	1.5 (0.67, 2.8)	–	–	–	1.4 (0.76, 2.3)	–	–	1.2 (0.63, 2.0)
Peptic ulcer, site unspecified	2.9 (0.92, 6.7)	3.6 (1.6, 6.8)	7.4 (3.2, 15)	2.3 (0.73, 5.3)	–	2.5 (0.81, 5.9)	7.2 (2.3, 17)	–	–	2.8 (1.4, 5.2)	–	–	3.1 (1.6, 5.4)
Gastritis and duodenitis	3.2 (2.3, 4.2)	2.2 (1.7, 2.9)	3.4 (2.5, 4.5)	2.3 (1.7, 3.1)	1.1 (0.35, 2.5)	2.9 (2.1, 3.8)	2.2 (1.3, 3.5)	2.6 (1.5, 4.1)	–	2.5 (2.0, 3.1)	2.9 (1.7, 4.7)	–	2.8 (2.3, 3.4)
Acute appendicitis	1.6 (0.95, 2.4)	1.6 (1.1, 2.2)	1.9 (1.4, 2.6)	0.93 (0.45, 1.7)	–	1.2 (0.63, 2.0)	1.8 (1.1, 2.7)	–	–	1.6 (1.2, 2.1)	1.7 (0.70, 3.6)	2.5 (1.3, 4.5)	1.4 (1.1, 1.9)
Diverticula of the intestines	0.92 (0.49, 1.6)	1.3 (0.87, 1.8)	2.0 (1.1, 3.6)	1.2 (0.77, 1.7)	–	0.84 (0.49, 1.4)	1.7 (0.71, 3.2)	0.78 (0.29, 1.7)	1.6 (0.57, 3.4)	1.0 (0.71, 1.4)	1.7 (0.87, 3.1)	–	1.2 (0.84, 1.6)
Chronic enteritis and ulcerative colitis	1.9 (1.0, 3.2)	1.5 (0.96, 2.3)	1.9 (1.2, 2.8)	1.5 (0.77, 2.6)	–	1.8 (0.98, 3.0)	1.8 (0.96, 3.1)	–	–	1.7 (1.2, 2.4)	–	–	1.7 (1.2, 2.4)
Irritable bowel syndrome	1.8 (0.93, 3.2)	1.8 (1.3, 2.4)	1.8 (1.2, 2.5)	1.8 (1.1, 2.8)	–	1.5 (0.90, 2.5)	1.7 (0.99, 2.7)	2.3 (1.1, 4.3)	–	1.8 (1.3, 2.4)	1.9 (0.75, 3.9)	–	1.9 (1.4, 2.4)
Acute and subacute necrosis of the liver	3.4 (2.3, 4.8)	3.1 (2.0, 4.5)	3.4 (1.9, 5.7)	3.2 (2.3, 4.4)	–	2.2 (1.3, 3.4)	2.7 (1.1, 5.2)	5.4 (3.2, 8.5)	–	3.0 (2.2, 4.0)	4.7 (2.4, 8.5)	4.4 (1.8, 9.1)	3.1 (2.3, 4.1)
Cholelithiasis	1.3 (0.82, 2.0)	1.5 (1.2, 1.8)	1.6 (1.2, 2.0)	1.4 (1.0, 1.8)	1.4 (0.60, 2.8)	1.4 (1.1, 1.9)	1.7 (1.2, 2.4)	1.2 (0.72, 2.0)	1.4 (0.52, 3.1)	1.4 (1.1, 1.7)	2.3 (1.5, 3.4)	1.3 (0.65, 2.4)	1.5 (1.2, 1.8)
Cholecystitis and cholangitis	2.5 (1.1, 4.8)	1.6 (0.84, 2.9)	1.9 (0.84, 3.8)	1.5 (0.67, 3.1)	–	2.4 (1.2, 4.2)	–	–	–	2.2 (1.3, 3.4)	–	–	2.0 (1.2, 3.1)
Pancreatitis	3.0 (1.7, 5.0)	2.9 (1.8, 4.4)	3.0 (1.7, 5.0)	3.2 (2.0, 5.1)	–	2.5 (1.4, 4.3)	3.2 (1.5, 6.1)	3.2 (1.2, 7.0)	–	2.3 (1.5, 3.6)	5.1 (2.2, 10)	–	2.9 (2.0, 4.1)

Note: Results not presented when fewer than 5 incident gastrointestinal disorder cases were identified in a stratification subgroup.