


Changes in Health Status in the Ft. Devens Gulf War Veterans Cohort: 1997-2017

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ABSTRACT: Gulf War veterans (GWVs) were exposed to numerous neurotoxicants during deployment. Upon returning home, many reported a multitude of symptoms including fatigue, pain, gastrointestinal and respiratory issues, and neurological, cognitive, and mood complaints, collectively termed “Gulf War Illness (GWI).” Now, nearly 30 years post-war, many GWVs continue to suffer from these symptoms, in addition to health concerns associated with normal aging. While most research on GWVs has been cross-sectional, it is important to evaluate the progression and onset of new GWI symptoms longitudinally. The current study investigated the health of GWVs 25+ years after the war by resurveying the Ft. Devens Cohort and comparing their current health to their health reported 15 to 20 years earlier. The sample consists of 317 GWVs (~54 years old at the latest survey, 38 women) who responded to both surveys (1997-1998 and 2013-2017). Multivariable regression analyses were used to assess changes in GWI symptomatology and prevalence of medical conditions. The rates of 12 of 25 health symptoms increased significantly from the prior 1997-1998 survey. Anxiety, numbness in extremities, depressed mood, and joint pain had the greatest increase in endorsement. The rates of 7 of 16 medical conditions increased significantly from the prior 1997-1998 survey. High blood pressure, diabetes, and cancer had the greatest increase in prevalence. In summary, this study demonstrates that both symptoms and physician-diagnosed medical conditions associated with GW deployment/exposure increased in prevalence. For GWVs, focus by providers on the treatment of cognitive and mental health issues as well as cardiovascular and cerebrovascular risk factors is warranted. Targeting symptom alleviation would help improve the quality of life in these veterans until treatments addressing the entire illness become available.

KEYWORDS: Gulf War, veterans, epidemiology, neurotoxicant exposures, health symptoms, longitudinal

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As Gulf War veterans age, it is of utmost importance to assess changes in their health over time. In our study, we found that the prevalence of 12 health symptoms increased significantly over a span of 20 years. The greatest increases in prevalence were found in include anxiety, numbness in extremities, depressed mood, and joint pain. In addition, the rates of 7 self-reported doctor diagnosed medical conditions increased

significantly over this period. The greatest increases were found in prevalence of high blood pressure, diabetes, and cancer. Provider focus on treatment of cognitive and mental health issues as well as cardiovascular and cerebrovascular risk factors (ie, high blood pressure and diabetes) in this population is recommended. Targeting symptom alleviation would help improve the quality of life in these veterans until treatments addressing GWI become available.

Introduction

Beginning shortly after the 1991 Gulf War (GW), concerns focused initially on health symptoms, whether there was a “GW Illness (GWI),” and on defining appropriate case criteria.^{1,2} Eventually, agreement was reached on using the term GWI to describe the chronic multisystem symptoms. The 2 criteria most

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often used in GW veteran research are the Center for Disease Control (CDC)'s Chronic Multisymptom Illness (CMI) and the Kansas Gulf War Illness Criteria, both of which were based on factor-analytic studies of symptoms experienced by GW veterans shortly after war.^{3,4} Recently, there has been a shift to track progression of this illness and its constituent symptoms over time. The Ft. Devens Cohort (FDC) of GW veterans, originally established in 1991, is ideal for studying GWI progression. The FDC began with a baseline survey in 1991 designed to assess psychological well-being and health functioning upon returning from deployment. Follow-up surveys (1992, 1997-1998, and 2013-2017) also assessed neurotoxicant exposures as well as a variety of self-reported health outcomes (ie, symptoms, medical conditions, functional status).

The FDC surveys and in-person neurocognitive and imaging studies provided initial documentation of health symptoms, cognitive decrements, differences in structural neuroimaging outcomes including lower white matter volumes, rates (60% in 1997-1998) and risk factors for GWI, the comorbidity of symptoms with a history of mTBI (mild traumatic brain injury), and rates of chronic medical conditions compared to the general population.⁵⁻¹⁰

The current state of GW veterans' health, more than 20 years post deployment, has been documented in multiple cross-sectional studies.⁹⁻¹⁵ Rates of health conditions are greater in GW veterans than in various comparison groups (ie, GW-era nondeployed veterans, the general population, and those who do not meet criteria for GWI). These studies, overall, indicate that GW deployed veterans have higher rates of health symptoms, chronic medical conditions, higher rates of GWI in association with mTBI, greater mood dysfunction, and poorer physical functioning.^{9,10,12-16} While research has established a pattern of GW veterans' symptoms, less is known about how these symptoms change or evolve over time as these veterans age into midlife.

Few studies have longitudinally assessed health trajectories in GW veterans.^{11,17-19} Research from an Australian cohort of GW veterans compared groups of deployed versus non-deployed GW veterans in 2000-2003 and again in 2011-2012 and found new onset of sleep apnea, musculoskeletal, psychological, and cardiovascular conditions in those deployed.¹⁷ Additionally, these researchers have found that the overall prevalence of symptoms among GW veterans was higher than 10 years prior, and even higher than in the comparison group of non-deployed GW-era veterans.¹⁸ Similarly, a study utilizing the National Health Survey of Gulf War Era Veterans and Their Families reported that at a 10-year follow-up, deployed GW veterans were more likely to report persistent health problems and new onset of adverse health and chronic diseases than non-deployed GW-era veterans.¹⁹ Recently, the Millennium Cohort Study evaluated CMI status over a 15-year period in GW veterans and era-personnel.¹¹ GW deployed veterans exhibited the highest prevalence of cases at each occasion, compared to era and non-era personnel. However, in the veteran comparison groups (era and non-era personnel), these symptoms were also increased over

time, and at a faster rate than in the GW-deployed veterans, which begs the question whether increases in some of these symptoms (ie, sleep dysregulation and joint pain) result from what could be expected with "normal aging" rather than from GW deployment itself. Therefore, as time goes on, this particular criteria and set of symptoms established over 20 years ago, may not distinguish between symptoms associated with deployment and symptoms associated with aging.

We aim to assess longitudinal change in health status in a group of deployed GW veterans to determine which symptoms and medical conditions have changed over time (either decreased or increased in prevalence), and which symptoms remained unchanged, in order to inform future revisions to the GWI criteria, among this aging group of veterans. The current study investigated the health of GW veterans 25+ years after the war, by resurveying the FDC and comparing their current health to their health 15 to 20 years prior (1997-1998).

Methods

Study population

The full cohort has been described in previous papers.^{5,6,8-10,16,20} In summary, the Ft. Devens Cohort (FDC) is the longest running cohort study of GW veterans, with participants initially assessed in 1991 within 5 days of their return to the US from deployment. The initial survey included questions regarding trauma and behavioral syndromes and was later revised to include questions assessing neurotoxicant exposures, physical symptoms, and physician reports of medical conditions. 466 GW veterans responded to the most recent ODS (Operation Desert Storm) Reunion Survey of 2013-2017. Of the 466 GWVs, 317 (68%) had responded to the prior survey (1997-1998). All participants gave informed consent at each occasion. Institutional review boards at VA Boston Healthcare System and Boston University provided approval.

Health symptom checklist

Adapted from Bartone et al, the health symptom checklist asks participants to report whether or not they have experienced specific health symptoms.²¹ The 1997-1998 resurvey included a 52-item Expanded Health Checklist, which asks participants whether or not the symptom has been bothersome for the past 4 weeks (yes or no).^{5,22} The 2013-2017 resurvey included a 32-item Health Symptom Checklist which asked participants whether or not they experienced the symptom (yes or no) within the past 30 days. A total of 24 health symptoms were assessed at both occasions.

Medical conditions

In the 1997-1998 survey, participants were asked whether or not they had ever had 35 different medical conditions. In the 2013-2017 resurvey, participants were asked whether or not they had ever been doctor-diagnosed or self-diagnosed with 37

Table 1. Demographics.

DEMOGRAPHIC/CHARACTERISTIC	1997-1998 SURVEY FULL SAMPLE (N = 1291) N (%) MEAN ± SD (RANGE)	STUDY SAMPLE (N = 317)
Age at Baseline Survey, years	32.0 ± 9.0 (19-65)	32.3 ± 8.4 (19-54)
Age at 1997-1998 Survey, years	37.8 ± 9.0 (24.5-71.1)	37.9 ± 8.4 (25.1-59.5)
Age at 2013-2017 Survey, years		54.2 ± 8.5 (41-78)
Male, n (%)	1160 (89.9%)	279 (88.0%)
Caucasian, n (%)*	1147 (88.8%)	294 (92.7%)
Active Duty, n (%) (vs Reserve, National Guard)	298 (23.1%)	59 (18.6%)
Mississippi PTSD scale-score	61.7 ± 13.3 (36-120)	62.1 ± 14.4 (37-120)
Clinical cutoff on Mississippi scale-score (>89), n (%)	62 (4.8%)	19 (6.0%)

* $P < .05$.

different medical conditions. For this study, we employed a conservative approach, and only included doctor-diagnosed responses from the 2013-2017 survey. A total of 16 such medical conditions were assessed at both occasions.

Criteria for Gulf War Illness

CMI is defined as the presence of persistent symptoms over 6 months in 2 out of 3 domains: fatigue, musculoskeletal, cognitive/mood.³ For purposes of this longitudinal evaluation, the symptoms in the CMI criteria included: fatigue, joint pain, and mood and cognitive domain (depressed mood, difficulty concentrating, anxiety, and restless sleep). Based on participants' responses to items within these domains, they were classified as meeting or not meeting CMI criteria.

The Kansas GWI inclusionary symptom criteria include 32 self-reported symptoms that have been experienced over the past 6 months. Participants were asked whether they have experienced each symptom (yes/no), to rate the problem (mild/moderate/severe), and state whether the symptom started before or during/after the Gulf deployment. The 32 items are categorized into 6 domains: fatigue, pain, neurological/cognitive/mood, skin, gastrointestinal, and respiratory.⁴ Because 2 different Health Symptom Checklists were used in the FDC surveys, a modified Kansas inclusionary criteria was used that included the symptoms that were consistently asked at both surveys. This included 16 symptoms experienced over the past month, categorized into the 6 domains. The symptoms included: fatigue, trouble sleeping, restless sleep, joint pain, headaches, dizziness, numbness, muscle twitching, difficulty concentrating, forgetfulness, depressed mood, skin rashes, diarrhea, nausea, stomach cramping, and difficulty breathing.

Statistical analyses

Multivariable regression analyses using a generalized estimating equation were used for the analyses conducted in this paper.

Repeated logistic regressions were used to assess changes in the proportions of GWI, individual symptoms, and medical conditions over time. All analyses included age in years and Post Traumatic Stress Disorder (PTSD) status (yes = score ≥ 89) on the Mississippi Combat PTSD Scale) at the baseline 1991 survey as covariates, to adjust for the effects of stress and timing of exposure on all health outcomes assessed. All data were adjusted for multiple comparisons using Bonferroni correction; two-sided P values of $\leq .001$ were considered significant.

Results

Demographics

A total of 317 veterans completed both the 1997-1998 and the 2013-2017 surveys. The mean age at time of 2013-2017 survey was 54.2 (SD = 8.5, range 41-78) years, and most veterans were male and Caucasian. Comparison of non-responders to responders on the 2013-2017 survey found that responders were more likely to be Caucasian and less likely to have been on Active Duty during the war. Most importantly, non-responders and responders did not significantly differ in clinical case status (CMI vs no-CMI) or number of symptoms endorsed at the 1997-1998 survey (see Supplemental Table 1). Demographics are summarized in Table 1.

Rates of health symptoms

The prevalence of 12 of the 25 health symptoms was significantly higher compared to the prior 1997-1998 survey. Anxiety, numbness in extremities, depressed mood, and joint pain had the greatest increase in endorsement. Common cold or flu was the only symptom in which the prevalence significantly decreased over time. The rates of health symptoms are summarized in Table 2.

Rates of medical conditions

The prevalence of 7 of the 16 medical conditions were significantly higher compared to the prior 1997-1998 survey. High

Table 2. Symptom analyses.

SYMPTOM	1997-1998 SURVEY N (%)	2013-2017 SURVEY N (%)	DIFFERENCE IN PREVALENCE (%)	OR [CI]	P-VALUE
Fatigue Symptoms					
Fatigue or easily tired/overly tired or lack of energy	170 (53.6)	199 (62.8)	9.2	1.486 [1.155-1.913]	.002
Restless or unsatisfying sleep/restless sleep	170 (53.6)	228 (71.9)	18.3	2.319 [1.747-3.078]	.000
Mood & Cognition Symptoms					
Frequent periods of feeling depressed/ depressed mood	102 (32.2)	172 (54.3)	22.1	2.608 [1.957-3.474]	.000
Difficulty Concentrating	124 (39.1)	174 (54.9)	15.8	1.987 [1.508-2.617]	.000
Crying Easily	47 (14.8)	64 (20.2)	5.4	1.462 [1.002-2.132]	.049
Frequent periods of anxiety or nervousness/ nervousness, tenseness, or anxiousness	95 (30.0)	190 (59.9)	29.9	3.758 [2.800-5.044]	.000
Forgetfulness	176 (55.5)	190 (59.9)	4.4	1.245 [0.949-1.632]	.113
Confusion	59 (18.6)	89 (28.1)	9.5	1.817 [1.312-2.517]	.000
Difficulty Learning New Material	64 (20.2)	93 (29.3)	9.1	1.684 [1.223-2.318]	.001
Neurological OR Physical Symptoms					
Joint Pain	167 (52.7)	233 (73.5)	20.8	2.696 [2.052-3.542]	.000
Common Cold or Flu	112 (35.3)	80 (25.2)	-10.1	0.598 [0.438-0.816]	.000
Dizziness or feeling lightheaded/faintness or dizziness	88 (27.8)	77 (24.3)	-3.5	0.856 [0.630-1.164]	.321
Hands sweating and feeling clammy	41 (12.9)	39 (12.3)	-0.6	0.959 [0.678-1.358]	.815
Headaches	142 (44.8)	147 (46.4)	1.6	1.083 [0.838-1.401]	.541
Muscle Twitching/Trembling	98 (30.9)	145 (45.7)	14.8	1.954 [1.518-2.515]	.000
Racing heart/rapid heart beat	39 (12.3)	87 (27.4)	15.1	2.993 [2.046-4.378]	.000
Skin Rash	93 (29.3)	96 (30.3)	1.0	1.070 [0.792-1.444]	.660
Nausea	95 (30.0)	106 (33.4)	3.4	1.206 [0.902-1.611]	.206
Stomach cramping or excessive gas	129 (40.7)	137 (43.2)	2.5	1.098 [0.8917-1.476]	.533
Rapid Breathing	33 (10.4)	45 (14.2)	3.8	1.509 [0.977-2.331]	.064
Irregular heart beats or "heart flutters"/ irregular heart rate	38 (12.0)	48 (15.1)	3.1	1.371 [0.932-2.018]	.109
Diarrhea or constipation/diarrhea	108 (34.1)	110 (34.7)	0.6	1.051 [0.796-1.388]	.725
Numbness in arms or legs/numbness or tingling in parts of the body	84 (26.5)	167 (52.7)	26.2	3.234 [2.398-4.361]	.000
Backaches	154 (48.6)	210 (66.2)	17.6	2.077 [1.596-2.703]	.000
Difficulty Breathing/Catching your breath	79 (24.9)	106 (33.4)	8.5	1.582 [1.180-2.121]	.002

1997-1998 Survey wording/2013-2017 Survey wording.
Analyses included Baseline Age and Baseline PTSD Status as covariates.

blood pressure, diabetes, and cancer had the greatest increase in prevalence. The prevalence of permanent stiffness in extremities and repeated trouble with neck, back, or spine were the only medical conditions that significantly decreased over time. The rates of medical conditions are summarized in Table 3.

Rates of Gulf War Illness (CMI and Kansas criteria)

The rate of CMI was 78.9%, a significant increase compared to the prior 1997-1998 survey (57.7%). The rate of GWI based on the Kansas criteria was 65.9%, a significant increase from

Table 3. Medical condition analyses.

MEDICAL CONDITION	1997-1998 SURVEY N (%)	2013-2017 SURVEY N (%)	DIFFERENCE IN PREVALENCE (%)	OR [CI]	P-VALUE
Asthma	36 (11.4)	30 (9.5)	-1.9	1.335 [0.894-1.993]	.158
Respiratory allergies or hayfever/respiratory allergies or sinus problems	135 (42.6)	94 (29.7)	-12.9	0.954 [0.703-1.293]	.760
Chronic respiratory disease such as emphysema, chronic bronchitis, or brown lung/chronic lung disease such as chronic bronchitis	32 (10.1)	29 (9.1)	-1.0	1.461 [0.941-2.270]	.091
Arthritis, rheumatism, or gout	82 (25.9)	86 (27.1)	1.2	1.900 [1.343-2.688]	.000
High sugar or diabetes	6 (1.9)	53 (16.7)	14.8	16.837 [7.396-38.330]	.000
High blood pressure or hypertension	54 (17.0)	150 (47.3)	30.3	5.380 [3.784-7.649]	.000
Stroke	3 (0.9)	11 (3.5)	2.6	7.862 [2.801-22.071]	.000
Any other heart attack trouble or condition affecting blood circulation/blood condition affecting circulation blocked arteries	14 (4.4)	28 (8.8)	4.4	4.147 [2.163-7.951]	.000
A myocardial infarction or any other heart attack/heart attack or myocardial infarction	3 (0.9)	19 (6.0)	5.1	12.254 [4.359-34.448]	.000
Cancer of any kind	7 (2.2)	32 (10.1)	7.9	8.228 [3.975-17.032]	.000
A chronic rash or skin condition such as eczema, psoriasis, cholracne, or dermatitis	92 (29.0)	60 (18.9)	-10.1	0.957 [0.676-1.356]	.804
Deafness in one of both ears, or any other serious trouble with hearing	64 (20.2)	52 (16.4)	-3.8	1.390 [0.941-2.054]	.098
Repeated seizures, convulsions, blackouts, or fainting spells/ Epilepsy	17 (5.4)	4 (1.3)	-4.1	0.357 [0.124-1.027]	.056
Repeated trouble with your neck, back, or spine	143 (45.1)	130 (41.0)	-4.1	1.608 [1.206-2.143]	.001
Permanent stiffness or any deformity of your body parts (such as your foot, back, or arm)/ permanent stiffness in limbs	51 (16.1)	10 (3.2)	-12.9	0.272 [0.130-0.569]	.001
Head injury, concussion, or period of being knocked unconscious/traumatic brain injury	46 (14.5)	20 (6.3)	8.2	0.663 [0.407-1.080]	.099

1997-1998 Survey wording/2013-2017 Survey wording.
Analyses included Baseline Age and Baseline PTSD Status as covariates.

Table 4. Gulf War Illness analyses.

	1997-1998 SURVEY N (%)	2013-2017 SURVEY N (%)	DIFFERENCE IN PREVALENCE (%)	OR [CI]	P-VALUE
Met CMI Criteria	183 (57.7)	250 (78.9)	21.2	2.725 [2.053-3.616]	.000
Met Kansas Criteria	142 (44.8)	209 (65.9)	21.1	2.468 [1.877-3.245]	.000

Analysis controlled for baseline age and baseline PTSD status.

the prior 1997-1998 survey (44.8%). Rates of GWI are summarized in Table 4.

Discussion

Over the 20 years between 1997 and 2017, a significant increase in prevalence was observed for 12 symptoms, all which fall into 2 of the 3 domains of the CDC's CMI criteria, fatigue, and

mood/cognition. Concerningly, reporting of both anxiety and depression symptoms showed increases exceeding 20% in endorsement. Our group has found that crying easily, depression, and trouble sleeping have been associated with exposure to PB pills, tent heaters, and the Khamisiyah weapons depot demolition.¹⁶ PB is an acetylcholinesterase inhibitor, which causes acetylcholine to accumulate in synapses, resulting in the

overstimulation of cholinergic receptors leading to adverse neurological consequences, such as cognitive, mood, and sleep dysfunction.^{23,24} Therefore, increased regular screening of GW veterans for mental health issues is recommended, as their potential exposures during GW deployment could increase the likelihood of developing or maintaining symptoms, including diminished sleep and fatigue.²⁵

Additionally, 7 of the doctor-diagnosed medical conditions increased significantly across the 20-year period. In a previous FDC study, the prevalence of these conditions are not only higher than in the general non-veteran population, but also they appear to be occurring earlier (in the fifth decade) compared to the sixth and seventh decades seen in the general population, perhaps because of their association with GW-specific neurotoxins.¹⁰ High blood pressure and diabetes, both showing increases over 15% in the current study, are of particular note, as these 2 conditions are risk factors for later cardiovascular and cerebrovascular disease, as well as accelerated brain aging and an increased risk for dementia.²⁶⁻³⁰ Of note, 2 medical conditions, repeated trouble with your neck, back, or spine and permanent stiffness in limbs, significantly decreased in prevalence over time (4% and 12% decrease, respectively). While not statistically significant, substantial decreases in prevalence of respiratory allergies and skin rash (13% and 10% decreases, respectively) were also observed. These results suggest that these symptoms have been able to be targeted and treated or have resolved over time, however further research regarding specific treatments of these symptoms is warranted.

The prevalence of GWI (according to both the CDC's CMI and the Kansas criteria) increased significantly over time. These findings are similar to those reported by Porter and colleagues⁹ who observed CMI increases over a 15-year period in GWV, and that GWV had a higher prevalence rate than did era or non-era personnel at all occasions. Interestingly, all veteran groups assessed in that study (GW, GW-era, and non-era) showed significant increases in rates of CMI over time. This suggests that CMI criteria may be particularly sensitive to normal changes in symptomatology that occur with age. Future research, utilizing age-matched healthy control groups, should investigate how aging affects different symptomatology and revise the current criteria to better distinguish between increases in symptoms over time that are due to GW exposures versus normal aging, as most GW veterans are now entering their 50s and 60s.

The current study has limitations that warrant consideration. First, the sample size is relatively small, due to the 20-year interval between surveys. Further, the FDC is comprised primarily of Army Reservists and National Guard, with a higher than average percentage of men, Caucasians, and those with higher postsecondary levels of education. Therefore, this study sample may not be representative of the larger GW veteran population. Second, it was beyond the scope of this study to review the relationship between deployment exposures and

changes in symptomatology. We recommend further research assess the impact of individual exposures on longitudinal progression of GWI symptomatology. Next, the GWI analyses included modified criteria in which the duration of symptoms was over 1 month instead of the 6 months required for both the CDC's CMI and the Kansas GWI criteria. This difference could potentially lead to an under-reporting of symptoms and illness rates. Lastly, within the FDC study, no comparison group of non-GWV or GWV era veterans was available.

In summary, this study has demonstrated that both symptomatology and doctor-diagnosed medical conditions are increasing in GW veterans. While treatments focusing on reducing the chronic neuroinflammatory and neuroimmune responses are currently being investigated in clinical trials (Prednisone, Co-Enzyme Q10 [CoQ10], and dietary supplements³¹⁻³³), focus on the treatment of cognitive and mental health issues as well as cardiovascular and cerebrovascular risk factors (ie, high blood pressure and diabetes) is warranted. Targeting symptom alleviation would help improve the quality of life in these veterans until treatments addressing the entire illness become available.

Author Contributions

Conceptualization, MK and KS; Methodology, CGZ, MK, TH and KS; Formal Analysis, CGZ and TH; Data Curation, CGZ; Writing—Original Draft Preparation, CGZ and MK; Writing—Review and Editing, CGZ, MHK, TH, AS, SPP, CMG and KS; Supervision, MK and KS;

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Supplemental Material

Supplemental material for this article is available online.

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