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The Epidemiology of Irritable Bowel Syndrome in the US Military: Findings from the Millennium Cohort Study

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OBJECTIVES: **Functional gastrointestinal disorders occur more frequently among deployed veterans, although studies evaluating the relative impact of risk factors, including stress and antecedent infectious gastroenteritis (IGE), are limited. We examined risk factors for new-onset irritable bowel syndrome (IBS) among active duty participants in the military's Millennium Cohort Study.**

METHODS: **Medical encounter data from 2001 to 2009, limited to Cohort members on active duty, were used to identify incident IBS cases (any and highly probable). IGE was identified using medical encounter or self-report. Covariate data were obtained from the Millennium Cohort Study surveys and analyzed using Cox proportional hazards methods.**

RESULTS: **Overall, 41,175 Cohort members met the eligibility criteria for inclusion and 314 new-onset cases of IBS were identified among these. Significant risk factors (adjusted hazard ratio, 95% confidence interval) included antecedent IGE (2.05, 1.53–2.75), female gender (1.96, 1.53–2.52), number of life stressors (1: 1.82, 1.37–2.41; 2: 2.86, 2.01–4.06; 3+: 6.69, 4.59–9.77), and anxiety syndrome (1.74, 1.17–2.58). Limited to highly probable IBS, a stronger association with antecedent IGE was observed, particularly when based on medical encounter records (any IGE: 2.20, 1.10–4.43; medical encounter IGE only: 2.84, 1.33–6.09). Precedent anxiety or depression and IGE interacted with increased IBS risk compared with IGE alone.**

CONCLUSIONS: **These results confirm previous studies on the association between sociodemographic or life stressors and IBS. IGE was significantly associated with IBS risk. Whether deployed or not, US service members often encounter repeated exposure to high levels of stress, which, combined with other environmental factors such as IGE, may result in long-term debilitating functional gastrointestinal disorders.**

Am J Gastroenterol 2016; 111:93–104; doi:10.1038/ajg.2015.386; published online 5 January 2016

INTRODUCTION

Functional gastrointestinal disorders, including irritable bowel syndrome (IBS), represent a significant burden of disease in the United States and globally, with an IBS prevalence estimate of 14% (ref. 1). A recent systematic review found direct medical costs related to IBS of $1,562–$7,547, and indirect costs of $791–$7,737 per patient per year (2). In addition to increased direct medical care costs, IBS negatively impacts a patient's quality of life, resulting in increased fatigue, limitations in physical capabilities, and an overall lower perception of general health compared with the general population (3). Although data are emerging on the complex and varied disease mechanisms of IBS, epidemiological studies remain important to further elucidate relationships between risk factors and disease development (4). Previous studies have described IBS incidence and risk factors among the US military members using the Department of Defense medical encounter databases, confirming other civilian population-based studies identifying gender and antecedent gastrointestinal infection as

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Received 11 August 2015; accepted 10 November 2015

risk factors (5). However, these previous reports, which relied on existing administrative databases containing medical encounter and demographic data, lacked information on many confounders such as life stressors and health behaviors, which are likely important in understanding risk and underlying causal mechanisms for this condition. To further explore incidence and risk factors for IBS in the US military, we used data from the Millennium Cohort Study, a large prospective study of military service members, to better understand associations between multiple exposures and risk of developing IBS.

METHODS

Study population

The Millennium Cohort Study is a 21-year longitudinal study initiated in 2001 to prospectively follow the US military personnel from all service branches to evaluate the impact of military service, including deployment, on short- and long-term health. The methodology has previously been described (6–8). In brief, it is a large, population-based cohort representing all military service branches and includes regular active duty, Reserve, and National Guard personnel. Since the first wave of invitations in 2001, over 200,000 participants have been enrolled as part of four separate accession panels: panel 1 (July 2001–June 2003), *N*=77,047; panel 2 (June 2004–February 2006), *N*=31,110; panel 3 (June 2007–December 2008), *N*=43,439; and panel 4 (April 2011–April 2013), *N*=50,052. More than 70% of the first two panels have submitted at least one follow-up questionnaire. Panel 1 was drawn from a population-based random sample of the US military in October 2000, with oversampling of Reserve/Guard personnel, women, and those with previous deployment experience in Bosnia, Kosovo, or Southwest Asia. Panels 2 and 3 sampled new accessions only, those with 1–3 years of military service, and oversampled for Marines and women. Study participants have completed a baseline survey, and they will continue to receive follow-up questionnaires approximately every 3 years.

The population for this study included Millennium Cohort Study participants who completed a baseline and at least one follow-up questionnaire between 2001 and 2009, who had not left active military service at the time of completing their first survey, and were without IBS or inflammatory bowel disease (IBD) at baseline. Excluded were subjects who endorsed every provider-based illness diagnosis on any survey, as well as those missing any data for covariates of interest. This latter exclusion contributes to slight differences in study populations for any IBS and highly probable IBS. For the any IBS model, all cases were censored at the date of diagnosis, and data on covariates were captured from the most recent survey completed before diagnosis. Depending on whether there were incomplete or missing data on that survey, the participant may or may not have been included in the final any IBS model. For the highly probable IBS model, cases that did not meet the stricter definition of highly probable IBS were assigned a new censoring date, therefore covariate data could have been chosen from a different survey than for the any IBS model. Depending on the status of missing data, this resulted in participants being included in the any IBS model but excluded from the highly probable IBS model or vice versa. The number of participants affected by this change in censoring date and survey assignment for covariates was small (any IBS: *n*=13; highly probable IBS: *n*=17) and did not affect the interpretation of any of the final models.

Participants were enrolled in the Millennium Cohort Study after providing full informed consent. The IBS study protocol was approved by the institutional review boards at the Uniformed Services University of the Health Sciences and the Naval Health Research Center (Protocol NHRC.2000.0007). Both studies were conducted in compliance with all applicable federal regulations governing the protection of human subjects in research.

Incident IBS

Incident cases of IBS were identified using the military medical encounter data from July 2001 to December 2009, received from the TRICARE Management Activity. Any person with at least two medical encounters occurring within a 365-day period and containing the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) code 564.1 (IBS) in any diagnosis field was considered an incident case of IBS and defined as any IBS. In addition, a more specific definition of highly probable IBS was used if an endoscopy was documented via procedure codes (451, 4511–4516, 4519, 4523, 4524) or Current Procedural Technology code (45330–45334, 45338, 45378, 45379, 45380, 45382, 45384, 45385) between the two medical encounters, and no evidence of a diagnosis of IBD between the two IBS medical encounters. IBD was defined as either self-report of provider-based IBD diagnosis on the Millennium Cohort survey or two IBD-related medical encounters (ICD-9-CM codes 555.0, 555.1, 555.9, and all 556 subgroups) in a 365-day period.

Baseline IBS and IBD

Assessment of baseline IBS and IBD cases based on medical encounter data were similar to incident IBS and IBD cases excluding the 365-day period. If IBS or IBD case definitions were met between 1 June 1998, and completion of the first survey for Panel 1 participants or between 1 June 2001, and completion of the first survey for Panel 2 participants, those Cohort members were excluded. Participants who self-reported being diagnosed with IBD by a medical provider on the baseline survey were considered baseline IBD cases and were similarly excluded.

Antecedent infectious gastroenteritis

Antecedent infectious gastroenteritis (IGE) data were collected from medical encounter records and self-reported post-deployment health assessments. Only those events occurring between completion of the baseline survey and IBS diagnosis or censure were considered. Any medical encounter containing a relevant ICD-9-CM code for IGE (all 001 subgroups, 003.0, 003.9, all 004 subgroups, 005.4, all 008.0 subgroups, 008.43, 008.44, 008.47, 008.49, 008.5, 009.0–009.3, all 005.8 subgroups, 005.9, 006.0–006.2, 006.9, all 007 subgroups, all 008.6 subgroups, and 008.8) in any diagnosis field was defined as an IGE episode. In addition, participants were deemed to have IGE if they self-reported diarrhea

during or after deployment on a post-deployment health assessment. Subjects with no medical encounters or self-report of IGE were considered to not have IGE.

Other covariates

Demographic and military characteristics, including deployment, were obtained from Defense Manpower Data Center records. Missing Defense Manpower Data Center data were supplemented with information from Millennium Cohort surveys when available. All behavioral and mental health characteristics were assessed using data collected from the Millennium Cohort surveys. Body mass index was calculated from self-reported height and weight. Never smokers were defined as those who had smoked <100 cigarettes in their lifetime. Among smokers, those who reported having successfully quit smoking were defined as former smokers, and all others were categorized as current smokers. Non-drinkers were defined as those who reported no drinking in a typical week or those who had <12 drinks in the past year. Moderate female drinkers reported having between 1 and 7 drinks in a typical week (or on average ≤1 drink/day), whereas heavy female drinkers reported having >7 drinks in a typical week (or, on average, >1 drink/day). Moderate male drinkers reported having between 1 and 14 drinks in a typical week (or, on average, ≤2 drinks/day), whereas heavy male drinkers reported having >14 drinks in a typical week (or, on average, >2 drinks/day).

Survey questions related to life stressors were categorized using a modified version of the Holmes–Rahe Social Readjustment Scale (9). Stress related to divorce/separation, major financial problems, sexual assault, sexual harassment, physical assault, illness or death of a loved one, and a disabling illness or injury was assessed at baseline (ever experienced) and in each follow-up survey (preceding 3 years). Because only a small number of stressors were available total number of stressors was counted rather than assigning a weight to each.

Mental health data were collected using standardized survey instruments embedded in the Millennium Cohort survey, including the Patient Health Questionnaire (PHQ) and the post-traumatic stress disorder (PTSD) Checklist-Civilian Version. Using defined criteria for the PHQ-9 items that constitute the depression module, (10,11) depression was identified if participants reported experiencing over the last 2 weeks either a depressed mood (little interest or pleasure in doing things) or anhedonia (feeling down, depressed, or hopeless), in addition to responding to experiencing a total of 5 or more depression items "more than half the days" or "nearly every day." Anxiety was identified by a positive screen for either panic syndrome or other anxiety syndrome on the PHQ. Panic syndrome was assessed using a 15-item module that asked whether the participants had experienced an anxiety attack in the last month and what symptoms they may have experienced. If participants endorsed all 4 questions regarding anxiety attacks and 4 of 11 symptoms listed, they were considered positive for panic syndrome. In addition, other anxiety syndromes were identified using criteria defined by the PHQ for a 7-item module; if participants endorsed experiencing "feeling nervous, anxious, on edge or worrying a lot about different things" in the prior 4 weeks and endorsed experiencing 3 or more of the remaining 6 anxiety symptoms on "more than half the days", (11–13) they were identified as screening positive for anxiety. The survey also included a question from the PHQ regarding current medication use for anxiety, depression, or stress. PTSD was assessed using the Checklist-Civilian Version-, a standardized 17-item survey instrument that inquires about PTSD symptoms experienced in the past month (14). For this study, PTSD was identified using the sensitive criteria, as defined by the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, only. All covariates were assessed at the time of the most recent survey prior to the censoring date for each participant, regardless of data source.

Time censoring calculations

For each member of the study population, start time for the period of observation was defined as the date of completion of first survey. Time was censored at the earliest of 5 dates: date of IBS diagnosis, date of IBD diagnosis, date of separation from military service, date of death, or end of study.

Statistical analysis

Survival analyses were performed using the PHREG procedure in SAS, Version 9.3 (SAS Institute, Cary, NC) for any IBS and highly probable IBS, modeled separately. The primary exposure of interest, antecedent IGE, was modeled as a time-varying covariate. Antecedent IGE was forced into the model, and then forward selection was used to add the remaining variables to the model, with a $P<0.05$ threshold for entry into the model. In addition, confounders of the IGE–IBS relationship were included in the final model if they changed the IGE parameter estimate by 10% or more. Interactions between each covariate in the model and the main exposure variable were examined. If an interaction term was significant at $P<0.05$, Akaike information criterion was used to select between models with and without the interaction term. If Akaike information criterion difference between 2 models was >4, the model without an interaction term was selected for model parsimony and interpretability (15). Two methods, Martingale residuals and interaction with time, were used to assess the proportional hazards assumption. Covariates that violated the assumption ($P<0.05$) using both methods included marital status in any IBS and all source IGE model, and marital status along with race/ethnicity in any IBS and medical encounter IGE model. A stratified Cox model was used when a violation of the proportional hazards assumption was observed. These analyses were repeated, restricting IGE to only those events identified using medical encounter data.

RESULTS

Of the 108,129 participants from Panels 1 and 2 who completed a baseline questionnaire, 203 were excluded for endorsing every provider-based diagnoses on at least 1 survey (pan-endorser). Participants were also excluded if they did not meet this study's definition of "active duty," meaning they remained on active duty for the duration of the study, separated directly from active

duty, or entered the reserves after active duty only owing to term fulfillment, leaving 68,203 participants. In addition, Millennium Cohort Study participants were excluded because they had not completed a follow-up survey (n=18,999), reporting IBS or IBD at baseline (n=482), having separated from the military before completion of their baseline survey (n=4,341),and missing data on covariates of interest (n=3206).This resulted in 41,175 participants with 222,081.54 person-years of follow-up available for analyses for any IBS and 41,179 participants with 222,634.88 person-years of follow-up for highly probable IBS (see **Figure 1**).

Demographic, military, and behavioral health characteristics of cohort members included for any IBS are presented in **Tables 1** and **2**. Women represented slightly more than a quarter of participants, with the majority (66.2%) of participants being of white, non-Hispanic race/ethnicity. Smoking history, either former or current, was found in ~42%. A majority of subjects (56.3%) reported one or more life stressors, whereas relative few reported that they were taking medication for a mental health issue (6.9%). Nearly 60% had one or more deployments. Descriptive characteristics of cohort members in the highly probable IBS population had similar distributions to cohort members for any IBS (data not shown).

New-onset IBS was identified in 314 participants, with an estimated incidence of 141.39/100,000 person-years, whereas the incidence of highly probable IBS was significantly lower at

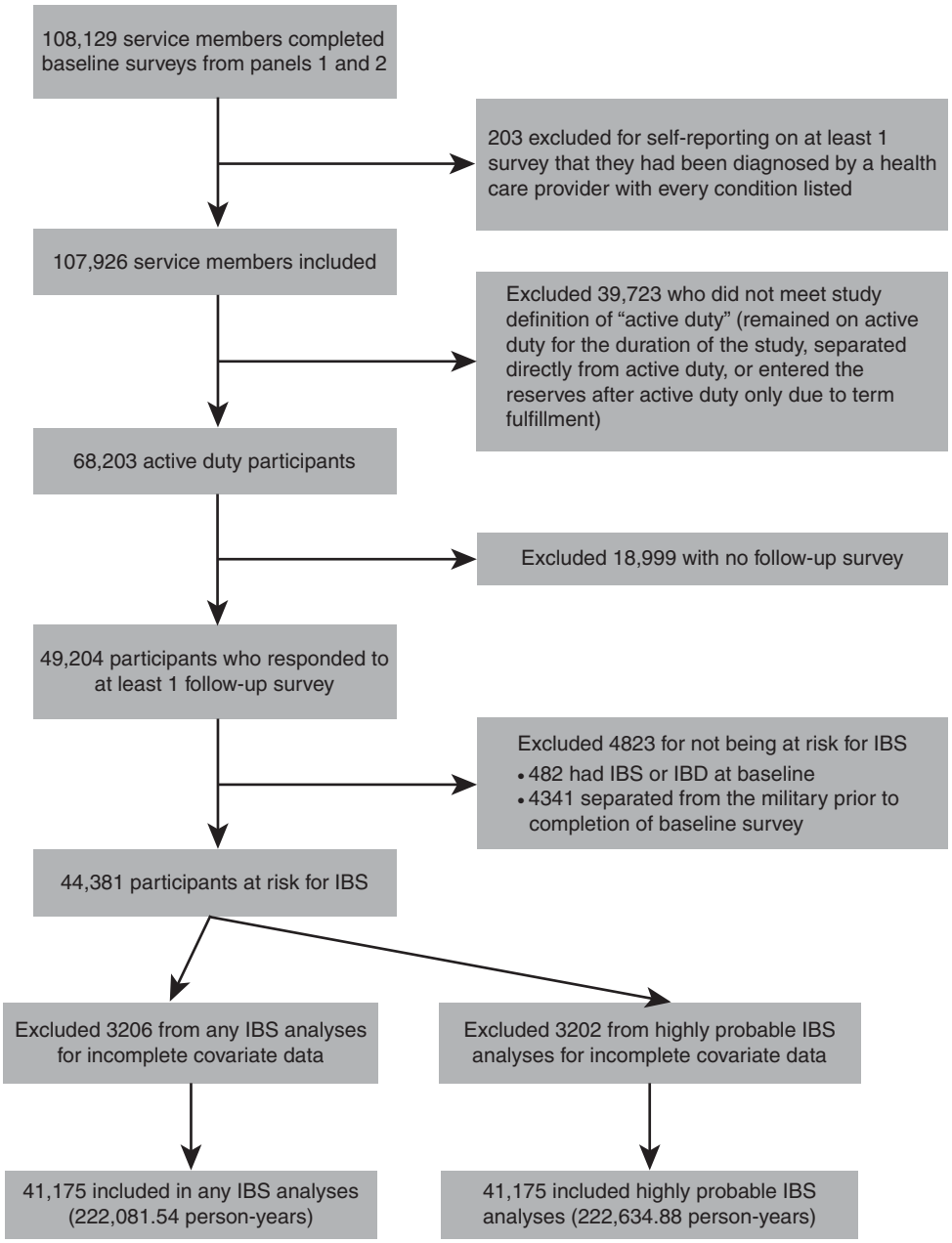

Figure 1. Inflammatory bowel disease (IBD) and irritable bowel syndrome (IBS) inclusion and exclusion criteria for final study population.

Table 1. Overall descriptive characteristics of active duty Millennium Cohort participants[a]

	Active duty (*N*=41,175)	
	n	%
Sex		
Male	30,023	72.9
Female	11,152	27.1
Birth year		
Pre-1960	3621	8.8
1960–1969	13,539	32.9
1970–1979	15,950	38.7
1980-present	8065	19.6
Race/ethnicity		
White, non-Hispanic	27,260	66.2
Black, non-Hispanic	5540	13.5
Other	8375	20.3
Marital status		
Single	9503	23.1
Married	29,070	70.6
Divorced/widowed/legally separated	2602	6.3
Education		
Less than a bachelor's degree	28,790	69.9
Bachelor's degree or higher	12,385	30.1
Service branch		
Army	16,647	40.4
Navy/Coast Guard	9171	22.3
Marine Corps	2604	6.3
Air Force	12,753	30.1
Rank		
Enlisted	30,347	73.7
Officer	10,828	26.3
Occupation		
Combat specialist	7839	19.0
Functional support	8443	20.5
Service and supply	3471	8.4
Health care	4602	11.2
Electrical/mechanical equipment repair	5755	14.0
Other	11,065	26.9

[a]Excludes participants who endorsed every provider-based illness diagnosis on at least one survey, and anyone who did not complete at least one follow-up survey.

Table 2. Health risk behaviors, stress and comorbid conditions among study participants

	Active duty (*N*=41,175)	
	n	%
Smoking[a]		
Never	23,817	57.9
Former	10,411	25.3
Current	6947	16.9
Alcohol consumption[b]		
Abstainer/light	16,735	40.6
Moderate	21,282	51.7
Heavy	3158	7.7
BMI[c]		
Normal/underweight	13,668	33.2
Overweight	21,323	51.8
Obese	6184	15.0
Number of life stressors[d]		
0	17,590	42.8
1	16,222	39.4
2	5188	12.6
3+	2175	5.2
Depression[e]		
Never	39,444	95.8
Ever	1731	4.2
Anxiety and panic[e]		
Never	39,464	95.8
Ever	1711	4.2
PTSD[f]		
Never	38,834	94.3
Ever	2341	5.7
Multiple deployments		
0	16,737	40.6
1	12,268	29.8
2+	12,170	29.6

BMI, body mass index; PTSD, post-traumatic stress disorder.

[a]Never=self-reported smoking <100 cigarettes in their lifetime, former=self-reported successful smoking cessation, current=reported never trying to quit or unsuccessful at quitting.

[b]No/light=self-reported 0 drinks on a typical week, moderate=self-reported an average of 1–7 drinks per week for women and 1–14 per week for men, heavy=self-reported an average of >7 drinks per week for women and >14 per week for men.

[c]Normal/underweight, <25; overweight, 25–29.9; obese, 30+.

[d]Assessed using the social readjustment rating scale.

[e]Assessed using responses to the patient health questionnaire.

[f]Assessed using responses to the PTSD checklist-civilian version.

27.40/100,000 person-years for a total of 61 incidence cases. IGE was associated with an increased risk of IBS in all models; however, when limited to medical encounters for IGE and highly probable IBS, the largest effect estimate was observed (univariate hazard ratio (HR), 3.80; 95% confidence interval (CI), 1.79–8.08; **Table 3**). Additional univariate analyses are also detailed in **Table 3**. In

Table 3. Univariate hazard ratios in the Millennium Cohort, 2001–2009[a]

	Any IBS		Highly probable IBS	
	N	**Univariate HR (95% CI)**	***N***	**Univariate HR (95% CI)**
Total	314		61	
Antecedent IGE, any				
None	250	Ref	50	Ref
Any	64	1.81 (1.36–2.40)	11	1.61 (0.82–3.14)
Antecedent IGE, medical encounter				
None	281	Ref	50	Ref
Medical encounter	33	2.87 (1.99–4.13)	8	3.80 (1.79–8.08)
Sex				
Male	148	Ref	31	Ref
Female	166	3.29 (2.63–4.10)	30	2.80 (1.70–4.63)
Birth year				
Pre-1960	14	0.66 (0.38–1.15)	6	1.53 (0.62–3.77)
1960–1969	113	1.08 (0.84–1.39)	24	1.25 (0.71–2.22)
1970–1979	126	Ref	23	Ref
1980-present	61	1.38 (1.01–1.87)	8	0.95 (0.42–2.13)
Race/ethnicity				
White non-Hispanic	218	Ref	38	Ref
Black non-Hispanic	48	1.05 (0.77–1.44)	13	1.64 (0.87–3.08)
Other	48	0.66 (0.48–0.90)	10	0.79 (0.40–1.60)
Marital status				
Single	93	Ref	14	Ref
Married	194	0.49 (0.38–0.63)	42	0.72 (0.39–1.32)
Divorced/widowed/legally separated	27	0.74 (0.48–1.13)	5	0.92 (0.33–2.57)
Education				
Less than a bachelor's degree	230	1.42 (1.10–1.82)	40	0.98 (0.58–1.66)
Bachelor's degree or higher	84	Ref	21	Ref
Panel				
2001–2003	234	Ref	53	Ref
2004–2006	80	1.47 (1.13–1.91)	8	0.59 (0.28–1.26)
Service branch				
Army	107	0.73 (0.56–0.95)	21	0.76 (0.42–1.38)
Navy/Coast Guard	80	1.03 (0.78–1.37)	16	1.09 (0.57–2.08)
Marine Corps	11	0.56 (0.3–1.04)	2	0.54 (0.13–2.30)
Air Force	116	Ref	22	Ref
Rank				
Enlisted	238	Ref	44	Ref
Officer	76	1.38 (1.06–1.78)	17	1.13 (0.64–1.98)
Occupation				
Combat specialist	37	Ref	9	Ref
Functional support	90	2.25 (1.54–3.30)	20	2.04 (0.93–4.48)
Service and supply	29	1.86 (1.15–3.03)	4	1.05 (0.32–3.41)
Health care	40	1.84 (1.18–2.87)	7	1.31 (0.49–3.52)

Table 3 continued on following page

Table 3. Continued

	Any IBS		Highly probable IBS	
	N	Univariate HR (95% CI)	*N*	Univariate HR (95% CI)
Electrical/mechanical equipment repair	30	1.21 (0.75–1.96)	10	1.64 (0.67–4.05)
Other	88	1.78 (1.21–2.62)	11	0.91 (0.38–2.19)
Smoking[b]				
Never	173	Ref	35	Ref
Former	81	1.12 (0.86–1.46)	15	1.02 (0.56–1.87)
Current	60	1.38 (1.03–1.85)	11	1.24 (0.63–2.44)
Alcohol consumption[c]				
No/light	163	Ref	29	Ref
Moderate	130	0.59 (0.47–0.75)	31	0.80 (0.48–1.33)
Heavy	21	0.76 (0.48–1.20)	1	0.20 (0.03–1.49)
BMI[d]				
Normal/underweight	141	Ref	23	Ref
Overweight	135	0.56 (0.45–0.72)	26	0.67 (0.38–1.18)
Obese	38	0.54 (0.38–0.77)	12	1.05 (0.52–2.12)
Number of life stressors[e]				
0	80	Ref	18	Ref
1	129	1.93 (1.46–2.55)	23	1.52 (0.82–2.82)
2	55	3.29 (2.33–4.64)	7	1.84 (0.77–4.41)
3+	50	9.56 (6.70–13.64)	13	10.97 (5.36–22.47)
Depression syndrome[f]				
No	289	Ref	54	Ref
Yes	25	2.41 (1.60–3.62)	7	3.59 (1.63–7.89)
Anxiety syndrome[f]				
No	284	Ref	57	Ref
Yes	30	2.86 (1.97–4.17)	4	1.88 (0.68–5.17)
PTSD[g]				
No	288	Ref	55	Ref
Yes	26	1.77 (1.18–2.64)	6	2.12 (0.91–4.92)
Self-reported prescribed medication for mental health				
No	282	Ref	55	Ref
Yes	32	2.17 (1.51–3.13)	6	2.06 (0.89–4.78)
Deployments				
0	159	Ref	41	Ref
1	83	0.58 (0.44–0.75)	11	0.30 (0.15–0.58)
2+	72	0.45 (0.34–0.60)	9	0.22 (0.11–0.46)

BMI, body mass index; IBS, irritable bowel syndrome; IGE, infectious gastroenteritis; PTSD, post-traumatic stress disorder.

Note: *N*=41,175 and 41,179 for any IBS and highly probably IBS, respectively.

[a]Excludes subjects who endorsed every provider-based illness diagnosis on any survey, and anyone who did not complete at least 1 follow-up survey.

[b]Never=self-reported smoking <100 cigarettes in their lifetime, former=self-reported successful smoking cessation, current=self-reported never trying to quit or unsuccessful at quitting.

[c]No/light=self-reported 0 drinks on a typical week, moderate=self-reported an average of 1–7 drinks per week for women and 1–14 per week for men, heavy=self-reported an average of >7 drinks per week for women and >14 per week for men.

[d]Normal/underweight, <25; overweight, 25–29.9; obese, 30+.

[e]Assessed using the social readjustment rating scale.

[f]Assessed using responses to the patient health questionnaire.

[g]Assessed using responses to the PTSD checklist-civilian version.

general, restricting analysis to the highly probable IBS definition and/or documented medical encounter IGE demonstrated consistency in the direction of effect estimates, although bias toward the null or loss of statistical significance due to smaller cell sizes was also observed.

The significantly increased risk of IBS associated with antecedent IGE persisted in the adjusted models for all source IGE (adjusted HR=2.05; 95% CI, 1.53–2.75) and for medical encounter IGE (aHR, 2.07; 95% CI,1.44–3.01) (**Table 4**). Models of highly probable IBS showed a similar increased risk following any IGE (aHR, 2.20; 95% CI, 1.10–4.43) and medical encounter-based IGE (aHR, 2.84; 95% CI, 1.33–6.09). Female gender (aHR=1.96), Army service (aHR=0.67), moderate alcohol consumption (aHR=0.68), body mass index (overweight: aHR=0.77; obese: aHR=0.67), number of life stressors (1: aHR=1.82; 2: aHR=2.86; 3+: aHR=6.69), anxiety syndrome (aHR=1.74), and number of deployments (1: aHR=0.61; 2+: aHR=0.52) remained significant in the adjusted Cox model for any IBS and all source IGE, whereas female gender (aHR=1.79), 3+ life stressors (aHR=6.80), depression syndrome (aHR=2.29), and deployments (1 deployment: aHR=0.29; 2+ deployments: aHR=0.22) remained associated when restricting to highly probable IBS and all source IGE. Similar HRs for covariates were found when restricting analysis to documented medical encounter IGE, with only Army service branch no longer significant in the any IBS model.

In addition to the primary effects, interactions between IGE and other covariates (e.g., smoking, stress, deployment, anxiety, PTSD, and depression) were explored. Consistent interactions among highly probable IBS and both IGE exposure categories were found for both depression and anxiety. In these interaction models, the combination of medical encounter IGE and either anxiety or depression and the combination of all source IGE and depression resulted in a differential risk of highly probable IBS compared with stratification by IGE or mental health condition alone, although the numbers were small (**Tables 5** and **6**).

DISCUSSION

Overall IBS incidence (any IBS definition) was estimated at 141.39 (89.38 male, 293.81 female) per 100,000 person-years in this study population, which is lower than 2 previous studies in civilian populations reporting incidence between 200 and 260 cases per 100,000 person-years (16,17). However, our rates for women are similar to those reported by Locke *et al.* (16) for similar age strata from Olmsted County, Minnesota. A nested case-control study using a Dutch national medical encounter data system estimated a 1-year incidence of ~300 per 100,000 person-years in individuals not reporting an antecedent acute IGE episode (18), which is also higher than our estimated incidence. Some possible explanations for our lower rates are the "healthy worker effect" among active duty military personnel, underrepresentation of female gender, and/or potential differences in health care-seeking behavior of individuals in the military compared with civilian populations.

Consistent with prior studies, we found a 2–3-fold increase in IBS risk after IGE, with higher effect estimates when IBS and IGE were more precisely defined. Although these point estimates are lower than pooled effect estimates reported in recent systematic reviews, (19,20) they do support a positive association between acute enteric infection and IBS and are consistent with individual effect estimates recently reported in a medical encounter system population-based Dutch study (relative risk, 4.85; 95% CI, 2.02–11.63), as well as a study among returning UK veterans from Iraq (self-reported IGE: odds ratio, 2.59, 95% CI, 1.83–2.67; medical encounter IGE: OR, 4.34, 95% CI, 2.55–7.39) (18,21). It is logical that study designs based on medical encounter data may result in lower effect estimates compared with active surveillance studies because of differences in non-differential misclassification of exposure and/or outcomes, as well as population-unique effects with an active duty healthier population that may be less susceptible to developing IBS.

Interestingly, this study identified other associations of particular interest in a military population. A consistently identified increase in IBS risk with PTSD has been described in studies of women veterans (22,23). A recent study by Maguen *et al.* of a population of over 600,000 Iraq and Afghanistan war veterans found that for both men and women, IBS was three times more likely to be present among those with PTSD than those without PTSD (24). Our finding of increased risk of incident IBS among those with PTSD in univariate analyses is consistent with these prior reports. There are biological and psychological explanations that might explain this association, such as the reported effect of PTSD and depression on systemic inflammation (25) and abnormalities in brain function, that could affect pain perception and awareness of visceral stimuli (26). However, significantly increased risk was not observed in our adjusted model; this could be attributed to insufficient power or the use of the most proximal survey data to assess PTSD. Additional studies focused on PTSD and chronic functional gastrointestinal disorders that consider the timing of association, as well as potential common pathological pathways are warranted. Another military-specific association was observed between decreased IBS risk and multiple deployments. Additional measures of deployment (i.e., cumulative time deployed, deployment before Operation Enduring Freedom/Operation Iraqi Freedom, self-report of combat exposure while deployed) were assessed in univariate analyses, and the same pattern of reduced risk was observed (data not shown). This may be indicative of a healthy worker effect as has been previously described (27). Interestingly, when a more specific definition of IBS (highly probable IBS) was used, this protective effect became more pronounced.

As in prior studies, a number of risk factors were found that continue to support a biopsychosocial model of disease. As described in other studies, we found that the number of life stressor events increased the risk of IBS (28,29). Furthermore, we found that self-reported anxiety and depression were independently associated with increased risk of IBS (univariate analyses only), similar to other studies (28,29). However, the joint effect of these

Table 4. Adjusted hazard ratios for the association between IGE[a] and IBS in the Millennium Cohort, 2001–2009[b]

	Any IGE		Medical encounter IGE	
	Any IBS (95% CI)[c] (Stratified Cox model)	Highly probable IBS (95% CI) (Cox PH model)	Any IBS (95% CI)[c] (Stratified Cox model)	Highly probable IBS (95% CI) (Cox PH model)
Antecedent IGE				
None	Ref	Ref	Ref	Ref
Any	2.05 (1.53–2.75)	2.20 (1.10–4.43)	2.07 (1.44–3.01)	2.84 (1.33–6.09)
Sex				
Male	Ref	Ref	Ref	Ref
Female	1.96 (1.53–2.52)	1.79 (1.06–3.03)	2.03 (1.58–2.61)	1.75 (1.04–2.96)
Service branch				
Army	0.67 (0.51–0.87)			
Navy/Coast Guard	0.99 (0.74–1.32)			
Marine Corps	0.66 (0.35–1.23)			
Air Force	Ref			
Alcohol consumption[d]				
No/light	Ref		Ref	
Moderate	0.68 (0.54–0.86)		0.69 (0.54–0.87)	
Heavy	0.68 (0.43–1.08)		0.64 (0.4–1.02)	
BMI[e]				
Normal/underweight	Ref		Ref	
Overweight	0.77 (0.61–0.99)		0.78 (0.61–1.00)	
Obese	0.67 (0.46–0.97)		0.68 (0.47–0.98)	
Number of life stressors[f]				
0	Ref	Ref	Ref	Ref
1	1.82 (1.37–2.41)	1.40 (0.76–2.60)	1.81 (1.37–2.39)	1.41 (0.76–2.61)
2	2.86 (2.01–4.06)	1.48 (0.61–3.59)	2.79 (1.96–3.96)	1.49 (0.61–3.60)
3+	6.69 (4.59–9.77)	6.80 (3.18–14.53)	6.44 (4.42–9.38)	6.81 (3.19–14.54)
Depression syndrome[g]				
No		Ref		Ref
Yes		2.29 (1.01–5.19)		2.36 (1.04–5.34)
Anxiety syndrome[g]				
No	Ref		Ref	
Yes	1.74 (1.17–2.58)		1.68 (1.14–2.49)	
Deployments				
0	Ref	Ref	Ref	Ref
1	0.61 (0.47–0.80)	0.29 (0.15–0.56)	0.64 (0.49–0.84)	0.32 (0.16–0.62)
2+	0.52 (0.39–0.70)	0.22 (0.10–0.47)	0.57 (0.43–0.76)	0.26 (0.13–0.55)

BMI, body mass index; IBS, irritable bowel syndrome; IGE, infectious gastroenteritis.
NOTE. *N*=41,175 and 41,179 for any IBS and highly probably IBS, respectively.
[a]From all sources or from medical encounter data only.
[b]Excludes subjects who endorsed every provider-based illness diagnosis on any survey, and anyone who did not complete at least 1 follow-up survey.
[c]Stratified on marriage and race/ethnicity.
[d]No/light=self-reported 0 drinks on a typical week, moderate=self-reported an average of 1–7 drinks per week for women and 1–14 per week for men, heavy=self-reported an average of >7 drinks per week for women and >14 per week for men.
[e]Normal/underweight, <25; overweight, 25–29.9; obese, 30+.
[f]Assessed using the social readjustment rating scale.
[g]Assessed using responses to the patient health questionnaire.

Table 5. Interaction between IGE and depression for risk of highly probable IBS

Any IGE	No IBS	IBS	OR (95% CI)
No IGE and no depression	32,611	47	1.00
IGE and no depression	6786	7	1.55 (0.62–3.33)
No IGE and depression	1324	3	1.18 (0.28–3.30)
IGE and depression	397	4	12.93 (3.69–34.77)
Medical encounter IGE			
No IGE and no depression	36,917	49	1.00
IGE and no depression	2480	5	1.88 (0.65–4.37)
No IGE and depression	1574	4	1.45 (0.43–3.68)
IGE and depression	147	3	22.26 (5.30–63.07)

CI, confidence interval; IBS, irritable bowel syndrome; IGE, infectious gastroenteritis, OR, odds ratio.
Note: both controlled for sex, stress, and deployment.

Table 6. Interaction between IGE and anxiety for risk of highly probable IBS

Any IGE	No IBS	IBS	OR (95% CI)
No IGE and no anxiety	32,615	49	1.00
IGE and no anxiety	6789	8	1.68 (0.71–3.49)
No IGE and anxiety	1320	1	0.17 (0.01–0.93)
IGE and anxiety	394	3	4.08 (0.86–14.08)
Medical encounter IGE			
No IGE and no anxiety	36,919	52	1.00
IGE and no anxiety	2485	5	1.76 (0.61–4.07)
No IGE and anxiety	1572	1	0.15 (0.01–0.80)
IGE and anxiety	142	3	9.59 (2.13–30.55)

CI, confidence interval; IBS, irritable bowel syndrome; IGE, infectious gastroenteritis, OR, odds ratio.
Note: both controlled for sex, stress, and deployment.

conditions, in combination with IGE exposure, resulted in an increased IBS risk greater than the risk from either of these exposures alone (**Tables 5** and **6**). Our understanding of the importance of the two-way "cross-talk" between the brain and the gut continues to grow, particularly how gut–brain interactions with the microbiome might result in dysbiosis and development of disease in the presence of nervous system disturbances. Multiple potential direct and indirect pathways exist through which altered gut microbiota can modulate the gut–brain axis (30). Under stressful conditions, the hypothalamus–pituitary–adrenal axis regulates cortisol, which can alter the immune system, gut permeability, and barrier function, and result in a change in gut microbiota composition. This has been described recently in military training settings where Singaporean Army rapid response troops were monitored for psychological and gastrointestinal symptoms, as well as immunological and intestinal biomarkers during intensive combat training (31). Interestingly, the anticipated increases in stress, anxiety, and depression were associated with gastrointestinal symptoms (noninfectious) and markers of pro-inflammatory immune activation and increased intestinal permeability. Although human participant studies have shown that risk of functional gastrointestinal disorders are associated with psychiatric comorbidities (32–34), it has also been described in animal models where microbiome changes (perhaps as a consequence of acute infection) can change behavior and brain neurochemistry (35). Thus, it is quite plausible that the combination of acute enteric infection and psychological stress interactions could prove to be the pathophysiological basis of some chronic gastrointestinal sequelae (36,37). A relevant mouse model, which has independently and concomitantly evaluated stress and *Citrobacter rodentium* infection, has been developed and provides support for this mechanism (38). Our emerging understanding of these concepts provides a framework to further investigate gut–brain axis relationships and ultimately identify potential solutions for chronic gastroenterological health conditions that are being observed among service members who are frequently exposed to both infection and stress during training and deployment situations (4,27).

This study had several limitations. Data were obtained from existing self-report questionnaires; however, the survey instruments used validated questions and were administered consistently (39). Furthermore, clinical examinations for confirmation of both self-reported symptoms and conditions could not be assumed, and ICD-9-CM-based medical encounter data on IGE exposure and IBS outcomes are also potentially susceptible to error or misclassification. Specifically, with respect to our primary outcome of IBS, misclassification for an ill-defined complex of unexplained GI symptoms may have been ascribed without the application of Rome criteria. Furthermore, whereas we excluded from eligibility those with pre-existing IBD, we did not exclude those who may have had other mimic conditions, such as celiac disease, tropical sprue, or intestinal malabsorption. It is possible that cohort subjects could have had these pre-existing diagnoses which were subsequently properly diagnosed or misclassified as IBS. However, the clinical incidence of these conditions is very low in this population and thus would unlikely have had a large bias on our results (40,41). Because it was necessary to use ICD-9-CM-based outcome diagnoses contained in medical encounter data (IBS is not among the health conditions on the survey), a more strict definition which required concomitant colonoscopy visit codes was used, and the cohort population was limited to individuals on active duty who received care at military treatment facilities. Such factors could explain both the relatively low IBS incidence and the effect estimates. Furthermore, the exclusion of those not meeting the active duty definition (~37%) may also limit generalizability and application of these results to reserve and guard populations. Prospective studies using validated and active functional gastrointestinal outcome surveillance among both deployed and garrison populations, as well reserve and guard components would be of value.

This study also had several strengths. Its population-based, prospective cohort design allowed for baseline and follow-up assessments (using time-varying covariates when appropriate) among individuals. In addition, the design enabled estimates of IBS incidence and strong statistical power for assessing primary effects, whereas controlling for multiple confounders and exploring novel-risk factors.

In summary, these findings represent additional data that contribute to an accumulating body of evidence linking acute gastrointestinal infections and chronic gastrointestinal sequelae. In addition to important findings from mechanistic studies also being reported, our findings add to the belief that this observed phenomenon is not exaggerated (42). A coordinated and resourced research agenda is needed to understand the heterogeneity in observed risk and disease outcomes based on host, agent, and environmental differences, including pathoetiological mechanisms (4). More urgently needed are potential measures to mitigate the burdensome consequences of acute gastroenteritis, which are known to have substantial impact on medical care costs and quality of life among millions of at-risk travelers and deployed military personnel.

ACKNOWLEDGMENTS

We thank Ashleigh Peoples and Kelly A. Jones from the Naval Health Research Center for statistical support, and The Millennium Cohort Study Team.

CONFLICT OF INTEREST

Guarantor of the article: Tomoko I. Hooper, MD, MPH, PhD.
Specific author contributions: Conception and design of the study: Mark S. Riddle, Chad K. Porter, Tomoko I. Hooper, and Edward J. Boyoko; generation, collection, assembly, analysis and/or interpretation of data: Marleen Welsh, Chiping Neih, Mark S. Riddle, and Chad K. Porter; drafting or revision of the manuscript: all authors; approval of the final version of the manuscript: all authors.
Financial support: This work was supported by the Military Operational Medicine Research Program, US Army Medical Research and Materiel Command (Fort Detrick, Maryland) and Uniformed Services University of the Health Sciences intramural grant R0879D. Resources from the VA Puget Sound Health Care System supported Dr Boyko's involvement in this research.
Potential competing interests: None.

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HUMAN SUBJECTS RESEARCH

Human participants were enrolled in the Millennium Cohort Study after providing full informed consent. The IBS study protocol was approved by the institutional review boards at the Uniformed Services University of the Health Sciences and the Naval Health Research Center (Protocol NHRC.2000.0007). Both studies were conducted in compliance with all applicable federal regulations governing the protection of human subjects in research.

Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ The risk of post-infectious functional bowel disorders including IBS is a well-described phenomenon.
- ✓ Previous studies have described IBS incidence and risk factors among the United States military members, however, they have lacked information on many important confounders, such as life stressors and health behaviors.
- ✓ Only a few studies exploring the combination of psychological and acute infection stresses have been reported.

WHAT IS NEW HERE

- ✓ An increased risk of incident IBS among those with PTSD compared with those without PTSD was found in univariate analyses.
- ✓ In a highly stressful military population setting, risk of IBS was strongly correlated with a number of preceding life stressors.
- ✓ Significant interactions were found to exist between infectious gastroenteritis, depression and anxiety and subsequent risk of IBS.

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