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Prevalence of Chronic Multisymptom Illness/Gulf War Illness Over Time Among Millennium Cohort Participants, 2001 to 2016

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Objective: Chronic multisymptom illness/Gulf War illness (CMI/GWI) is the defining illness of the 1990 to 1991 Gulf War. However, few studies have examined changes over time in CMI/GWI prevalence. **Methods:** Prevalence of CMI/GWI over time was compared between three groups of military personnel (9110 Gulf War veterans, 36,019 era personnel, 31,446 non-era personnel) enrolled in the Millennium Cohort Study. Post hoc analyses were conducted among participants with no reported mental and physical health conditions ($N = 30,093$). **Results:** CMI/GWI prevalence increased substantially over the study period among all groups. Gulf War veterans had the highest prevalence of CMI/GWI across the study period. This finding persisted after excluding participants with mental and physical health conditions. **Conclusions:** Gulf War veterans' increased risk of CMI/GWI persisted across the study period, highlighting the continued importance of screening and improving treatment options among this population.

Keywords: chronic multisymptom illness, gulf war, gulf war illness, military, millennium cohort study

Learning Objectives

- Review previous findings on the prevalence of chronic multisymptom illness/Gulf War Illness (CMI/GWI) among Gulf War veterans and nondeployed personnel.
- Summarize the new findings on changes in CMI/GWI prevalence over time, including Gulf War veterans and reference groups from the Gulf War era and from more recent years.
- Discuss the study implications for ongoing monitoring and treatment of Gulf War veterans.

Chronic multisymptom illness (CMI) is a complex medical condition that presents as a cluster of chronic, medically unexplained symptoms such as fatigue, pain, gastrointestinal symptoms, respiratory symptoms, dermatological symptoms, and neurological symptoms.[1,2] Called Gulf War illness (GWI) when presenting among veterans of the 1991 Persian Gulf War, it is considered to be the signature health condition of this conflict. Previous studies have reported prevalence estimates between 25% and 34% among Gulf War veterans.[1–6] Currently, there is no diagnostic test or single case definition for CMI/GWI and subsequently no diagnostic code.[7]

Numerous cross-sectional studies have reported the prevalence and identified risk factors associated with GWI in Gulf War veterans.[2,6,8–10] Few studies have examined symptom prevalence longitudinally, and when examined, only two time points have been included. Results from these studies indicate that the higher burden of symptoms among Gulf War veterans relative to nondeployed reference groups persists over time.[11–15] However, inconsistent findings were found regarding rates of symptom change, with some studies finding no differences compared with nondeployed reference groups[14,15] while others observed more rapidly increasing symptom prevalences among Gulf War veterans.[11] Understanding

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Clinical Significance: Results indicate that Gulf War veterans have an increased prevalence of CMI/GWI that persisted from 2001 to 2016. This increased burden of disease was not due to other mental or physical conditions. These results highlight the continued importance for screening and treatment of CMI/GWI among Gulf War veterans.

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the burden of GWI as Gulf War veterans age is critical to estimating current and future health care needs.

The Millennium Cohort Study is the largest prospective military cohort study conducted to date and has enrolled over 9000 Gulf War veterans who have completed up to five assessments since 2001.[16,17] As such, it is uniquely positioned to examine longitudinal changes in the prevalence of CMI/GWI among Gulf War veterans. Despite this history, few studies to date have examined either Gulf War and Gulf era veterans enrolled in the cohort[16,17] or chronic multisymptom illness.[18] The present analysis had three aims. The first aim was to describe the prevalence of CMI/GWI from 2001 to 2016 in deployed Gulf War veterans relative to nondeployed Gulf War era personnel and personnel not serving during the Gulf War era. The second aim was to determine how the prevalence of CMI/GWI changes over time and whether it changes at different rates among Gulf War veterans than reference groups. The third aim was to conduct analyses stratified by race and ethnicity to address the need for additional information about CMI/GWI among women and racial/ethnic minorities.[19] This is the first study to examine CMI/GWI longitudinally over five time points and 15 years in a large cohort.

METHODS

Study Population

A detailed description of the design and sampling framework of the Millennium Cohort Study have been described elsewhere.[20,21] Briefly, the Millennium Cohort Study enrolled service members from all branches and service components of the US military using military rosters from October 2000, with oversampling for women and personnel deployed to Bosnia, Kosovo, or Southwest Asia from 1998 to 2000. This initial enrollment included 9249 Gulf War veterans, 36,132 nondeployed personnel from the Gulf War era (era personnel), and 31,638 service members who were not serving in the military during the Gulf War (non-era personnel). The study protocol was approved by the Naval Health Research Center Institutional Review Board, and participants provided their written informed consent at enrollment. Participants completed a baseline survey in 2001 and completed follow-up surveys approximately every 3 years thereafter; the fifth and most recent survey was completed in 2014 to 2016.

Although no official end to the Gulf War has been declared, for the current study, the Gulf War period was restricted to August 1, 1990 to July 31, 1991. This period encompassed the active conflict (August 1, 1990 to February 28, 1991) as well as many environmental hazards, including smoke from burning oil well fires and sarin and cyclosarin dispersion resulting from munition disposal at Khamisiyah. Participants in the Gulf War roster file without a clear indication of their presence in theater during this period were excluded ($n = 119$). Additionally, participants with no outcome data ($n = 325$) were excluded, leaving 9110 Gulf War veterans, 36,019 era personnel, and 31,446 non-era personnel for these analyses.

Measures

Gulf War veterans and era personnel were identified from roster files maintained by the Defense Manpower Data Center. Non-era personnel were identified as participants not listed in either file. Additionally, personal and military demographic data for the entire sample were obtained from Defense Manpower Data Center records from October 2000 as a part of the Millennium Cohort enrollment effort.

CMI/GWI was defined using a modified Center for Disease Control definition consisting of endorsement of at least one item within at least two clusters assessing fatigue, musculoskeletal, and mood-cognition symptoms on the Millennium Cohort questionnaires.[1,7] Items for this measure were collected from a variety of available sources including Patient Health Questionnaire somatic symptom inventory (PHQ-15),[22–24] the Veterans' Rand 36-Item Health Survey (VR-36),[25], Posttraumatic stress disorder (PTSD) CheckList-Civilian Version (PCL-C),[26], Patient Health Questionnaire-Other Anxiety subscale (PHQ-OA),[22,24], and a measure of symptoms from a prior Gulf War SeaBee health survey (SeaBee).[27] The fatigue cluster consisted of two items, unusual fatigue (SeaBee) and having a lot of energy (VR-36; reverse coded). The musculoskeletal cluster consisted of unusual muscle pains (SeaBee), back pain (PHQ-15), and pain in arms, legs, or joints (PHQ-15). The mood-cognition cluster consisted of items assessing forgetfulness (SeaBee), confusion (SeaBee), trouble sleeping (SeaBee), nervousness/anxiety (PHQ-OA), feeling downhearted/blue (VR-36), irritability (PCL-C), and trouble falling/staying asleep (PCL-C).

Pesticide exposure was assessed on each survey from two items assessing personal (creams, sprays, uniform treatments, etc) and environmental pesticide exposure. Potential chemical/biological exposure was assessed by self-report of exposure to agents themselves, medical countermeasures due to exposure, and alarms necessitating wearing protective gear. At baseline, these items assessed lifetime exposure and thus included the Gulf War period.

Mental health screening measures were used to assess potentially diagnosable illnesses for use as covariates in models. Depression was assessed using the eight-item depression inventory from the Patient Health Questionnaire[22,28,29]; positive screens were determined through endorsing at least five symptoms of depression in the past 2 weeks, with one of the symptoms endorsed being either depressed mood or anhedonia. PTSD was assessed using the 17-item PTSD CheckList-Civilian version[26]; positive screens were determined as endorsing at least one re-experiencing symptom, two hyperarousal symptoms, and three avoidance symptoms in the past month. These measures used criteria comparable to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision criteria.[30] Panic disorder was determined from the Panic Disorder module of the Patient Health Questionnaire[22,24] using the original Primary Care Evaluation of Mental Disorders criteria[22] of endorsing an anxiety attack in the past month, a history of other attacks that come out of the blue, and are bothersome/worrisome along with at least five of 11 physiological symptoms as occurring during the last attack. Anxiety was assessed using Other Anxiety module from the Patient Health Questionnaire[22,24] using the original Primary Care Evaluation of Mental Disorders criteria[22]; positive screens were indicated by endorsing feeling nervous/anxious/worrying a lot and three of six additional symptoms.

Self-report of medical diagnosis of various physical and mental conditions were used as exclusion criteria for certain analyses. Participants were prompted with ''Has your doctor or other health professional [ever/in the past 3 years] told you that you have any of the following conditions'' followed by a list of conditions. Participants were asked ''ever'' on the baseline assessment and ''in the past 3 years'' on follow-up assessments. Prior research has demonstrated that these self-reported diagnoses have, on average, near perfect negative agreement and moderate positive agreement with electronic medical records.[31]

Statistical Analysis

Crude prevalence estimates were calculated for Gulf War veterans and the two reference groups. Nonlinear mixed models (NLMMs) estimated using the NLMIXED procedure in SAS software, version 9.4 (SAS Institute, Cary, NC) were used to quantify the association between predictors and CMI/GWI while modeling nonindependence between observations. Unadjusted NLMMs contained time (scaled in 5-year increments), Gulf War status, the interaction of time and Gulf War status, and a random intercept. Adjusted NLMMs included the same variables adjusted for sex,

race/ethnicity, service branch, service component, baseline chemical/biological exposure, recent chemical/biological exposure, anthrax vaccination, pesticide exposure, Operation Enduring Freedom/Operation Iraqi Freedom (OEF/OIF) deployment, anxiety, panic disorder, PTSD, and depression. Adjusted NLMMs stratified by sex and race/ethnicity were also examined.

Due to unexpected initial findings that suggested high collinearity of mental health conditions with CMI/GWI, additional adjusted models examined the above associations in two subpopulations. The first subpopulation ($N = 52,498$) excluded participants with mental health problems (schizophrenia, bipolar disorder, depression, generalized anxiety, PTSD, and panic disorder) at any time point determined from screening criteria (when available) and/or self-reported diagnoses. The second subpopulation ($N = 30,093$) excluded participants with any mental health or self-reported physical condition diagnosis (hypertension, coronary heart disease, chronic bronchitis, emphysema, repeated bladder infections, diabetes, hepatitis, cirrhosis, rheumatoid arthritis, multiple sclerosis, stroke, seizure, and cancer) at any of the five time points.

Missing Data

Of the eligible participants, 29,800 (38.9%) completed all five surveys, 15,927 (20.8%) completed four surveys, and 30,848 (40.3%) completed three or fewer surveys. Missing outcome data due to survey nonresponse were handled with full information maximum likelihood estimation.[32] On completed surveys, item-level missingness was less than 2% for each item and was addressed with multiple imputation. Fifty imputations were created using an imputation model containing all variables from the current analyses and principal components derived from the complete data set.[32,33] The discriminant function was used to retain the categorical nature of variables in the imputations.

RESULTS

Table 1 details demographic information of the included participants. Gulf War veterans were more likely to report potential chemical/biological agent exposure and receipt of the anthrax vaccine at baseline than era personnel or non-era personnel. Non-era personnel were the most likely to deploy in support of OEF/OIF, although these deployments were also common among Gulf War veterans and era personnel. Era personnel were the least likely of the three groups to screen positive for each of the mental health conditions.

At each survey assessment, Gulf War veterans had a higher crude prevalence of CMI/GWI than the other groups (Fig. 1). At baseline, the crude prevalence of CMI/GWI was 28.4% among Gulf War veterans, 18.7% among era personnel, and 23.0% among non-era personnel. Of participants who screened positive for CMI/GWI at baseline and responded to all time points, 57.3% remitted at one

TABLE 1. Demographic Characteristics, Self-Reported Exposures, and Mental Health of Gulf War Veterans, Era Personnel, and Non-Era Personnel, Millennium Cohort Study, 2001 to 2016.

	Gulf War Veterans ($n = 9110$)	Era Personnel ($n = 36,019$)	Non-Era Personnel ($n = 31,446$)
Characteristics*	***N* (%)**	***N* (%)**	***N* (%)**
Sex			
Male	7834 (86.0%)	27,460 (76.2%)	20,799 (66.1%)
Female	1276 (14.0%)	8559 (23.8%)	10,647 (33.9%)
Race/ethnicity			
White non-Hispanic	6557 (72.0%)	27,448 (76.2%)	22,686 (72.1%)
Black non-Hispanic	1653 (18.1%)	5120 (14.2%)	4146 (13.2%)
Asian/Hispanic/Other	895 (9.8%)	3431 (9.5%)	4584 (14.6%)
Age, yr			
<35	2895 (31.8%)	9626 (26.7%)	28,859 (91.8%)
35–44	4937 (54.2%)	18,285 (50.8%)	2046 (6.5%)
44+	1278 (14.0%)	8108 (22.5%)	541 (1.7%)
Military branch			
Army	4636 (50.9%)	15,579 (43.3%)	16,005 (50.9%)
Navy/Coast Guard	1714 (18.8%)	6788 (18.9%)	5702 (18.1%)
Marine Corps	599 (6.6%)	965 (2.7%)	2357 (7.5%)
Air Force	2161 (23.7%)	12,687 (35.2%)	7382 (23.5%)
Service component			
Active duty	5855 (64.3%)	16,989 (47.2%)	20,760 (66.0%)
Reserve	3255 (35.7%)	19,030 (52.8%)	10,686 (34.0%)
Self-reported exposures			
Potential chemical/biological agents	5779 (63.4%)	5200 (14.4%)	3696 (11.8%)
Anthrax vaccination	4589 (50.4%)	9887 (27.5%)	10,102 (32.1%)
Pesticide	3762 (41.3%)	13,666 (37.9%)	9659 (30.7%)
Positive screens for mental health conditions			
Anxiety	237 (2.6%)	555 (1.5%)	836 (2.7%)
Depression	320 (3.5%)	855 (2.4%)	1362 (4.3%)
Panic	135 (1.5%)	332 (0.9%)	428 (1.4%)
PTSD	465 (5.1%)	1125 (3.1%)	1685 (5.4%)
Deployments			
OEF/OIF (ever)	4621 (50.7%)	15,257 (42.4%)	17,362 (55.2%)

OEF, Operation Enduring Freedom; OIF, Operation Iraqi Freedom; PTSD, posttraumatic stress disorder; SW Asia, Southwest Asia.
*These are baseline measurements, unless otherwise noted.

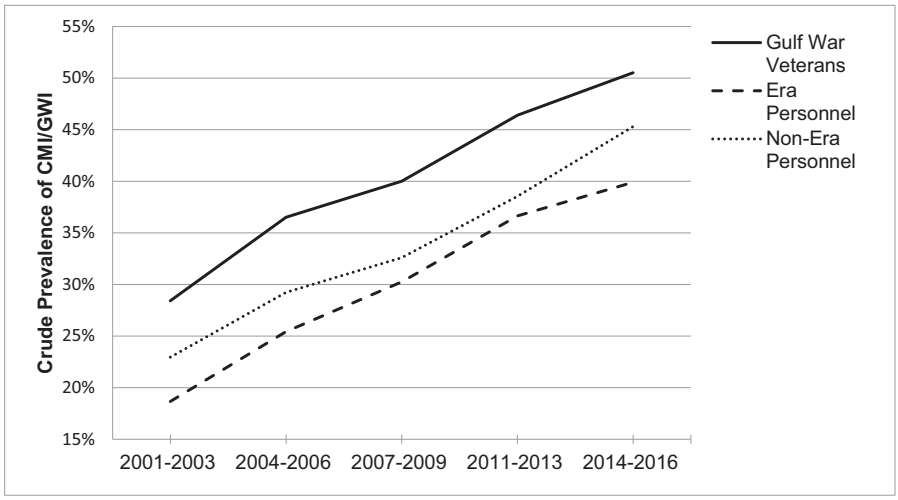

FIGURE 1. Crude prevalence of chronic multisymptom illness/Gulf War illness, Millennium Cohort Study, 2001 to 2016. Prevalence is the proportion of responding participants only.

or more time points following baseline (Gulf War veterans, 47.9%; era personnel, 58.2; non-era personnel, 61.5%). Alternatively, 49.7% of participants who did not screen positive for CMI/GWI at baseline and responded to all time points screened positive at one or more of the follow-up time points (Gulf War veterans, 53.8%; era personnel, 47.7%; non-era personnel, 51.7%).

In the unadjusted NLMMs, era personnel and non-era personnel had lower odds of screening positive for CMI/GWI than did Gulf War veterans (Table 2, Model 1). The odds of screening positive for CMI/GWI increased over time for all participants, but the odds among era personnel increased more rapidly than among Gulf War veterans over the study period (interaction $P = 0.001$). After adjusting for covariates, era personnel and non-era personnel remained at lower odds of screening positive for CMI than Gulf War veterans, although the association was attenuated by the inclusion of covariates (Table 2, Model 2). Similar to unadjusted models, the odds of screening positive for CMI/GWI increased more rapidly among era personnel than Gulf War veterans (interaction $P = 0.01$). Results from adjusted NLMMs stratified by sex and by race/ethnicity are presented in supplementary tables (Supplemental Digital Content 1 [http://links.lww.com/JOM/A644] and Supplemental Digital Content 2 [http://links.lww.com/JOM/A645], containing results by sex and by race/ethnicity, respectively). Although some differences in significance were found, the effect sizes of associations between modeled variables and CMI/GWI were comparable across stratified and nonstratified models.

In addition to Gulf War deployment status, OEF/OIF deployment was associated with greater odds of screening positive for CMI/GWI. Service in branches other than the Army, active duty service, and being in the younger age group at baseline were associated with higher odds of CMI/GWI. Alternatively, racial/ethnic minorities and women were at higher odds of CMI/GWI. Additionally, all self-reported exposures included in the model (ie, baseline and time-varying chemical exposures, pesticide exposure, anthrax vaccination) were associated with greater odds of CMI/GWI.

However, the strongest associations were observed between positive screens for mental health disorders and CMI/GWI with adjusted odds ratios between 6.39 (95% confidence interval [CI]: 5.66, 7.22) and 19.88 (95% CI: 17.58, 22.48). After excluding participants with mental health disorders at any time point (Table 2, Model 3), estimates for deployment status and the other covariates remained largely unchanged. After excluding participants with mental or physical health conditions at any time point (Table 2, Model 4), non-era personnel did not have lower odds of screening positive for CMI/GWI than did Gulf War veterans, and the rate of change in odds of era personnel were not significantly different from that of Gulf War veterans, in contrast to Models 1–3.

DISCUSSION

The current study has the longest follow-up and most assessments of any published study examining CMI/GWI among Gulf War veterans to date. Additionally, it is the first to examine CMI/GWI among the Gulf War and Gulf War era personnel enrolled in the Millennium Cohort Study. We observed a significant association between Gulf War deployment and CMI/GWI, a finding consistent with previous studies.[1,2,8,9,34] The crude prevalence between these Gulf War veterans and nondeployed era veterans differed by approximately 10% across the study period. Post hoc analyses observed that associations between Gulf War deployment and CMI/GWI remained consistent, even after excluding individuals with physical or mental health conditions. This suggests that although personnel with mental and physical conditions were more likely to screen positive for CMI/GWI, the increased prevalence of CMI/GWI among Gulf War veterans was not attributable to mental health conditions. All groups showed a substantial increase in the prevalence of CMI/GWI over time. A statistically significant interaction demonstrated the odds of CMI/GWI increased more rapidly among era personnel relative to Gulf War veterans, but the magnitude of this association was modest.

The large variance of the random intercept indicated a large degree of consistency of CMI/GWI within participants. However, many participants who screened positive for CMI/GWI at baseline screened negative at a future assessment (eg, 3442/6005 with five time points). Notably, Gulf War veterans with CMI/GWI at baseline were less likely to remit across the study period. Similarly, Gulf War veterans without CMI/GWI at baseline were more likely to screen positive later in the study period.

We also examined CMI/GWI in relation to sex and race/ethnicity because the paucity of such research has been noted in prior publications and government documents.[17,19] Results from the adjusted models indicated that female participants had higher odds of screening positive for CMI/GWI, which has been shown for other disorders characterized by diffuse symptoms like chronic fatigue syndrome, fibromyalgia, and certain autoimmune diseases.[35–39] White, non-Hispanic participants were less likely to screen positive for CMI/GWI than other racial or ethnic groups, although the magnitude of this association was small, albeit consistent. Stratified analyses indicated that among those of other races/ethnicities, era personnel did not have a significantly different odds of screening positive for CMI/GWI than Gulf War veterans. However, the

TABLE 2. Odds Ratios for Positive Screens for Chronic Multisymptom Illness/Gulf War Illness, Millennium Cohort Study, 2001 to 2016*

		Model 1 Unadjusted No Exclusions ($N = 76,575$) OR (95% CI)	Model 2 Adjusted No Exclusions ($N = 76,575$) OR (95% CI)	Model 3 Adjusted Excluding Mental Health Disorders ($N = 52,498$) OR (95% CI)	Model 4 Adjusted Excluding Mental Health and Physical Disorders ($N = 30,093$) OR (95% CI)
Deployment status	Gulf War veteran (reference)	1.00	1.00	1.00	1.00
	Era personnel	0.41 (0.38, 0.44)	0.76 (0.70, 0.83)	0.77 (0.69, 0.86)	0.74 (0.63, 0.88)
	Non-era personnel	0.59 (0.54, 0.64)	0.74 (0.68, 0.81)	0.79 (0.70, 0.89)	0.88 (0.75, 1.04)
Time (in 5-yr increments)	Time	1.90 (1.84, 1.96)	1.71 (1.65, 1.77)	1.71 (1.63, 1.79)	1.69 (1.57, 1.83)
	Time × era personnel	1.06 (1.02, 1.10)	1.05 (1.01, 1.09)	1.05 (1.00, 1.11)	1.02 (0.94, 1.11)
	Time × non-era personnel	1.04 (1.00, 1.08)	0.99 (0.95, 1.03)	0.97 (0.92, 1.02)	0.93 (0.86, 1.01)
Age (at study baseline)	0–34 (reference)		1.00	1.00	1.00
	35–44		1.03 (0.97, 1.08)	0.99 (0.93, 1.06)	0.85 (0.77, 0.93)
	>44		0.89 (0.83, 0.96)	0.85 (0.78, 0.93)	0.60 (0.51, 0.70)
Sex	Male (reference)		1.00	1.00	1.00
	Female		2.14 (2.04, 2.23)	1.73 (1.63, 1.83)	1.66 (1.52, 1.81)
Race/ethnicity	White non-Hispanic (reference)		1.00	1.00	1.00
	Black non-Hispanic		1.14 (1.08, 1.21)	1.30 (1.21, 1.39)	1.24 (1.12, 1.38)
	Other race/ethnicity		1.18 (1.11, 1.25)	1.20 (1.11, 1.30)	1.15 (1.04, 1.28)
Service branch	Army (reference)		1.00	1.00	1.00
	Navy/Coast Guard		0.53 (0.50, 0.56)	0.54 (0.51, 0.58)	0.51 (0.46, 0.56)
	Marine Corps		0.70 (0.64, 0.76)	0.79 (0.71, 0.89)	0.75 (0.65, 0.87)
	Air Force		0.46 (0.44, 0.49)	0.54 (0.51, 0.57)	0.49 (0.45, 0.54)
Component	Active duty (reference)		1.00	1.00	1.00
	Reserves/National Guard		0.64 (0.61, 0.67)	0.63 (0.60, 0.67)	0.60 (0.55, 0.64)
Baseline chemical exposure	No exposure (reference)		1.00	1.00	1.00
	Baseline exposure		1.81 (1.71, 1.91)	1.60 (1.49, 1.72)	1.40 (1.27, 1.56)
Time-varying chemical exposure	No exposure (reference)		1.00	1.00	1.00
	Time-varying exposure		1.21 (1.15, 1.27)	1.22 (1.15, 1.30)	1.35 (1.23, 1.49)
Pesticide exposure	No exposure (reference)		1.00	1.00	1.00
	Time-varying reported		1.53 (1.49, 1.58)	1.51 (1.45, 1.57)	1.47 (1.39, 1.55)
Anthrax vaccine	None reported at baseline (reference)		1.00	1.00	1.00
	Reported at baseline		1.13 (1.08, 1.18)	1.18 (1.12, 1.25)	1.16 (1.07, 1.25)
OEF/OIF deployment	Never deployed (reference)		1.00	1.00	1.00
	Previously deployed		1.46 (1.41, 1.51)	1.35 (1.29, 1.41)	1.34 (1.25, 1.43)
PTSD screen	Negative screen (reference)		1.00		
	Positive screen		15.20 (14.00, 16.50)		
Depression screen	Negative screen (reference)		1.00		
	Positive screen		19.88 (17.58, 22.48)		
Panic disorder screen	Negative screen (reference)		1.00		
	Positive screen		6.39 (5.66, 7.22)		
Anxiety screen	Negative screen (reference)		1.00		
	Positive screen		15.76 (13.39, 18.54)		
Random intercept variance†		5.26	3.51	3.57	3.33

CI, confidence interval; OEF, Operation Enduring Freedom; OIF, Operation Iraqi Freedom; OR, odds ratio; PTSD, posttraumatic stress disorder.
*Odds ratios were estimated using the NLMIXED procedure in SAS software, version 9.4.
†These results were not exponentiated.

magnitude of this association was comparable to those of other strata (ORs: 0.82 within service members of other race/ethnicities vs 0.79 within white, non-Hispanic participants and 0.65 within black, non-Hispanic participants). Other than this finding, no major differences were found between the nonstratified and stratified models.

The association between Gulf War deployment and CMI/GWI was attenuated after adjusting for covariates. This attenuation was likely due to confounding with mental health problems: psychiatric conditions are known outcomes of military deployment and CMI/GWI was associated with mental health.[40] The strong relationship between mental health and CMI/GWI found in the current study may be due to overlap between mental health symptoms and the Centers for criteria for CMI/GWI (eg, fatigue, cognitive problems, and emotional disruption). As in previous studies,[41] we observed that mental health conditions did not fully account for the higher prevalence of symptoms in deployed Gulf War veterans. More research is needed to better understand the underlying association between mental health conditions and CMI/GWI. However, given the large observed association between mental health and CMI/GWI in the current study, researchers should be wary about

possible confounding with mental health, particularly in epidemiological data sets that lack the detail of clinical interviews.

Several covariates were significantly associated with odds of screening positive for CMI/GWI and merit discussion. Army service was associated with higher odds of CMI/GWI. This finding has been observed in some prior studies[2,34] but has been non-significant in others.[3] Self-report of previous exposures was also associated with screening positive for CMI/GWI, although it should be noted that the assessment of these exposures in 2001 to 2003 may have been after the onset of symptoms. Active duty service in 2001 was associated with higher odds of CMI/GWI than Reserve/National Guard service in the current study.

The current study highlights how aging complicates the identification of cases of GWI because as personnel age, it becomes less clear whether symptoms are related to Gulf War deployment, aging, or other conditions. One counterintuitive finding was that older participants were at a decreased risk of CMI/GWI. This may be due to their increased history of serving in the military and having to maintain health/physical standards. However, the trend of increasing risk of CMI/GWI over time implies a positive association between aging and CMI/GWI. As can be seen in Fig. 1, by the end of the study period all groups had higher crude CMI/GWI prevalence than even Gulf War veterans at the outset of the study. Regarding other conditions, in a 2012 survey conducted by the Department of Veterans Affairs, 82% of Gulf War veterans and 78% of era personnel reported at least one chronic medical condition.[6] In the current sample, 69% of Gulf War veterans and 64% of era personnel were excluded from our most restrictive study population because of physical or psychiatric conditions at one or more of the time points. Presuming the expected trends continue, research on GWI will be increasingly complicated by natural aging and conditions with similar symptomatology to CMI/GWI. Future research identifying biological markers of GWI or more precise measures of GWI would be particularly useful in circumventing these challenges.

The current study had limitations that warrant acknowledgment. As noted earlier, the definition used for CMI/GWI was a modification of the Centers for Disease Control criteria similar to those used in previous studies.[3,5,18,34,42] We were not able to determine whether symptoms began after the Gulf War, assessed symptoms occurring over different timeframes (both shorter and longer) than the CDC criteria, and the Centers for Disease Control criteria have been criticized for being too liberal. However, the same symptoms were assessed on every survey, so we were able to apply a consistent definition of CMI/GWI. Additionally, the Millennium Cohort Study sampled participants serving in the military in 2000. Therefore, the sampling frame excluded individuals who separated from the military before 2000, including those precluded from continuing their military service due to health concerns following their Gulf War service. Therefore, the current analyses may underestimate the prevalence of CMI/GWI, although prior research indicates that the conclusions drawn from this sample mirror those of the larger population.[16]

Despite these limitations, notable strengths included that study participants completed up to five surveys across a 15-year period, and thus, the Millennium Cohort Study is one of the few data sources that can describe how prevalence of CMI/GWI changes over time. The use of multiple imputation and full information maximum likelihood ensured over 99% of participants were retained for analysis and mitigated potential biases from differential missingness or complete case analysis.[32,33] Furthermore, we were able to account for subsequent OEF/OIF deployment, which has been shown to be associated with CMI/GWI.[18,42]

In the current study, we observed a consistent elevated prevalence of CMI/GWI among Gulf War veterans from 2001 through 2016 in a large, representative military population. This elevated prevalence remained consistent, controlling for mental and physical health conditions. Our findings suggest that the increased burden of GWI in Gulf War veterans relative to nondeployed personnel is not resolving nor worsening as these Gulf War veterans age.

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14. ABSTRACT

Background: Chronic multisymptom illness/Gulf War illness (CMI/GWI) is the defining illness of the 1990-1991 Persian Gulf War. However, few studies have examined how the prevalence of CMI/GWI changes over time among Gulf War veterans compared to reference groups not deployed to the Gulf War.

Method: The current analysis examined prevalence of CMI/GWI across five time points collected between 2001 and 2016. Gulf War veterans were compared to non-deployed Gulf War era personnel and personnel not in service during the Gulf War. Non-linear mixed modeling was used to estimate the impact of time and Gulf War deployment on odds of CMI/GWI. An unexpectedly strong associations of CMI/GWI with mental health conditions prompted post hoc analyses among participants with no reported mental and physical health conditions.

Results: Gulf War veterans had the highest prevalence of CMI/GWI at baseline and this increased prevalence persisted across the study period. Odds of CMI/GWI increased over time and this increase was slightly more rapid for non-deployed Gulf War era personnel relative to Gulf War veterans. No substantive differences in the associations between CMI/GWI and Gulf War deployment were observed in models stratified by sex and race/ethnicity. Additionally, excluding participants with mental and physical health conditions did not substantively change the association between Gulf War deployment and CMI/GWI.

Conclusions: Prevalence of CMI/GWI increased substantially over time for all groups studied. Relative to reference groups, Gulf War veterans have an increased prevalence of CMI/GWI that persists across time.

15. SUBJECT TERMS

Chronic multisymptom illness, Gulf War, CMI/GWI, Millennium Cohort, veterans, service members

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