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AP&T Alimentary Pharmacology and Therapeutics

Epidemiology of inflammatory bowel disease among participants of the Millennium Cohort: incidence, deployment-related risk factors, and antecedent episodes of infectious gastroenteritis

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SUMMARY

Background
Crohn's disease (CD) and ulcerative colitis (UC) are two pathotypes of inflammatory bowel disease (IBD) with unique pathology, risk factors and significant morbidity.

Aim
To estimate incidence and identify IBD risk factors in a US military population, a healthy subset of the US population, using information from the Millennium Cohort Study.

Methods
Incident IBD was identified from medical encounters from 2001 to 2009 or by self-report. Our primary risk factor of interest, infectious gastroenteritis, was identified from medical encounters and self-reported post-deployment health assessments. Other potential risk factors were assessed using self-reported survey responses and military personnel files. Hazard ratios were estimated using Cox proportional hazards analysis.

Results
We estimated 23.2 and 21.9 diagnoses per 100 000 person-years, respectively, for CD and UC. For CD, significant risk factors included [adjusted hazard ratio (aHR), 95% confidence interval]: current smoking (aHR: 2.7, 1.4–5.1), two life stressors (aHR: 2.8, 1.4–5.6) and prior irritable bowel syndrome (aHR: 4.7, 1.5–15.2). There was no significant association with prior infectious gastroenteritis. There was an apparent dose–response relationship between UC risk and an increasing number of life stressors. In addition, antecedent infectious gastroenteritis was associated with almost a three-fold increase in UC risk (aHR: 2.9, 1.4–6.0). Moderate alcohol consumption (aHR: 0.4, 0.2–0.6) was associated with lower UC risk.

Conclusions
Stressful conditions and the high risk of infectious gastroenteritis in deployment operations may play a role in the development of IBD in military populations. However, observed differences in risk factors for UC and CD warrant further investigation.

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INTRODUCTION

Inflammatory bowel disease (IBD) comprises a group of bowel diseases of likely immune-mediate aetiology and primarily occurs in two forms, chronic inflammatory enteritis [Crohn's Disease(CD)] and chronic inflammatory colitis [ulcerative colitis (UC)]. Incidence rates in North America have been estimated to range from approximately 2 to 15 cases per 100 000 person-years for both forms with peak onset between the ages of 15 and 30 years.[1–3] In contrast, throughout much of the developing world, rates are lower; however, IBD incidence appears to be increasing in those regions that are becoming more westernised.[4, 5] The symptoms of IBD include abdominal pain, vomiting, diarrhoea, hematochezia, weight loss and weight gain and treatments can involve immunosuppression and/or surgery with direct medical costs in the USA exceeding $1.8 billion,[6] and indirect costs due to lost work production alone estimated to exceed $3.6 billion annually.[7]

The challenges of population-based epidemiologic studies of IBD include confounding by co-morbid conditions and/or limited data on risk factors and/or specific study populations compromising validity and limiting generalisability.[8] One population that may be well-suited to study disease incidence is active duty US military personnel. The US active duty military population represents a healthier segment of the general population with almost unrestricted access to available medical care, which makes them suitable for epidemiologic studies on disease incidence and risk factors, due to the likely capture of these outcomes from the military health care system. Prior studies in military populations have identified important and unique risk factors, but have been limited to data available in electronic medical records which often lack detailed information on life stressors and health risk behaviours that may be important in understanding the epidemiology of disease.[9–11] To address these limitations, we utilised a hypothesis-generating approach in leveraging data from the Millennium Cohort Study, a large prospective study of more than 200 000 military service members that includes a triennial survey of health conditions, to describe IBD incidence and assess potential risk factors not previously explored in this population.

MATERIALS AND METHODS

Study population

Launched in 2001, the Millennium Cohort Study is a prospective longitudinal study to investigate any impact of military service among US military personnel even after separation from military service. The methodology has previously been described elsewhere.[12–14] The cohort contains four enrolment panels (Panel 1, 2001–2003, N = 77 019; Panel 2, 2004–2006, N = 31 110; Panel 3, 2007–2008, N = 43 439; Panel 4, 2011–2013, N = 50 052). Panel 1 was a population-based random sample of the U.S. military in October 2000 with oversampling of Reserve/Guard personnel, women, and those deployed to Bosnia, Kosovo or Southwest Asia. Panels 2, 3 and 4 targeted new accessions (1–5 years of military service) with oversampling of Marines and women. Participants completed a baseline survey and were resurveyed at approximately 3-year intervals. For purposes of our study, we focused on responses to two questions: whether the participant had been diagnosed by a healthcare provider with either 1) CD, or 2) UC or proctitis.

The population for this IBD study was defined as active duty Millennium Cohort Study participants from Panels 1 and 2 who completed a baseline questionnaire (while still serving in the military) and at least one follow-up questionnaire between 2001 and 2009. Participants with evidence of IBD at baseline, either by self-report on the baseline survey or from Military Health System medical encounter (ME) data (≥2 MEs within 365 days with one or more of the following International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes: 555.0, 555.1, 555.9, 556.x), were excluded from this analysis. Self-report of provider diagnosed "ulcerative colitis or proctitis" was also exclusionary because even though proctitis is not a type of IBD, the survey question precluded disease differentiation. In addition, participants who reported they had received a diagnosis of every listed health outcome (pan-endorsers) on any survey questionnaire were excluded as were subjects with incomplete data for risk factors of interest.

Incident IBD

Incident IBD was determined based on medical encounter data or self-report as follows. Active duty participants with ≥2 MEs for IBD (ICD-9-CM codes 555.0, 555.1 and 555.9 for CD and ICD-9-CM code 556.x for UC, in any diagnostic field) within a 365 day period were considered incident IBD cases. Self-reported CD was defined as a participant responding "yes" to having been diagnosed with CD by a provider on a follow-up Millennium Cohort Study questionnaire. Due to the inability to differentiate UC and proctitis in the Millennium Cohort Study questionnaire data, only medical encounter data

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were utilised to identify incident UC cases. For diagnoses derived from medical encounter data only, the date of the first of the two encounters was identified as the diagnosis date. For self-reported CD, respondents had the option to report the year of diagnosis. If year of diagnosis was documented, we used the mid-point of the self-reported year. However, if no year was reported, we used the survey date for their first self-reported CD diagnosis. In cases where a subject met both the medical encounter definition and the self-reported definition of IBD, the diagnosis date derived from medical encounter data was preferentially used.

Primary risk factor of interest: antecedent infectious gastroenteritis

Infectious gastroenteritis data were collected from both ME data and self-reported post-deployment health assessments. Medical encounters between the baseline survey and IBD diagnosis (cases) or censor (noncases) with an infectious gastroenteritis-associated ICD-9-CM code (all 001 subgroups, 003.0, 003.9, all 004 subgroups, all 008.0 subgroups, 008.43, 008.44, 005.4, 008.47, 008.49, 008.5, 009.0, 009.1, 009.2, 009.3, all 005.8 subgroups, 005.9, 006.0, 006.1, 006.2, 006.9, all 007 subgroups, all 008.6 subgroups, and 008.8) were defined as infectious gastroenteritis episodes. In addition, self-reported diarrhoea during or after deployment on a post-deployment health assessment completed between the baseline survey and censoring were considered infectious gastroenteritis episodes. As with IBD, for diagnoses of infectious gastroenteritis derived from medical encounter data, the date of the first of the two encounters was identified as the diagnosis date. For self-reported episodes of diarrhoea, the date of completion of the post-deployment health assessment was used as the diagnosis date.

Other risk factors

Demographic and military-specific data, including sex, birth year, education, marital status, race/ethnicity, branch of service, occupation, rank, military separation, deployment status and number of deployments, were obtained from Defense Manpower Data Center records and the Millennium Cohort questionnaires. Body mass index (BMI) was calculated from self-reported height and weight. Behavioral and mental health characteristics, including smoking, drinking, life stressors, depression, anxiety or post-traumatic stress disorder (PTSD), as well as self-reported medications for these conditions, were also assessed from Millennium Cohort survey responses. Detailed definitions of each of these risk factors have been described elsewhere.[15]

Time censoring calculations

The date of the first survey's submission was defined as the start time for the period of observation. Noncases were then censored differently for CD and UC analyses. For UC, censoring at the earliest of four dates: date of UC diagnosis; date of separation from military service; date of death; end of study (31 December 2009). The use of the survey-based diagnosis for CD complicated censoring. Similar to UC, the date of diagnosis, the date of death, and the end of the study were censoring events. In contrast, for those who separated after completion of their last survey, the censoring date was the date of separation. For those who separated before completion of their last survey, the date of the last Millennium Cohort survey completion was the censor date.

Statistical analysis

Survival analyses were performed using the PHREG procedure in SAS (Version 9.3, SAS Institute, Cary, NC, USA) for CD and UC, modelled separately. The primary exposure of interest, antecedent infectious gastroenteritis, was forced into all models as a time-varying covariate. Forward selection with a $P < 0.05$ threshold was used for all other risk factors entering into the model; all of these variables were examined as fixed effects. Confounders of the infectious gastroenteritis-CD relationship or infectious gastroenteritis-ulcerative colitis relationship in their respective models were included if they changed the IGE parameter estimate by 10% or more. Interactions between infectious gastroenteritis and each covariate in the model 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 two models was less than four, the model without interaction term was selected for model parsimony and interpretability.[16] Proportional hazards assumption was examined using Martingale residuals and interaction with time methods.

RESULTS

Of the 108 129 participants from Panels 1 and 2 who completed a baseline questionnaire, 203 pan-endorsers of provider-based diagnoses on at least one survey were excluded (Figure 1). We were unable to calculate an accurate censoring time on an additional 39 723 participants, because they were not on active duty for the

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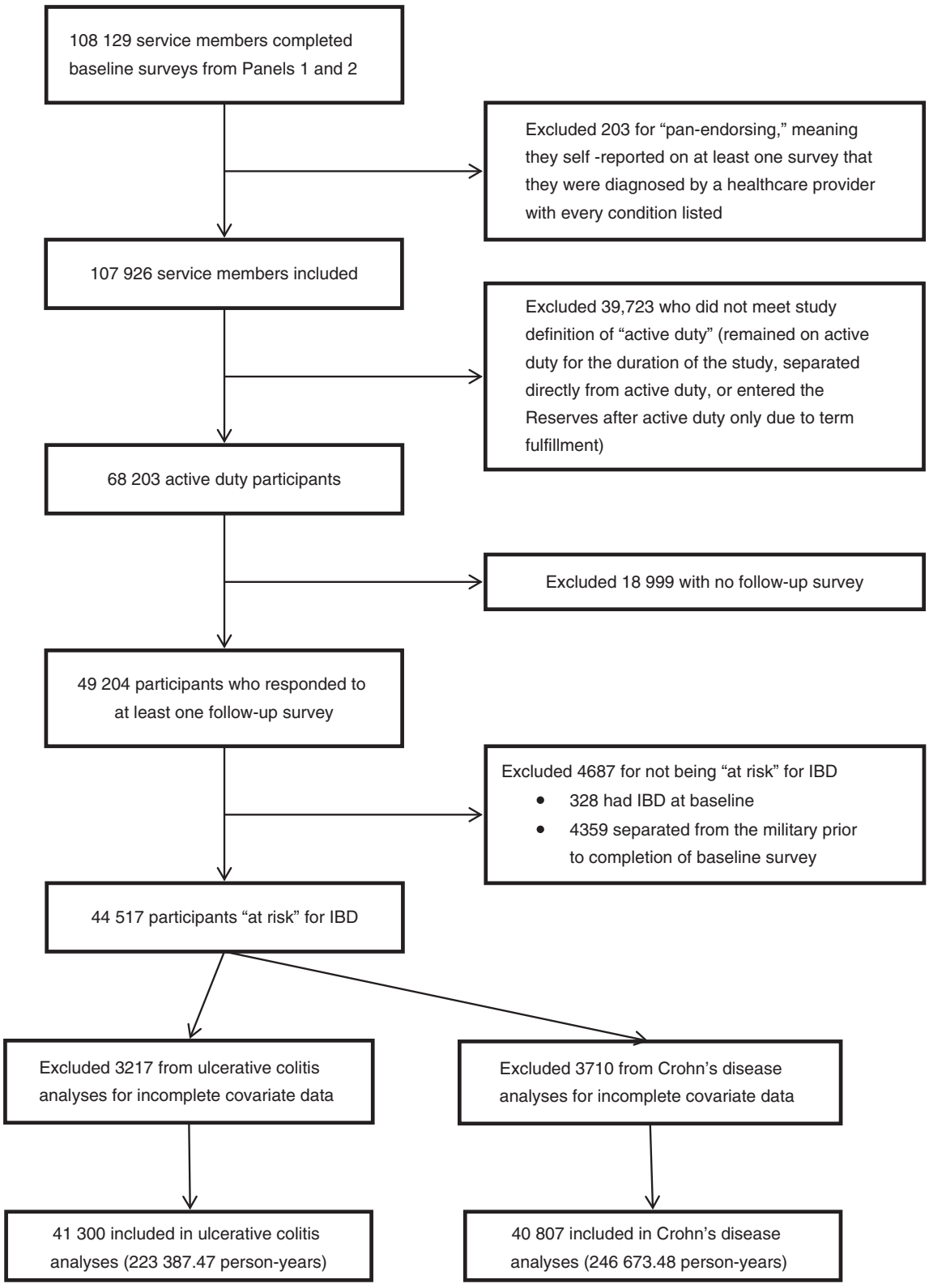

Figure 1 | Subject selection for analysis.

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entire course of study and did not have precise separation date. These subjects were excluded from the analysis. Participants were also excluded if they failed to complete a follow-up survey (n = 18 999) or had IBD at baseline (n = 328), separated from the military before the completion of the baseline survey (n = 4359), or had missing values on risk factors of interest (UC: n = 3217; CD: n = 3710). Compared to included subjects, excluded subjects were older (19.8% vs. 8.9% born before 1960), more commonly single (43.1% vs. 23.1%), in the Army (52.1% vs. 40.4%), more commonly had life stressors (77.1% vs. 57.5%), and more frequently had no deployment history at baseline (57.0% vs. 40.9%).

These exclusions yielded a final study population of 40 807 participants with 246 673.48 person-years of follow-up for CD, and 41 300 participants with 223 387.47 person-years of follow-up for UC ulcerative colitis.

Demographic, military and behavioural characteristics of study participants are shown in Table 1. Nearly, three quarters of the study population were male (72.8%), with the majority born between 1960 and 1979 (71.6%), married (69.6% for CD and 70.6% for UC), with less than a bachelor's degree (69.7% for CD and 69.9% for UC), and being of white, nonHispanic race/ethnicity (66.1 for CD and 66.2% for UC). Approximately 40% of the study population served in the Army, followed by the Air Force, Navy/Coast Guard and Marine Corps. A majority of participants were never smokers, followed by former smokers and current smokers. Approximately half of the participants reported moderate alcohol consumption, and over 50% reported having one or more life stressors; however, only a small proportion of participants reported experiencing depression, anxiety/panic or PTSD. With regard to military experience, approximately 60% of the participants had at least one deployment, and about 26% of the participants reported combat exposure.

A total of 58 new onset CD cases were identified, for an incidence of 23.15/100 000 person-years [95% CI 18.20–30.37] with approximately 80% identified from either the medical encounter data only (21/58; 36.2%) or the survey only (24/58; 41.4%). As shown in Table 2, younger age [born 1980 or later, hazard ratio (HR): 2.07], service and supply occupation (HR: 3.52), anxiety (HR: 2.62) and prior Irritable bowel syndrome (IBS) (HR: 5.08) were all associated with significantly increased CD risk. Both current (HR: 2.78) and past (HR: 1.54) smoking were associated with an increased CD risk, though only current smokers had a significantly increased risk (P = 0.0011). An increasing number of life stressors was also associated with an increased CD risk with an apparent dose–response effect. Several psychological co-morbidities were associated with increased CD risk, including anxiety syndrome (HR: 2.62) and PTSD (HR: 1.82), though the latter was not significant. Infectious gastroenteritis was not associated with a significant increase in developing CD (HR: 1.05, 95% CI: 0.47–2.36) though a nonsignificant increase in the effect estimate (HR: 1.94, 95% CI: 0.70–5.41) was observed when limiting to medical encounter only infectious gastroenteritis episodes (data not shown). Being married (HR: 0.49) was associated with a decreased CD risk compared to being single. In addition, there was an inverse association between BMI and CD risk with those classified as overweight or obese having lower CD risk (HR: 0.54, 95% CI: 0.31–0.93 and HR: 0.36, 95% CI: 0.14–0.93 respectively). Military deployments similarly appeared to be associated with a decreased CD risk, though the effect was not statistically significant. In the adjusted Cox proportional hazards model, service and supply occupation [adjusted hazard ratio (aHR): 3.32], current smoking (aHR: 2.65), two life stressors (aHR: 2.75) and prior IBS (aHR: 4.70) remained associated with a significantly increased CD risk while being married (aHR: 0.53) and divorced, widowed, legally separated (aHR: 0.12), remained associated with a decreased CD risk.

There were 49 reported new onset UC cases, yielding an estimated incidence of 21.94/100 000 person-years (95% CI: 16.60–28.98). In univariate Cox models, similar to CD, there were specific occupational risk factors with work in electrical and equipment repair (univariate HR 3.43) associated with a significantly increased UC risk (Table 2). In addition, there was an increasing UC hazard ratio with increasing number of life stressors (1: 1.25, 2: 2.12, 3 + : 4.84). Documented infectious gastroenteritis was associated with an increased risk of UC (HR: 2.62, 95% CI: 1.28–5.37), an effect that increased to 4.86 (95% CI: 2.14–11.05) when limiting analyses to only medical encounter-related infectious gastroenteritis events (data not shown). Similar to CD, prior IBS was associated with increased UC risk (univariate HR: 3.71), but unlike CD, this effect was not significant. Being of younger age (born 1980 or later, HR: 0.20), married (HR: 0.51) and moderate alcohol consumption (HR: 0.34) were associated with significantly decreased UC risk. In contrast to CD, current smoking was associated with a nonsignificantly decreased risk of UC, and a slight, nonsignificantly increased UC risk was observed among past smokers. Similar to CD, UC risk was lower in subjects with prior deployments, though the effect was not statistically significant.

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Table 1 | Overall descriptive characteristics of study population included for Crohn's disease and ulcerative colitis

Characteristic	Crohn's disease (*N* = 40 807)		Ulcerative colitis (*N* = 41 300)	
	n	%	*n*	%
Gender				
Male	29 711	72.8	30 071	72.8
Female	11 096	27.2	11 229	27.2
Birth year				
Pre-1960	3588	8.8	3635	8.8
1960–1969	13 344	32.7	13 574	32.9
1970–1979	15 876	38.9	16 002	38.7
1980-present	7999	19.6	8089	19.6
Race/ethnicity				
White, non-Hispanic	26 993	66.1	27 349	66.2
Black, non-Hispanic	5487	13.4	5553	13.4
Other	8327	20.4	8398	20.3
Marital status				
Single	9693	23.8	9510	23.0
Married	28 413	69.6	29 177	70.6
Divorced, widowed, legally separated	2701	6.6	2613	6.3
Education				
Less than a bachelor's degree	28 423	69.7	28 875	69.9
Bachelor's degree or higher	12 384	30.3	12 425	30.1
Panel (accession into cohort study)				
2001–2003	30 329	74.3	30 701	74.3
2004–2006	10 478	25.7	10 599	25.7
Branch of service				
Army	16 546	40.5	16 679	40.4
Navy/Coast Guard	9123	22.4	9197	22.3
Marine Corps	2576	6.3	2609	6.3
Air Force	12 562	30.8	12 815	31.0
Rank				
Enlisted	30 118	73.8	30 438	73.7
Officer	10 689	26.2	10 862	26.3
Occupation				
Combat specialist	7802	19.1	7 835	19.0
Functional support	8245	20.2	8 499	20.6
Service and supply	3475	8.5	3483	8.4
Healthcare	4554	11.2	4624	11.2
Electrical/mechanical equipment repair	5720	14.0	5766	14.0
Other	11 011	27.0	11 093	26.9
Separated				
No	23 012	56.4	23 012	55.7
Yes	17 795	43.6	18 288	44.3
Smoking*				
Never	23 586	57.8	23 896	57.9
Former	10 315	25.3	10 449	25.3
Current	6906	16.9	6955	16.8
Alcohol consumption†				
Abstainer/light	16 947	41.5	16 809	40.7
Moderate	20 644	50.6	21 331	51.6
Heavy	3216	7.9	3160	7.7
BMI‡				
Normal/underweight	13 612	33.4	13 708	33.2
Overweight	20 991	51.4	21 393	51.8
Obese	6204	15.2	6199	15.0

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Table 1 | (Continued)

Characteristic	Crohn's disease (*N* = 40 807)		Ulcerative colitis (*N* = 41 300)	
	n	%	*n*	%
Number of life stressors§				
0	18 310	44.9	17 662	42.8
1	15 981	39.2	16 251	39.3
2	4680	11.5	5221	12.6
3+	1836	4.5	2166	5.2
Depression¶				
Never	39 180	96.0	39 565	95.8
Ever	1627	4.0	1735	4.2
Anxiety and panic¶				
Never	39 269	96.2	39 565	95.8
Ever	1538	3.8	1735	4.2
PTSD**				
Never	38 600	94.6	38 941	94.3
Ever	2207	5.4	2359	5.7
Self-reported prescribed medication for mental health				
No	38 766	95.0	39 102	94.7
Yes	2041	5.0	2198	5.3
Deployment experience††				
Neither	10 853	26.6	11 009	26.7
Before OEF/OIF only	5726	14.0	5794	14.0
OEF/OIF only	14 837	36.4	15 004	36.3
Both	9391	23.0	9493	23.0
Combat exposure‡‡				
Not deployed	16 579	41.1	16 803	41.4
Deployed, no combat	13 226	32.8	13 158	32.4
Deployed, combat	10 523	26.1	10 640	26.2
Multiple deployments				
0	16 579	40.6	16 803	40.7
1	12 188	29.9	12 312	29.8
2+	12 040	29.5	12 185	29.5

* Never: self-reported smoking <100 cigarettes in their lifetime. Past smoking: reporting successful smoking cessation, Current: reported never trying to quit or unsuccessful at quitting.

† 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.

‡ Normal/underweight, <25; overweight, 25–29.9, obese, 30+.

§ Assessed using the Social Readjustment Rating Scale.[46]

¶ Assessed using responses to the Patient Health Questionnaire.

** Assessed using responses to the PTSD Checklist- Civilian Version.

†† Previous deployments include only Kosovo, Bosnia, SW Asia, and 1991 GW.

‡‡ MISSING: Combat exposures *n* = 479 (Crohn's disease); *n* = 699 (Ulcerative colitis).

In the adjusted Cox proportional hazards models, the associations between UC and younger age (born 1980 or later, aHR: 0.15), being married (aHR: 0.37), electrical/mechanical equipment repair occupation (aHR: 2.96) and moderate alcohol consumption (aHR: 0.35) remained. Increasing number of life stressors continued to demonstrate an association with increasing UC risk which only reached significance in those with 3 + stressors (aHR: 5.07, 95% CI: 1.93–13.30). In addition, the risk of ulcerative colitis associated with antecedent infectious gastroenteritis remained significant in the adjusted Cox proportional hazards models (aHR: 2.90). Significant interaction was observed between infectious gastroenteritis and occupation; however, the data were sparse due to the large number of occupation categories, such that there, were UC cases with infectious

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Table 2 | Risk factors associated with Crohn's disease and ulcerative colitis in the Millennium Cohort Study participants between 2001 and 2009* (*N* = 40 807 and 41 300 for Crohn's disease and ulcerative colitis respectively)

	Crohn's disease			Ulcerative colitis		
Characteristic	*N*	Univariate HR	Adjusted HR	*N*	Univariate HR	Adjusted HR
Antecedent infectious gastroenteritis						
None	51	Ref	Ref	38	Ref	Ref
Any	7	1.05 (0.47–2.36)	1.10 (0.47–2.53)	11	2.62 (1.28–5.37)	2.90 (1.39–6.04)
Gender						
Male	44	Ref		36	Ref	
Female	14	0.91 (0.5–1.67)		13	1.04 (0.55–1.97)	
Birth year						
Pre-1960	6	1.35 (0.54–3.34)		3	0.63 (0.19–2.07)	0.73 (0.22–2.46)
1960–1969	16	0.90 (0.47–1.72)		17	0.75 (0.41–1.38)	0.85 (0.46–1.58)
1970–1979	21	Ref		27	Ref	Ref
1980-present	15	2.07 (1.06–4.08)		2	0.20 (0.05–0.84)	0.15 (0.04–0.64)
Race/ethnicity						
White non-Hispanic	42	Ref		33	Ref	
Black non-Hispanic	6	0.69 (0.29–1.62)		6	0.87 (0.36–2.07)	
Other	10	0.74 (0.37–1.47)		10	0.92 (0.45–1.86)	
Marital status						
Single	20	Ref	Ref	15	Ref	Ref
Married	37	0.49 (0.29–0.86)	0.53 (0.30–0.92)	31	0.51 (0.27–0.95)	0.37 (0.19–0.70)
Divorced, widowed, legally separated	1	0.14 (0.02–1.04)	0.12 (0.02–0.89)	3	0.53 (0.15–1.84)	0.35 (0.10–1.27)
Education						
Less than a bachelor's degree	40	1.08 (0.62–1.88)	0.65 (0.35–1.21)	37	1.56 (0.81–2.99)	
Bachelor's degree or higher	18	Ref	Ref	12	Ref	
Panel						
2001–2003	44	Ref		40	Ref	
2004–2006	14	1.52 (0.81–2.85)		9	0.93 (0.44–1.95)	
Branch of service						
Army	21	1.00 (0.52–1.92)	0.86 (0.44–1.68)	14	0.65 (0.32–1.31)	0.60 (0.29–1.24)
Navy/Coast Guard	17	1.49 (0.75–2.94)	1.19 (0.60–2.38)	15	1.30 (0.65–2.61)	1.18 (0.58–2.42)
Marine Corps	4	1.31 (0.44–3.93)	1.13 (0.37–3.42)	3	1.00 (0.29–3.43)	1.10 (0.32–3.80)
Air Force	16	Ref	Ref	17	Ref	Ref
Rank						
Enlisted	43	Ref		39	Ref	
Officer	15	1.15 (0.64–2.07)		10	1.67 (0.83–3.34)	
Occupation						
Combat specialist	8	Ref	Ref	6	Ref	Ref
Functional support	6	0.71 (0.25–2.04)	0.67 (0.23–1.95)	10	1.53 (0.56–4.21)	1.19 (0.43–3.30)
Service and supply	12	3.52 (1.44–8.62)	3.32 (1.35–8.21)	4	1.56 (0.44–5.53)	1.29 (0.36–4.60)
Healthcare	6	1.33 (0.46–3.83)	1.15 (0.39–3.37)	4	1.13 (0.32–4.01)	0.84 (0.23–3.01)
Electrical/mechanical equipment repair	11	2.00 (0.81–4.98)	1.79 (0.69–4.65)	14	3.43 (1.32–8.94)	2.96 (1.12–7.82)
Other	15	1.39 (0.59–3.29)	1.25 (0.52–2.98)	11	1.36 (0.50–3.67)	1.12 (0.41–3.05)
Smoking‡						
Never	24	Ref	Ref	28	Ref	Ref
Past	16	1.54 (0.82–2.90)	1.57 (0.82–2.98)	19	1.61 (0.90–2.88)	1.59 (0.88–2.89)
Current	18	2.78 (1.51–5.12)	2.64 (1.38–5.07)	2	0.28 (0.07–1.16)	0.25 (0.06–1.07)
Alcohol consumption§						
No/light	27	Ref		33	Ref	Ref
Moderate	25	0.74 (0.43–1.28)		15	0.34 (0.19–0.63)	0.35 (0.19–0.64)
Heavy	6	1.27 (0.52–3.07)		1	0.18 (0.02–1.29)	0.16 (0.02–1.19)
BMI¶						
Normal/underweight	28	Ref		18	Ref	
Overweight	25	0.54 (0.31–0.93)		27	0.89 (0.49–1.62)	

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Table 2 | (Continued)

Characteristic	Crohn's disease			Ulcerative colitis		
	N	Univariate HR	Adjusted HR	*N*	Univariate HR	Adjusted HR
Obese	5	0.36 (0.14–0.93)		4	0.45 (0.15–1.33)	
Number of life stressors**						
0	20	Ref	Ref	17	Ref	Ref
1	21	1.25 (0.68–2.30)	1.21 (0.66–2.25)	18	1.25 (0.64–2.42)	1.23 (0.63–2.40)
2	13	2.86 (1.42–5.75)	2.75 (1.35–5.62)	8	2.12 (0.91–4.91)	2.19 (0.93–5.16)
3+	4	2.50 (0.85–7.32)	2.25 (0.75–6.75)	6	4.84 (1.90–12.33)	5.07 (1.93–13.30)
Depression syndrome ††						
No	56	Ref		47	Ref	
Yes	2	0.96 (0.23–3.92)		2	1.15 (0.28–4.72)	
Anxiety syndrome††						
No	53	Ref		48	Ref	
Yes	5	2.62 (1.05–6.55)		1	0.55 (0.08–3.96)	
PTSD‡‡						
No	53	Ref		45	Ref	
Yes	5	1.82 (0.73–4.55)		4	1.70 (0.61–4.72)	
Self-reported prescribed medication for mental health						
No	54	Ref		46	Ref	
Yes	4	1.44 (0.52–3.97)		3	1.22 (0.38–3.92)	
Deployments						
0	26	Ref	Ref	21	Ref	
1	17	0.86 (0.47–1.58)	0.82 (0.44–1.53)	13	0.71 (0.35–1.42)	
2+	15	0.73 (0.39–1.38)	0.72 (0.37–1.40)	15	0.75 (0.39–1.46)	
Prior IBS						
No	55	Ref	Ref	47	Ref	
Yes	3	5.08 (1.59–16.23)	4.70 (1.46–15.15)	2	3.71 (0.90–15.28)	

IBS, irritable bowel syndrome.

* Excludes pan endorsers and anyone who did not complete at least one follow-up survey.

‡ Never: self-reported smoking <100 cigarettes in their lifetime. Past smoking: reporting successful smoking cessation, Current: reported never trying to quit or unsuccessful at quitting.

§ 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.

¶ Normal/underweight, <25; overweight, 25–29.9, obese, 30+.

** Assessed using the Social Readjustment Rating Scale.[46]

†† Assessed using responses to the Patient Health Questionnaire.

‡‡ Assessed using responses to the PTSD Checklist- Civilian Version.

gastroenteritis in only two occupation categories, healthcare and electrical/mechanical equipment repair (data not shown).

DISCUSSION

In our population of current and former military members, we estimated an overall UC and CD incidence of 21.94 and 23.15/100 000 person-years respectively. Importantly, subjects with missing data on important risk factors for the survival analyses were excluded from these estimates though their exclusion yielded no substantial change in overall incidence for either CD or UC (data not shown). Several prior studies have estimated the incidence of CD and UC in various populations with comparable estimates.[17] In the USA, studies reporting CD and UC incidence in comparably aged populations have estimated CD incidence between 5.7 and 28.4 per 100,000 person-years with a slightly higher incidence of UC reported in some studies.[1, 18, 19] We observed no significant difference in the incidence of CD and UC in our study. A single study has previously reported overall IBD incidence (CD and UC) in this population at just less than 30 cases per 100 000 person-years[10]; however, that study was limited to medical encounters occurring

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during the active duty service period which may account for the lower rates than reported here.

On the basis of several prior lines of evidence, we took a focused look at the role of infectious gastroenteritis in increasing IBD risk. While we observed no association between CD incidence and infectious gastroenteritis, we did see an almost three-fold increase in UC incidence in subjects with prior infectious gastroenteritis. Separate studies have previously reported a positive association between antecedent Campylobacter and Salmonella infection and IBD [20, 21] while others have noted an association with nonspecific exposures such as those included in our models.[10, 22] While studies of the potential mechanisms underlying this association are in their infancy, *in vivo* and *in vitro* data are emerging that may increase understanding of these findings. To that end, recent data show that *C. jejuni* facilitates the translocation of commensal flora leading to the aberrant immune response seen in IBD patients.[23] In addition, data are emerging that suggest a proliferation of anti-commensal T cells is evident following an acute gastrointestinal (GI) infection which coincides with a loss in regulatory T cells.[24, 25] Furthermore, increased levels of antibodies directed at commensal flora are evident in the serum of IBD patients; however, similar commensal responses present in healthy populations points to a more nuanced effect that may be based on genetic predisposition, repeated exposure or extra-intestinal exposures.[24]

In contrast to other studies, we found no association between infectious gastroenteritis and CD.[10, 20–22] This may be due to nondifferential exposure misclassification; however, studies using similar exposures and those focused on *Campylobacter* and *Salmonella* reported comparable positive association between infectious gastroenteritis and both IBD pathotypes. Importantly, there were differences in how incident CD and UC cases were identified. Specifically, incident CD was identified from both the medical encounter data as well as an affirmative response on the Millennium Cohort Study questionnaire. In contrast, UC cases were limited to medical encounter data. Given the prior report of 17.1% positive agreement between CD-specific Millennium Cohort responses and corresponding medical records,[26] we re-ran our analyses including only cases identified by medical encounter data in an attempt to assess whether inclusion of self-reported diagnosis introduced case-status misclassification. In that re-analysis, we found a nonsignificant 1.5-fold increase in CD risk among those with prior infectious gastroenteritis (data not shown). Similarly, we also assessed the role of infectious gastroenteritis identified solely from medical encounter data to minimise potential biases in self-reported exposures. The adjusted HR for antecedent infectious gastroenteritis in the UC model increased to 4.4 (95% CI: 1.9–10.0) and to 1.6 for CD (95% CI: 0.6–4.6), though not statistically significant (data not shown).

While the mechanisms behind the association between acute enteric infection and IBD are unclear, this is not the only study to report this association.[10, 20–22] It is possible that the observation represents an increased risk of infectious gastroenteritis (or even severe gastroenteritis) in those with undiagnosed IBD. While this is feasible, other studies reporting this phenomenon have described a delay in the observed effect (development of IBD following infectious gastroenteritis) of more than 5 years.[10, 20–22] In our study, the median time was approximately 2.5 years. While again, this may represent subclinical IBD that likelihood is reduced the more distal in time from the antecedent infectious gastroenteritis episode.

It has been argued that the association between antecedent enteric infection and increased IBD risk may be due to diagnostic misclassification due to increased culturing in the IBD work-up.[21] While this may in fact play a role, the data to date are insufficient to support this purported bias and carefully designed studies are needed to assess the role of a surveillance bias and include the clinical presentation of subjects at the time of culture.[27]

In our study, CD was most strongly linked to antecedent IBS after controlling for other risk factors (adjusted HR: 4.70; $P = 0.01$); however, there was no association with UC in the multivariable model. Garcia-Rodriguez *et al.* similarly reported a strong association between antecedent IBS and IBD, an effect that was more pronounced for CD than UC.[28] In addition, Porter *et al.* previously described an eightfold increase in IBD risk in those with IBS at baseline compared to those with no evidence of IBS at baseline, an effect which was twice as high for CD than UC.[9] Others have also observed an increase in organic GI disorders subsequent to IBS[9, 29, 30]; however, the potential mechanisms underlying this association remain poorly characterised. It may be that an IBS diagnosis represents misdiagnosed IBD, a potential effect that is confounded by the lack of a diagnostic test for functional bowel disorders.

Stress has been repeatedly evaluated as a potential risk factor for CD and UC with varying results, likely due to variability in study design and how stress is measured.[31] We observed an increase in UC and CD in those with more than one life stressor prior to disease. Furthermore, for UC, the effect appeared to be a positive dose–

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response relationship with increasing UC risk corresponding to an increasing number of life stressors. In a case–control study of UC risk factors, Tocchi *et al.* reported a fourfold increase in the prevalence of a stressful life condition in 12 months prior to study enrolment; however, due to the study design, a temporal relationship could not be established.[32] Lerebours *et al.* reported an association between stressful life events with CD but not UC; however, exposures were limited to the 6 month period prior to the onset of symptoms, potentially biasing effect estimates towards the null.[33] It may be that the effect we observed represents increasing symptoms in undiagnosed patients subsequently leading to treatment and diagnosis. Increasing symptoms following stress in IBD patients has been reported previously and studies have also reported an increase in IBD among those with depression-like symptoms;[34] however, we found no significant effect of depression or anxiety on IBD risk.

Of specific interest in this population is the potential effect of post-traumatic stress disorder (PTSD) in the modulation of IBD risk. We reported a slight, albeit not statistically significant, increase in UC and CD risk among subjects with PTSD; however, the number of cases with PTSD was quite low. O'Donovan *et al.* recently reported on the increase in several autoimmune disorders among US veterans of war in Iraq and Afghanistan.[35] This observation included a significant 1.3-fold increase in the risk of IBD; however, the disease pathotypes were not differentiated. Our study was not powered to identify this effect size; nonetheless, our CIs include these parameter estimates.

We observed several occupations with significantly increased CD and UC risk. Specifically, being in a service and supply category or occupation was associated with more than a threefold increase in CD risk while a similar magnitude of UC risk was observed in those whose occupations included electrical and/or mechanical equipment repair. Occupation risk factors for IBD were recently summarised by Lesso *et al.*[36] In particular, the authors report several pathotype-specific risk factors; however, the authors also note the considerable lack of quantifiable exposure data and highlight the need for prospective cohort studies with monitored exposures over time. Importantly, such studies remain difficult for relatively rare diseases and focused efforts to simply describe an increased prevalence with specific occupations may guide additional such focused studies.

Smoking is a well-described risk factor for CD and a protective factor for UC; we observed nearly a fourfold increased risk in CD among current smokers and a fourfold decreased risk of UC.[31] We also saw a non-significant 1.6-fold increase in CD and UC risk among those who self-reported former smoking. This finding is consistent with prior reports that increased CD risk continues many years after quitting smoking, though the magnitude of the risk decreases.[37, 38] Higuchi *et al.* reported an increase in UC risk among women within 2 years of smoking cessation, an effect that persisted for more than 10 years.[37] Similarly, Jiang *et al.* reported current smoking as a protective factor in UC (OR: 0.28, $P < 0.0001$) while being an ex-smoker was a risk factor (OR: 4.36, $P = 0.008$).[39] Despite a previous report of the relationship between smoking and IBD risk being more pronounced in females than males,[31] we observed similar effects in our predominately male population. The reason for the discrepant effects of cigarette smoking remains elusive and more research in this area is needed in military and other populations.

We observed an inverse dose–response in the risk of UC among those reporting moderate and heavy alcohol consumption and no significant association between alcohol consumption and CD risk. Three prior studies assessed the role of alcohol in IBD and found a similar decrease in risk.[39–41] The potential beneficial effect of alcohol in preventing UC has been theorised to be associated with phenols present in alcoholic drinks that may inhibit pro-inflammatory cytokines;[42] however, studies of disease activity in IBD patients have reported an increase in GI symptoms among UC patients consuming alcohol due to increasing intestinal permeability and subsequent antigenic exposure.[43] Clearly, additional studies on moderate and heavy alcohol consumption and IBD risk are needed.

This study had some inherent limitations such as potential misclassification from data obtained from self-reported survey responses; however, many of the questions embedded in the survey are standardised and previously validated.[13] In addition to self-reported exposures, IBD was identified from electronic medical encounter data. Importantly, these outcomes have not been validated through medical record review. However, they have been utilised in several other large epidemiologic studies in this population.[10, 11] In addition, other studies in similar populations have shown a high positive predictive value in the use of these medical billing codes to accurately identify those with IBD.[44] We were unable to exclude those with other conditions mimicking IBD, such as coeliac disease or tropical sprue; however, these outcomes are rare. Despite these limitations, this study did utilise data from a population-based prospective

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cohort study, with time-varying covariates that enabled estimation of disease incidence and risk factors.

While many of the findings reported here confirm previously published literature on IBD risk factors, we find these confirmatory results reassuring in the context of the more novel findings we observed in this study. In addition, we feel that ongoing IBD research in military populations is of utmost importance. The US military population is a cross-section of the general US population. In addition, the majority of the Millennium Cohort has separated from service and is now part of the civilian population. Because a stratified random sample of eligible military personnel are invited to join the Millennium Cohort Study without regard to any exposures or health outcomes, internal comparison groups are readily available in this Cohort.

Our findings contribute to the growing body of literature on the incidence of and risk factors for inflammatory bowel disease in a young, healthy subset of the US population. In addition to highlighting previously described epidemiologic risk factors, we were able to quantify the role of selected life stressors, PTSD and antecedent infectious gastroenteritis on IBD risk. These are important characteristics to address in this population given operational deployments, often in combat settings, and the high risk of infectious gastroenteritis during these operations.[45] Clearly, additional well-designed focused research is needed and may include expansion to additional survey panels within the Millennium Cohort Study, enhanced characterisation of life stressors and more expanded data on exposures and clinical presentation of disease.

AUTHORSHIP

Guarantor of the article: Chad Porter.

Author contributions: MSR, CKP, TIH, EJB: conception and design of the study; MW, CN, MSR, CKP: generation, collection, assembly, analysis and/or interpretation of data; all authors: drafting or revision of the manuscript.

All authors approved the final version of the manuscript.

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