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TITLE: Examination of Neuroimaging, Cognitive Functioning, and Plasma Markers in a Longitudinal Cohort of Gulf War Deployed Veterans: The Fort Devens Cohort

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14. ABSTRACT This study aims to conduct follow-up longitudinal cognitive evaluations on a sub-sample of 100 Time 3 Ft. Devens Cohort veterans, most of whom were last evaluated in-person for cognitive functioning and with neuroimaging in the mid-1990s, to compare objective measurement of reported decline; and to determine cross-sectional blood and neuroimaging biomarkers (blood and structural volumetrics will also include longitudinal analyses) at 25+ years post deployment to the Gulf region, that may be consistent with cognitive outcomes and presumed pathobiological mechanisms (oxidative stress, ROS) of GWI. These data will evaluate the utility of previously unavailable blood and neuroimaging markers of oxidative stress, to devise a new diagnostic test for GWI in subgroups of GW veterans (TBI and OP exposed), and to provide a potential objective biomarker of treatment efficacy in clinical trials.					
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1. Introduction:

Background and Purpose: One of the earliest and longest running studies of Gulf War veteran's (GWV) health was conducted with the Ft. Devens, MA army cohort (FDC) from the VA Boston Healthcare System (VABHS). The cohort was first surveyed within 5 days of their return and multiple cross sectional survey and in-person data provided some of the earliest cognitive, neuroimaging and environmental exposure outcomes since the 1990s. These findings included early documentation of the most common health symptoms, cognitive decrements in environmentally exposed GWV, and differences in structural neuroimaging, including lower white matter volumes (Proctor et al., 1998; White et al., 2001; Heaton et al., 2007). The FDC has been followed with longitudinal health surveys, and we are completing a resurvey and biomarker study in which 50% of prior surveyed individuals have responded. This most recent resurvey is providing valuable information pertaining to longitudinal health symptoms and the trajectory of health symptoms over time. Additionally, we are able to use this longitudinal self-report data to monitor CDC and Kansas GWI criteria over time. However, these data are self-report and only a small portion of individuals are being seen for cross-sectional analyses of proteins in the blood (GW100046). Since subsamples of the FDC took part in cognitive and neuroimaging studies between 1994 and 1996, we are now extending these studies by reassessing neurocognitive and neuroimaging status to more fully capitalize on the longitudinal nature of this cohort and the recent findings of oxidative stress markers in GWI.

Scope: The overarching objective of this work study is to build on previous longitudinal studies to gain a better understanding of Gulf War Illness and to devise targeted treatment strategies. This study aims to conduct follow-up longitudinal cognitive evaluations on a sub-sample of 100 Time 3 FDC veterans, most of whom were last evaluated in-person for cognitive functioning and with neuroimaging in the mid-1990s, to compare objective measurement of reported decline; and to determine cross-sectional blood and neuroimaging biomarkers (blood and structural volumetrics will also include longitudinal analyses) at 25+ years post deployment to the Gulf region, that may be consistent with cognitive outcomes and presumed pathobiological mechanisms (oxidative stress, ROS) of GWI. These data will evaluate the utility of previously unavailable blood and neuroimaging markers of oxidative stress, to devise a new diagnostic test for GWI in subgroups of GWV (TBI and OP exposed), and to provide a potential objective biomarker of treatment efficacy in clinical trials.

2. Key Words: Gulf War Illness, central nervous system, biomarkers, glutathione, MR Spectroscopy, Cognition, oxidative stress

3. Accomplishments:

- What were the major goals of the project?
 - The major goals of the project as stated in the approved SOW for year 2 is listed in the table below. Specifically, during year 2, the primary goals were to screen, recruit, and complete longitudinal assessments of FDC veterans, as well as data cleaning and MRI/MRS post-image processing. Milestones/target dates for important activities or phases of these dates are listed in the table and actual completion dates are listed below.

Tasks	Timeline
Task 1. Obtain necessary authorization prior to initiation of human subjects	Months
1a. Obtain Institutional Review Board (IRB) approval for research sites at VA Boston (VABHS), Boston University Medical Campus (BUMC), and Nova University (NSU) for protocols	1-4
1b. Obtain DOD Human subjects Research Protections Office (HRPO) approvals	5-7
1c. Complete hiring of necessary staff and ensure all mandatory IRB research related trainings are completed by all staff members	1-8
Task 2. Preparation and Training for Clinical Study Procedures	Months
2a. Obtain Time 3 cognitive and MRI neuroimaging data for longitudinal analyses and participant contact information from the Ft. Devens cohort (FDC) study through the share drive at VABHS.	1-2
2b. Develop manuals for neuropsychological testing protocol, structural MRI and Magnetic Resonance Spectroscopy (MRS) of glutathione oxidative stress marker (GSH) protocols and blood specimen collection protocols for several oxidative stress markers.	1-6
2c. Train researchers and staff on cognitive, neuroimaging and phlebotomy protocols and quality control measures.	6-9
Task 3. Screening, recruitment and longitudinal assessment of FDC Gulf War veterans	Months
3a. Obtain informed consent from potentially eligible GW veterans	9-36
3b. Assess 150 FDC veterans and obtain demographics, medical history, self-report questionnaires and neuropsychological testing for planned longitudinal analyses.	9-36
3c. Perform brain GSH MR Spectroscopy and structural MRI imaging and blood draw for oxidative stress markers from 100 Gulf War veterans for cross-sectional study.	9-36
Task. 4. Data Cleaning and MRI/MRS image Post-processing	Months
4a. Post-process MRI/MRS neuroimaging data for data analysis.	18-40
4b. Score neuropsychological test data and upload summary data to VA Share drive for entry, cleaning and analyses.	18-38
4c. Ship blood samples to Nova University for analysis of GSH oxidative stress markers including (HNE, 8-iso-PGF2 α).	18-36
4d. Perform analyses of plasma oxidative stress markers.	18-40
Task. 5. Merge Data and Perform Interim Data analyses	Months
5a. Data entry of all questionnaires, cognitive evaluations and quality control measures will be ongoing.	18-42

5b. Interim Statistical analyses of data obtained from cognitive evaluations, blood markers, neuroimaging and questionnaire data will be performed periodically.	18-42
5c. Annual reports of progress will be written.	18-36
Task 6. Perform Final Data Analysis and Prepare Manuscripts for Publication (months 42-48)	Months
6a. Perform cross-sectional analyses comparing central and peripheral markers of oxidative stress in brain MRS (GSH) and plasma (HNE, 8-iso-PGF2 α) compared with cognitive functioning and health symptom report in FDC veterans.	42-45
6b. Perform longitudinal analyses of structural MRI imaging, cognitive, and health symptom outcomes from Time 3 and Time 6 in FDC veterans.	42-46
6c. Write final study report	47-48
6d. Present findings at scientific meetings	42-48
6e. Prepare manuscripts for submission for cross-sectional and longitudinal studies.	42-48

- What was accomplished under these goals?
- Task 1:
 - We obtained necessary authorization prior to initiation of study (IRB approvals, DoD HRPO approvals).
 - We completed the hiring of staff and ensured that all mandatory trainings are now completed.
- Task 2:
 - We have obtained Time 3 cognitive and MRI neuroimaging data for the longitudinal analysis and participant contact information from the Ft. Devens cohort (FDC) study and Treatment Seeking Cohort (TSC) through the share drive at VA Boston Health Care System (VABHS).
 - We developed manuals for the neuropsychological testing protocol as well as structural MRI and MRS of glutathione oxidative stress marker (GSH) protocols and blood specimen collection protocols for oxidative stress markers.
 - We have trained the researchers and staff on cognitive neuroimaging and phlebotomy protocols and questionnaires.
- Task 3:
 - We have obtained informed consent and longitudinal assessment of 21 FDC veterans.
- Task 4:
 - The neuropsychological test data was scored and uploaded to the VA share drive for the 21 subjects who have complete assessments.
 - Two shipment of blood samples has been sent to the NOVA university for analysis, for the 21 subjects who have complete assessments.

- How were the results disseminated to communities of interest?
 - Three Ft. Devens Cohort longitudinal manuscripts have been published.
 - Zundel, C. G., Kregel, M. H., Heeren, T., Yee, M. K., Grasso, C. M., Janulewicz Lloyd, P. A., Coughlin, S. S., & Sullivan, K. (2019). Rates of Chronic Medical Conditions in 1991 Gulf War Veterans Compared to the General Population. *International journal of environmental research and public health*, 16(6), 949.
 - Zundel, C. G., Heeren, T., Grasso, C. M., Spiro, A., 3rd, Proctor, S. P., Sullivan, K., & Kregel, M. (2020). Changes in Health Status in the Ft. Devens Gulf War Veterans Cohort: 1997-2017. *Neuroscience insights*, 15, 2633105520952675. <https://doi.org/10.1177/2633105520952675>
 - Yee, M. K., Zundel, C. G., Maule, A. L., Heeren, T., Proctor, S. P., Sullivan, K. A., & Kregel, M. H. (2020). Longitudinal Assessment of Health Symptoms in Relation to Neurotoxicant Exposures in 1991 Gulf War Veterans: The Ft. Devens Cohort. *Journal of occupational and environmental medicine*, 62(9), 663–668. <https://doi.org/10.1097/JOM.0000000000001910>
- What do you plan to do during the next reporting period to accomplish the goals?
 - As per COVID 19 guidelines, we have been unable to see participants in person. Therefore, we plan to conduct neuropsychological testing via-telehealth using pre-established assessment tools considered to be reliable and valid for clinical and research use. We are currently obtaining IRB approval from VA Boston to conduct such measures.
 - We plan to recruit 50 more study participants by the next reporting period and present the preliminary results at appropriate National and International meetings.
 - We plan to submit other manuscripts of preliminary results from the GWI case-control medical conditions, and trajectory of symptom analyses and the cognitive, MR Spectroscopy glutathione brain imaging and blood oxidative stress markers during the next reporting period.

4. Impact:

- What was the impact on the development of the principal discipline(s) of the project?
 - Gulf War Illness (GWI) can have a dramatic impact on the lives and well-being of GW veterans who experience chronic and often debilitating symptoms. The results of this study will help address a critical knowledge gap regarding the nature of continued cognitive symptoms and other chronic health effects of GWI.
 - This project will distinguish itself by examining the nature and trajectory of symptoms by adding objective markers of longitudinal neurocognitive decline, traditional structural MRI imaging and cutting-edge MRS brain imaging techniques of oxidative stress markers (glutathione) compared with plasma oxidative stress markers. When combined with the prior rich 20+ year longitudinal data from the Ft. Devens and Treatment-seeking cohorts, this provides an unprecedented opportunity to further characterize objective biomarkers of illness in a well-characterized cohort of GW veterans.

- Defects in modulation of oxidative stress may well predispose individuals to damage from reactive oxygen species (ROS) from environmental exposures, TBI or other sources that could potentially be used as a diagnostic marker of illness.
- This analysis also offers an opportunity to determine whether a given therapeutic strategy such as antioxidants including co-enzyme Q-10 or quercetin supplementation in subgroups with low brain glutathione levels may be chosen as a treatment option to improve a susceptible individual's ability to modulate oxidative stress, reduce accelerated aging and improve the symptoms of GWI utilizing a personalized medicine approach.
- What was the impact on other disciplines?
 - A major advantage of work with the Ft. Devens cohort showing mTBI to be related to rates of GWI in our two most recent papers suggests that the results of this study with oxidative stress glutathione markers may be relevant not only to GWI but also to other veteran and civilian groups with mTBI and neurotoxicant exposures as part of a multiple-hit hypothesis.
 - Blood and neuroimaging-based biomarkers of GWI provide an effective way to enhance its management:
 - It can be used as a diagnostic and prognostic tool with the ability to provide information about rate of disease progression.
 - It would help in identification of novel and effective treatments for multiple disorders and environmental exposure groups (i.e. pesticides, nerve agents).
 - It could be used for monitoring therapeutic efficacy for multiple disorders
 - It could provide a cost-effective option for recruitment into clinical trials
- What was the impact on technology transfer?
 - The biomarker that we hope to develop will be cost effective, available, and do not need expensive technicians if we can identify an oxidative stress biomarker in blood that be correlated with MR spectroscopy brain imaging markers that we will also collect and analyze.
- What was the impact on society beyond science and technology?
 - Our blood and brain imaging biomarkers should improve the quality of life for the veterans of the GW who have GW illness because:
 - Our biomarkers can provide objective evidence thereby validating the chronic health symptoms of ill GW veterans.
 - Our biomarkers should lead to studies to develop treatment of brain injury that may lead to improvement of their clinical condition.

5. Changes for approach and reasons for change:

- Changes: Tele-health neuropsychological measures per COVID-19 restrictions

Changes that had significant impact on expenditures

- None

- Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents:
 - Significant changes in use or care of human subjects: None
 - Significant changes in use or care of vertebrate animals: None
 - Significant changes in use of biohazards, and/or select agents: None

6. Products:

- **Publications, conference papers, and presentations**
 - **Journal Publications**
 - Zundel, C.G., Krengel, M. H., Yee, M.K., Grasso, C.M., Januelwicz Lloyd, P., Sullivan, K.A. Rates of Chronic Medical Conditions in 1991 Gulf War Veterans Compared to the General Population. International Journal of Environmental Research and Public Health
 - Yee MK, Janulewicz PA, Seichepine DR, Sullivan KA, Proctor SP, Krengel MH. Multiple Mild Traumatic Brain Injuries Are Associated with Increased Rates of Health Symptoms and Gulf War Illness in a Cohort of 1990-1991 Gulf War Veterans. Brain Sci. 2017 Jul 9;7(7). pii: E79. doi: 10.3390/brainsci7070079. See Appendix 1.
 - Yee, M., Seichepine, D., Januelwicz Lloyd P., Sullivan, K., Proctor, SP & Krengel, M. Traumatic brain injury, health and rate of chronic multisymptom illness in veterans from the 1990-1991 Gulf War. Journal of Head Trauma Rehabilitation. 2016 Sep-Oct;31(5):320-8. doi: 10.1097/HTR.000000000000173.
 - Yee, M. K., Zundel, C. G., Maule, A. L., Heeren, T., Proctor, S. P., Sullivan, K. A., & Krengel, M. H. (2020). Longitudinal Assessment of Health Symptoms in Relation to Neurotoxicant Exposures in 1991 Gulf War Veterans: The Ft. Devens Cohort. Journal of occupational and environmental medicine, 62(9), 663–668. <https://doi.org/10.1097/JOM.0000000000001910>
 - Zundel, C. G., Heeren, T., Grasso, C. M., Spiro, A., 3rd, Proctor, S. P., Sullivan, K., & Krengel, M. (2020). Changes in Health Status in the Ft. Devens Gulf War Veterans Cohort: 1997-2017. Neuroscience insights, 15, 2633105520952675. <https://doi.org/10.1177/2633105520952675>
 - **Books or other non-periodicals, one-time publications**
 - None
 - **Other publications, conference papers, and presentations**
 - Price, K., Zundel, C.G., Krengel, M.K. (2020). Longitudinal Change in PTSD Symptomatology and Associations with Neurotoxicant Exposures in Gulf War Veterans. University of Massachusetts Boston – Psychology Honors Student Presentation Day.
 - Zundel, C.G., Yee, M.K., Sullivan, K., Krengel, M.K. (2020). A Longitudinal Assessment of Health Symptoms and the Associations with Neurotoxicant Exposures in 1991 Gulf War Veterans: The Ft. Devens

Cohort. International Neuropsychological Society 2020 Conference, Denver, CO.

- Grasso, C.M., Zundel, C.G., Krengel, M.H. (2020). Exposures, Health, and Neuropsychological Outcomes in Gulf War Veterans 25+ Years Post War. International Neuropsychological Society 2020 Conference, Denver, CO, Massachusetts Neuropsychological Society Science Symposium, and VA Research Week.
- Zundel, C.G., Yee, M.K., Maule, A., Grasso, C.M., Sullivan, K., Krengel, M. (2019). Health Symptoms Associated with Gulf War-Specific Exposures in Male and Female Veterans: A Longitudinal Assessment. International Neuropsychological Society 2019 Conference, New York, NY.
- Cohen, A.B., Zundel, C.G., Krengel, M.K., Sullivan, K.A. (2018). Preliminary Findings of Gender Differences and Symptomatology within Gulf War Veterans. Massachusetts Neuropsychology Society Science Symposium 2018
- Zundel, C.G., Lad, S.S., Yee, M.K., Grasso, C.M., Janulewicz Lloyd, P.A., Sullivan, K.A., Krengel, M.H. Rates of medical conditions: Do Gulf War veterans differ from the general population? Presented at international Neuropsychological Society 2018 Conference, Washington D.C.
- Krengel MH, Yee M, Nolan T, Janulewicz Lloyd PA, Sullivan K & Seichepine DR. Multiple Self-Reported Exposures to Mild Traumatic Brain Injury and Neurotoxicants Predict Current Total Health Symptoms in a Cohort of 1990-1991 Gulf War Veterans. Journal of International Neuropsychological Society. Supplement 1, March 2016.
- Yee, M., Seichepine DR, Nolan T, Janulewicz Lloyd PA, Sullivan K & Krengel MH. Multiple Self-Reported Brain Injuries are Associated with Increased Health Symptoms in a Cohort of 1990-1991 Gulf War Veterans. Journal of International Neuropsychological Society. Supplement 1, March 2016.

- **Other products**

- **Website(s) or other Internet site(s)**

- None

- **Technologies or techniques**

- None

- **Other products**

- None

7. Participants and other Participating Organizations

Site 1: VA Boston Health Care System (VABHS)
(BUMC) 150 S. Huntington Avenue
Boston, MA 02130
Initiating PI: Maxine Krengel, PhD

Site 2: Boston University Medical Campus
715 Albany Street
Boston, MA 02118

Partnering PI: Kimberly Sullivan, PhD
Co-Investigator: Carole Palumbo, PhD
Co-Investigator: Ronald Killiany, PhD

Site 3: Nova Southeastern University (NSU)
3200 South University Drive

Fort Lauderdale, Florida 33328-2018
Co-Investigator: Richard C. Deth, PhD
Collaborator: Nancy Klimas, MD

Study Sites Responsibilities

Site 1: Dr. Krengel and her VABHS team will be responsible for recruiting FDC study participants and conducting cognitive evaluations and phlebotomy to send to NOVA investigators. Specifically, she will oversee the recruitment and blood draws/cognitive evaluations of FDC study participants and the processing of plasma samples that will be shared for the proposed study. Dr. Krengel will also oversee the experimental design, data analysis and interpretation and presentation of study results in collaboration with Dr. Sullivan and the other study investigators. **Tasks 1-6**

Site 2: Dr. Sullivan and her BUMC team will be responsible for performing the MRS/MRI imaging protocols and post-processing the imaging data for cross-sectional (MRS) and longitudinal analyses (structural MRI). Specifically, she will oversee the imaging acquisition and post-processing protocols in collaboration with Drs. Killiany and Palumbo. Dr. Sullivan will also assist with the experimental design, data analysis and interpretation and presentation of study results in collaboration with Dr. Krengel and the other study investigators. **Tasks 1-6**

Site 3: Dr. Deth and Klimas will be responsible for receiving the plasma samples from the Boston site and performing oxidative stress marker analyses for GSH, HNE and 8-iso-PGF2 α for 100 blood samples (50 GWI, 50 controls). Dr. Deth will also assist with the experimental design, interpretation of data, report and manuscript writing and presentation of results at scientific meetings. **Tasks 1, 2, 4, 5, 6**

Reporting Requirements:
None

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

Clara G Zundel^{1,2} , Timothy Heeren³, Claudia M Grasso¹, Avron Spiro III^{4,5,6}, Susan P Proctor^{1,7}, Kimberly Sullivan^{*8} and Maxine Krengel^{*1,9}

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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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SIGNIFICANCE STATEMENT: Identifies 2-3 of the most important points of the study (100 characters each) that contribute to advancement of knowledge in the field of neuroscience. If your study verifies previous research or presents negative findings, please note this here.

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

*Equal Contribution



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 $\pm$ SD (RANGE)	STUDY SAMPLE (N = 317)
Age at Baseline Survey, years	32.0 $\pm$ 9.0 (19-65)	32.3 $\pm$ 8.4 (19-54)
Age at 1997-1998 Survey, years	37.8 $\pm$ 9.0 (24.5-71.1)	37.9 $\pm$ 8.4 (25.1-59.5)
Age at 2013-2017 Survey, years		54.2 $\pm$ 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 $\pm$ 13.3 (36-120)	62.1 $\pm$ 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 $\geq$ 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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Article

Rates of Chronic Medical Conditions in 1991 Gulf War Veterans Compared to the General Population

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Abstract: Prevalence of nine chronic medical conditions in the population-based Ft. Devens Cohort (FDC) of GW veterans were compared with the population-based 2013–2014 National Health and Nutrition Examination Survey (NHANES) cohort. Excess prevalence was calculated as the difference in prevalence estimates from the Ft. Devens and NHANES cohorts; and confidence intervals and *p*-values are based on the standard errors for the two prevalence estimates. FDC males were at increased risk for reporting seven chronic medical conditions compared with NHANES males. FDC females were at decreased risk for high blood pressure and increased risk for diabetes when compared with NHANES females. FDC veterans reporting war-related chemical weapons exposure showed higher risk of high blood pressure; diabetes; arthritis and chronic bronchitis while those reporting taking anti-nerve gas pills had increased risk of heart attack and diabetes. GW veterans are at higher risk of chronic conditions than the general population and these risks are associated with self-reported toxicant exposures.

Keywords: Gulf War; veterans; Gulf War Illness; Fort Devens Cohort; NHANES; chronic conditions; pyridostigmine bromide; chemical weapons

1. Introduction

From August 1990 to June 1991, nearly 700,000 U.S. troops were deployed to the Persian Gulf to serve in Operations Desert Shield and Desert Storm. Shortly after returning, many Gulf War (GW) veterans began reporting a variety of symptoms in multiple body systems that medical professionals could not diagnose. This array of symptoms was termed “Gulf War Illness” (GWI) or “Chronic Multisymptom Illness” (CMI) [1,2]. Researchers have found that this illness continues to affect about a third of all GW veterans [3]. A recent meta-analysis of health symptoms experienced by GW veterans conducted by our research team found that the most commonly reported concerns were fatigue, pain, cognitive and mood problems, skin rash, gastrointestinal and respiratory conditions [4]. This symptom complex was consistent with what was found in a Kansas cohort, which was used to determine one of the two most widely used case criteria [1].

While the exact etiology and pathobiology of these symptoms remains undetermined, research clearly suggests that neurotoxicant exposures in theater contributed to the disorder [5–8]. GW exposures that have been implicated in the etiology of GWI include low-level sarin chemical warfare agent, pesticides and prophylactic anti-nerve agent pills (pyridostigmine bromide; PB) [5,8]. These exposures can result in both immediate and delayed health effects including chronic cognitive and mood problems and have recently been termed ‘toxic wounds’ to describe this cause-effect relationship [5,7].

Correspondingly, GW veterans have shown increased prevalence of chronic multisymptom illnesses, including GWI, fibromyalgia [1,3,9,10], chronic fatigue syndrome (CFS) [1,3,5,8–14] irritable bowel syndrome (IBS) [9,13], and functional gastric disorders, for which they can receive presumption for health care service at VA hospitals. GW veterans are also more likely to develop chronic neurological disorders, which may or may not be associated with GWI but have been associated with exposures during the war, including amyotrophic lateral sclerosis (ALS) [15–17], brain cancer [3,5,18–20], repeated seizures [1,3,5,9,21,22], neuralgias and neuritis [3,5,9,22] and chronic migraine headaches [1,3,5,11–13,22,23].

For non-neurological disorders, there have been reports of higher rates of arthritis [1,9,11–14,22], various lung diseases [1,9,12–14,21,22,24], eye or vision problems [1,22], high blood pressure [1,9,10,12–14,22], and heart disease [1,9,11,14,21,22] in GW veterans relative to other veteran control groups (GW vs. GW-era veterans, deployed vs. non-deployed veterans, GWI vs. non-GWI veterans). We are unaware of any studies to date in which GW veterans have been compared with the general population on chronic health outcomes. Therefore, it remains unknown whether GW veterans are showing more age-related chronic conditions than the general population and whether or not toxicant exposures are associated with these conditions. There is precedent for this type of toxicant-induced disorder in veterans from other wars. For instance, many Vietnam veterans developed chronic conditions of high blood pressure, diabetes and many types of cancers which the National Academy of Sciences’ (NAS) Institute of Medicine (IOM) concluded were related to remote exposure to Agent Orange [25]. The conditions mentioned above related to GW deployment are also of particular relevance, as one of the most commonly used GWI criteria, the Kansas criteria, excludes chronic medical conditions such as heart disease and diabetes. It is, therefore, necessary to compare the rates of various medical conditions in GW veterans to the general population using a well-established national data set.

One of the earliest and the longest-running studies of GW veterans’ health symptoms was conducted with the Ft. Devens, MA Cohort (FDC). This cohort was surveyed in regard to their health symptom reporting and provided important information regarding the rates and types of current health patterns [26,27]. Results of initial studies from the early 1990s revealed that joint pain, headaches, memory and attention difficulties, skin rash, gastrointestinal difficulties and sleep problems were the most commonly reported chronic symptoms 24 months post-deployment. Early FDC studies also showed that women and those reporting taking 20 or more PB pills were more likely to meet criteria for GWI [26]. In the most recent survey of this cohort it was found that individuals are still experiencing health symptoms at high rates [28]. What was not initially clear was whether or not these rates were higher than those in the general public.

Epidemiologic studies of health symptoms have compared rates of cohort samples to the National Health and Nutrition Examination Survey (NHANES) data set. This is a program of studies created by the Centers of Disease Control and Prevention (CDC) to assess the health and nutritional status of adults in the United States. The NHANES surveys began in the early 1960s and continue to this day.

In the current study, we build upon, extend and update prior work by comparing the rates of chronic conditions in GW veterans to that of the general population. Specifically, we compared the FDC survey data to the general population (2013–2014 NHANES), to compare rates of self-reported doctor diagnosed chronic medical conditions between cohorts. We also investigated the health status of GW veterans from the FDC survey of 2013–2014 as it relates to self-reported neurotoxicant exposures. We hypothesized that GW veterans would have higher rates of chronic conditions than the general

population. We also hypothesized that GW veterans who reported neurotoxicant exposures would have higher rates of chronic conditions than GW veterans who did not report neurotoxicant exposures, similar to other deployment-related toxicant exposed veteran groups.

2. Materials and Methods

2.1. Participants

Comparison data for this study came from two different population-based cohorts. The first cohort included the Ft. Devens, MA Cohort of GW veterans (FDC), and the second cohort was the NHANES dataset. The FDC is one of the few longitudinal cohorts of GW veterans and is the longest running cohort of GW veterans. The most recent Time 5 resurvey began in 2013 and 448 participants who had data for at least one medical condition responded to the FDC Reunion Survey (47 women). Data for the comparison group ($n = 2949$) was obtained from the NHANES survey for the year 2013–2014, restricted to the age range of the FDC respondents. For the current analyses, veterans were excluded from the NHANES sample.

2.2. Self-Report of Medical Conditions

The FDC veterans were asked to self-report if a doctor had ever diagnosed them with 9 chronic medical conditions: high blood pressure (HBP), high cholesterol, heart attack, diabetes, stroke, cancer, asthma, arthritis, and chronic bronchitis. Responses were recorded dichotomously (yes/no). NHANES participants also self-reported whether or not a doctor had ever diagnosed them with these conditions (yes/no) and these data were compared with the FDC survey data.

2.3. Self-Report of Exposures

FDC veterans were asked during this resurvey to self-report if they were ever exposed to chemical or biological warfare (CBW) agents or pyridostigmine bromide (PB) anti-nerve agent pills. CBW was used as a proxy for chemical weapons (sarin/cyclosarin) exposure.

2.4. Statistical Analysis

Since the FDC and NHANES used different sampling strategies, prevalence estimates and their standard errors were calculated separately for each cohort. NHANES employed a complex survey design and prevalence was estimated using SAS survey procedures to account for weighting and clustering in estimating both parameters estimates and standard errors. The FDC was analyzed as a random sample from the Ft. Devens population. Excess prevalence was calculated as the difference in prevalence estimates from the Ft. Devens and NHANES cohorts, and confidence intervals and p -values are based on the standard errors for the two prevalence estimates. Odds ratios and test-based confidence intervals were calculated from the prevalence estimates and standard errors from the two cohorts, similar to what was done in Yun et al. 2006 [29].

Comparisons were made separately for men and women to assess for gender- and age-specific associations. For the age-specific associations, we compared three different age groupings: 40s, 50s, and 60s+ by cohort. Reflecting the Ft. Devens population, the FDC sample was largely white (94%), with high school education or higher (99%). To account for demographic differences between cohorts, we restricted both cohorts to White/Caucasian individuals with a high school or above education. After restriction, there were some demographic differences between cohorts on age (Ft. Devens women were younger) and education (Ft. Devens men were more likely to have other training or some college), and analyses adjusted for these demographic differences by modifying the NHANES weights to match the age and education distribution, for men and women separately, of the Ft. Devens cohort. After restriction and weighting (now listed as restricted analyses), there were no significant differences in current smoking between the two cohorts.

Chi-square tests of independence were used to examine the association between gender and medical conditions, as well as the association between exposures and medical conditions, and to calculate odds ratios in the FDC. Multinomial logistic regressions were run to obtain the adjusted ORs, when applicable. For all analyses, two-sided $p < 0.05$ was considered significant, and no adjustments were made for multiple comparisons.

Data Availability Statement: Analyses were performed using raw data that are only available within the US Department of Veterans Affairs firewall in a secure research environment. VA privacy and data security policies and regulatory constraints provide that only aggregate summary data may be removed from the VA for publication. The authors have provided detailed results of these analyses in the paper. These restrictions are in place in order to maintain patient privacy and confidentiality. Access to these data can be granted to persons who are not an employee of the VA; however, there is an official protocol that must be followed for doing so. The authors invite those wishing to access the raw data that were used for this analysis to contact Maxine Krengel (Maxine.Krengel@va.gov) to discuss the details of the VA data access approval process.

3. Results

3.1. Demographics

The mean age of the FDC was 53.93 years. The mean age of the NHANES cohort was 55.86 years. The two cohorts differed significantly in age, sex, race, education, and current smoking status. For the FDC exposure analyses, veterans who were exposed and unexposed did not differ on any of the demographic variables. However, adjusted analyses for exposure were performed to control for gender and current smoking, potential risk factors for these chronic conditions. Demographics are reported in Table 1.

Table 1. Demographics.

Demographics	Ft. Devens ($n = 448$) Mean $\pm$ SD or N (%)	NHANES ($n = 2959$) Mean $\pm$ SD or N (%)
Age *	53.93 $\pm$ 8.33	55.86 $\pm$ 10.23
Male *	54.13 $\pm$ 8.38	54.74 $\pm$ 9.04
Female *	52.15 $\pm$ 7.75	56.68 $\pm$ 10.90
Sex *		
Male	401 (89.5)	1249 (42.3)
Female	47 (10.5)	1710 (57.7)
Race/Ethnicity *		
Black/African American	12 (2.7)	592 (10.4)
White/Caucasian	416 (92.9)	1189 (69.2)
Hispanic	7 (1.6)	731 (12.7)
Asian	1 (0.2)	389 (5.6)
Other/Multiracial	10 (2.2)	58 (1.9)
Missing	2 (0.4)	0 (0)
Education *		
Less than a high school diploma	1 (0.2)	762 (25.8)
High School Diploma	80 (17.9)	660 (22.3)
Other Training or Some College	171 (38.2)	803 (27.1)
College or Above	195 (43.5)	731 (24.7)
Missing	1 (0.2)	3 (0.1)
Current Smoking *		
Yes	73 (16.3)	588 (19.9)
No	372 (83.0)	2370 (80.1)
Missing	3 (0.7)	1 (0.0)

Table 1. Cont.

Demographics	Ft. Devens (<i>n</i> = 448) Mean ± SD or N (%)	NHANES (<i>n</i> = 2959) Mean ± SD or N (%)
Exposures		
Self-reported Exposures		
Chemical/Biological Warfare (CBW)	178 (39.7)	
Missing CBW Data	131 (29.2)	
Pyridostigmine Bromide (PB) pills	247 (55.1)	
Missing PB Data	89 (19.9)	
Prevalence of Gulf War Illness (GWI)		
Fukuda Criteria	265 (59.2)	
Male	237 (59.1)	
Female	28 (59.6)	
Fukuda—Severe Criteria	58 (21.9)	
Male	52 (21.9)	
Female	6 (21.4)	
Kansas Criteria	147 (32.8)	
Male	132 (32.9)	
Female	15 (31.9)	
Prevalence of Chronic Fatigue Syndrome (CFS)	26 (9.4)	
Male	21 (8.7)	
Female	5 (13.5)	
Prevalence of Irritable Bowel Syndrome (IBS)	47 (16.4)	
Male	38 (15.4)	
Female	9 (23.1)	
Prevalence of Fibromyalgia	11 (3.7)	
Male	8 (3.1)	
Female	3 (7.7)	

* $p < 0.05$.

3.2. Chronic Conditions in the FDC and NHANES Cohort

Non-restricted analyses are presented in Table 2. Non-restricted analyses revealed that FDC males had significantly higher odds of reporting HBP, high cholesterol, heart attack, arthritis, and chronic bronchitis than NHANES males. Restricted analyses revealed that the FDC males had significantly higher odds of reporting HBP, high cholesterol, heart attack, diabetes, stroke, arthritis, and chronic bronchitis ($p < 0.05$). The FDC excess prevalence ranged from 2.7 to 12.2% higher for these conditions (Table 2). This resulted in the FDC men having more than 2.5 times the odds of reporting a heart attack (OR = 2.63) and more than 4 times the odds of reporting chronic bronchitis (OR = 4.50). The odds of HBP, diabetes, and arthritis was at least 1.47 times higher in the FDC (Table 2).

Table 2. Cohort comparison of prevalence of medical conditions—non-restricted sample.

Condition	Ft. Devens % (<i>n</i> = 401)	NHANES % (<i>n</i> = 1249)	Excess Prevalence [CI]	<i>p</i> -Value	OR [CI]
Men					
Self-reported doctor diagnosed medical conditions					
High Blood Pressure	52.9%	40.7%	12.3% [6.5–18.1]	0.000	1.64 [1.299–2.073]
High Cholesterol	59.5%	49.7%	9.8% [3.8–15.9]	0.001	1.49 [1.165–1.904]
Heart Attack	9.2%	4.7%	4.5% [0.6–8.4]	0.025	2.04 [1.093–3.805]
Diabetes	20.9%	15.5%	5.4% [−0.03–10.8]	0.051	1.44 [0.998–2.078]
Stroke	4.4%	2.3%	2.1% [−0.6–4.7]	0.133	1.93 [0.819–4.549]
Cancer	14.4%	12.3%	2.1% [−2.7–6.9]	0.391	1.20 [0.791–1.819]
Asthma	15.3%	10.4%	4.9% [−0.07–9.9]	0.053	1.56 [0.994–2.448]
Arthritis	35.9%	25.4%	10.5% [4.5–16.6]	0.001	1.65 [1.238–2.192]
Chronic Bronchitis	10.7%	2.6%	8.0% [4.1–11.9]	0.000	4.41 [2.138–9.078]

Table 2. Cont.

Condition	Ft. Devens % (n = 401)	NHANES % (n = 1249)	Excess Prevalence [CI]	p-Value	OR [CI]
Women % (n = 47) % (n = 1710)					
Self-reported doctor diagnosed medical conditions					
High Blood Pressure	22.2%	46.8%	−24.6% [−37.3–(−11.8)]	0.000	0.32 [0.181–0.582]
High Cholesterol	37.2%	45.5%	−8.3% [−23.1–6.5]	0.271	0.71 [0.385–1.308]
Heart Attack	2.5%	4.5%	−2.0% [−7.0–3.1]	0.440	0.55 [0.117–2.541]
Diabetes	37.2%	17.4%	19.8% [5.1–34.4]	0.008	2.81 [1.308–6.035]
Stroke	0%	4.1%	−4.1% [−5.1–(−3.1)]	N/A	N/A
Cancer	12.2%	12.8%	−0.6% [−10.8–9.5]	0.904	0.94 [0.373–2.387]
Asthma	9.5%	18.1%	−8.6% [−17.8–0.6]	0.067	0.48 [0.215–1.054]
Arthritis	29.3%	41.2%	−11.9% [−26.2–2.4]	0.104	0.59 [0.314–1.113]
Chronic Bronchitis	17.1%	9.6%	7.4% [−4.3–19.1]	0.213	1.93 [0.686–5.424]
Men – Restricted Analyses % (n = 372) % (n = 373)					
Self-reported doctor diagnosed medical conditions					
High Blood Pressure	52.7%	40.6%	12.2% [4.7–19.6]	0.001	1.63 [1.208–2.211]
High Cholesterol	59.6%	51.9%	7.7% [0.2–15.2]	0.044	1.37 [1.009–1.855]
Heart Attack	9.4%	3.8%	5.6% [1.3–9.9]	0.010	2.63 [1.255–5.530]
Diabetes	20.5%	13.4%	7.1% [0.9–13.4]	0.025	1.67 [1.066–2.620]
Stroke	4.3%	1.4%	2.9% [0.1–5.6]	0.041	3.19 [1.050–9.679]
Cancer	14.9%	15.7%	−0.8% [−6.6–5.0]	0.782	0.94 [0.602–1.465]
Asthma	13.6%	10.9%	2.7% [−3.1–8.6]	0.362	1.29 [0.746–2.228]
Arthritis	35.0%	26.7%	8.2% [1.5–15.0]	0.017	1.47 [1.073–2.026]
Chronic Bronchitis	10.2%	2.5%	7.7% [3.6–11.8]	0.000	4.50 [2.017–10.029]
Women – Restricted Analyses % (n = 42) % (n = 639)					
Self-reported doctor diagnosed medical conditions					
High Blood Pressure	17.5%	33.9%	−16.4% [−30.3–(−2.5)]	0.021	0.41 [0.196–0.874]
High Cholesterol	38.5%	47.7%	−9.2% [−25.6–7.0]	0.266	0.68 [0.351–1.334]
Heart Attack	0%	5.6%	−5.6% [−8.4–(−2.8)]	N/A	N/A
Diabetes	38.5%	19.0%	19.5% [3.4–35.6]	0.017	2.67 [1.189–6.001]
Stroke	0%	3.7%	−3.7% [−5.9–(−1.5)]	N/A	N/A
Cancer	13.2%	13.0%	0.2% [−11.1–11.4]	0.977	1.01 [0.377–2.733]
Asthma	10.3%	18.6%	−8.3% [−18.5–1.8]	0.109	0.50 [0.215–1.166]
Arthritis	29.7%	40.4%	−10.6% [−26.4–5.1]	0.187	0.63 [0.312–1.255]
Chronic Bronchitis	13.2%	10.6%	2.5% [−8.9–14.0]	0.663	1.28 [0.427–3.820]

* Actual N of each medical conditions may vary due to missing data.

Non-restricted and restricted analyses revealed that the FDC females reported a significantly lower rate of HBP and a significantly higher rate of diabetes compared with the NHANES females ($p < 0.05$). The FDC women had a 16.4% lower prevalence of HBP and a 19.5% higher prevalence of diabetes compared to the NHANES general population. There was no significant association between cohort and high cholesterol, heart attack, stroke, cancer, asthma, arthritis, and chronic bronchitis ($p > 0.05$). FDC and NHANES cohort comparison results are shown in Figure 1 and Table 2.

3.3. Age and Gender Comparisons in FDC and NHANES Cohorts

For males in their 40s, the non-restricted analyses indicated significant associations between cohort and HBP and high cholesterol ($p < 0.05$), with the FDC reporting higher prevalence (Table 3). In the restricted analyses, there was a significant association between cohort and heart attack ($p < 0.05$), with the FDC reporting a higher prevalence than the NHANES cohort. The excess prevalence for heart attack was 4.4% (Table 3). The odds of FDC men reporting a heart attack was 27.36 times higher than NHANES men (Table 3). There was no significant association between cohort and the eight other chronic conditions.

Non-restricted and restricted male age comparison results of prevalence and odds ratios are summarized in Table 3. Due to the small number of women in the FDC, female age grouping analyses did not yield sufficient power, and thus are not reported.

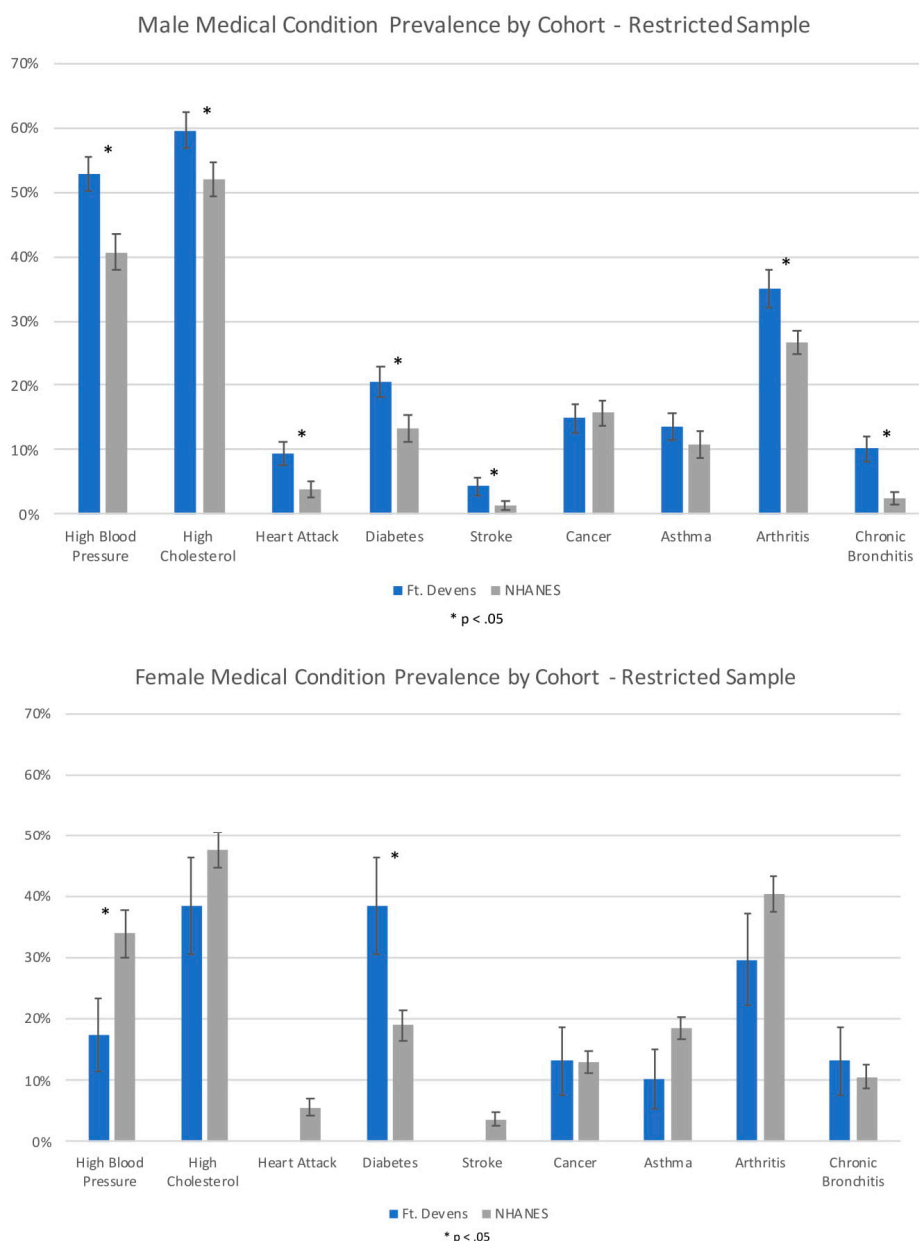


Figure 1. Prevalence of medical conditions in male and female participants from FDC and NHANES cohorts in the restricted sample. (Error bars represent Standard Error).

Table 3. Cohort comparison of male rates of medical conditions by age group.
Table 3. Cohort comparison of male rates of medical conditions by age group.

Condition	Ft. Devens % (n ₀ = 142)	NHANES % (n ₀ = 387)	Excess Prevalence [CI]	p-Value	OR [CI]
Self-reported doctor diagnosed medical conditions					
High Blood Pressure	43.6%	26.4%	17.2% [7.9–26.5]	0.000	2.16 [1.423–3.272]
High Cholesterol	50.8%	37.6%	13.2% [9.8–21.1]	0.000	2.76 [1.444–5.301]
Heart Attack	4.5%	1.8%	2.7% [1.3–23.1]	0.009	2.57 [1.114–5.961]
Diabetes	14.2%	9.3%	4.9% [2.1–14.6]	0.019	2.62 [1.082–6.320]
Stroke	0%	0.8%	−0.8% [−1.2–1.0]	N/A	1.62 [0.608–3.232]
Cancer	5.4%	2.8%	2.6% [−1.6–1.0]	N/A	1.95 [0.599–6.373]
Asthma	12.8%	10.9%	2.0% [−5.0–9.0]	0.578	1.21 [0.618–2.373]
Arthritis	17.0%	12.2%	4.8% [−3.1–12.7]	0.231	1.48 [0.780–2.789]
Chronic Bronchitis	4.7%	1.8%	2.9% [−1.2–7.0]	0.187	2.66 [0.829–8.236]
Arthritis	17.0%	12.2%	4.8% [−3.1–12.7]	0.231	1.48 [0.780–2.789]

Table 3. Cont.

Condition	Ft. Devens	NHANES	Excess Prevalence [CI]	p-Value	OR [CI]
50s	% (n = 149)	% (n = 382)			
High Blood Pressure	55.1%	40.8%	14.3% [4.8–23.7]	0.003	1.78 [1.215–2.602]
High Cholesterol	61.3%	45.8%	15.5% [5.6–25.4]	0.002	1.87 [1.253–2.805]
Heart Attack	9.3%	4.2%	5.1% [−1.0–11.2]	0.103	2.34 [0.842–6.503]
Diabetes	20.0%	15.2%	4.8% [−3.7–13.3]	0.270	1.39 [0.773–2.509]
Stroke	2.1%	2.6%	−0.5% [−3.8–2.7]	0.746	0.79 [0.188–3.311]
Cancer	17.6%	6.5%	11.1% [3.3–18.9]	0.005	3.06 [1.393–6.723]
Asthma	13.4%	10.2%	3.2% [−4.3–10.6]	0.404	1.36 [0.662–2.782]
Arthritis	43.8%	22.0%	21.8% [11.4–32.1]	0.000	2.76 [1.700–4.471]
Chronic Bronchitis	13.1%	2.6%	10.5% [3.7–17.4]	0.003	5.62 [1.824–17.335]
60s	% (n = 96)	% (n = 480)			
High Blood Pressure	67.4%	58.6%	8.8% [−1.6–19.2]	0.098	1.46 [0.932–2.286]
High Cholesterol	71.1%	54.4%	16.7% [5.9–27.4]	0.002	2.06 [1.292–3.279]
Heart Attack	20.3%	10.2%	10.1% [−0.5–20.8]	0.062	2.25 [0.960–5.252]
Diabetes	34.4%	29.9%	4.4% [−8.0–16.8]	0.483	1.23 [0.694–2.166]
Stroke	16.1%	5.8%	10.2% [0.4–20.1]	0.042	3.08 [1.041–9.139]
Cancer	27.6%	15.2%	12.4% [0.4–24.3]	0.043	2.12 [1.026–4.398]
Asthma	23.2%	9.8%	13.4% [2.0–24.8]	0.021	2.79 [1.168–6.643]
Arthritis	55.0%	34.5%	20.5% [7.2–33.8]	0.003	2.32 [1.342–4.004]
Chronic Bronchitis	15.1%	3.8%	11.3% [1.5–21.1]	0.024	4.54 [1.226–16.837]
40s – Restricted Analyses	% (n = 134)	% (n = 124)			
High Blood Pressure	42.4%	29.0%	13.4% [−0.2–27.0]	0.054	1.80 [0.991–3.279]
High Cholesterol	50.0%	47.3%	2.7% [−11.1–16.5]	0.704	1.11 [0.641–1.933]
Heart Attack	4.6%	0.2%	4.4% [0.5–8.4]	0.029	27.36 [1.413–529.776]
Diabetes	13.8%	7.2%	6.6% [−2.9–16.1]	0.175	2.06 [0.725–5.867]
Stroke	0%	0%	0%	N/A	N/A
Cancer	5.6%	6.7%	−1.2% [−8.0–5.7]	0.741	0.82 [0.246–2.709]
Asthma	11.4%	11.0%	0.4% [−7.9–8.7]	0.918	1.04 [0.454–2.405]
Arthritis	16.3%	19.0%	−2.7% [−13.5–8.2]	0.629	0.83 [0.394–1.757]
Chronic Bronchitis	4.8%	0.9%	3.9% [−0.4–8.2]	0.077	5.51 [0.829–36.651]
50s – Restricted Analyses	% (n = 135)	% (n = 123)			
High Blood Pressure	56.4%	43.1%	13.3% [−2.7–29.4]	0.104	1.71 [0.896–3.259]
High Cholesterol	63.1%	49.9%	13.2% [−0.1–26.4]	0.051	1.71 [0.997–2.947]
Heart Attack	10.5%	3.6%	6.9% [−0.8–14.6]	0.080	3.14 [0.871–11.340]
Diabetes	20.2%	14.4%	5.9% [−5.1–16.8]	0.295	1.51 [0.698–3.272]
Stroke	2.4%	1.7%	0.7% [−3.3–4.7]	0.732	1.43 [0.184–11.088]
Cancer	18.7%	17.0%	1.7% [−10.4–13.8]	0.788	1.12 [0.490–2.559]
Asthma	11.6%	10.2%	1.4% [−7.6–10.5]	0.755	1.16 [0.458–2.934]
Arthritis	43.0%	25.1%	17.9% [5.9–29.9]	0.004	2.25 [1.306–3.876]
Chronic Bronchitis	12.5%	3.5%	9.0% [1.4–16.6]	0.020	3.94 [1.242–12.507]
60s+ - Restricted Analyses	% (n = 89)	% (n = 126)			
High Blood Pressure	67.0%	54.2%	12.9% [−1.5–27.2]	0.079	1.72 [0.939–3.153]
High Cholesterol	70.5%	62.0%	8.5% [−6.6–23.6]	0.269	1.47 [0.744–2.892]
Heart Attack	19.6%	9.6%	10.0% [−2.3–22.4]	0.112	2.30 [0.824–6.441]
Diabetes	32.8%	21.4%	11.4% [−2.2–25.0]	0.100	1.79 [0.894–3.597]
Stroke	15.1%	3.0%	12.1% [1.9–22.2]	0.020	5.69 [1.313–24.695]
Cancer	28.6%	27.4%	1.2% [−13.7–16.0]	0.877	1.06 [0.507–2.215]
Asthma	20.8%	11.8%	8.9% [−3.8–21.7]	0.170	1.96 [0.750–5.101]
Arthritis	55.4%	40.7%	14.6% [−0.9–30.2]	0.065	1.80 [0.963–3.379]
Chronic Bronchitis	13.7%	3.2%	10.5% [0.6–20.5]	0.038	4.83 [1.092–22.359]

* Actual N may vary due to missing data.

For males in their 50s, the non-restricted analyses indicated significant associations between cohort and HBP, high cholesterol, cancer, arthritis and chronic bronchitis ($p < 0.05$), with the FDC reporting more chronic conditions. In the restricted analyses, there was a significant association between cohort and arthritis and chronic bronchitis ($p < 0.05$) with the FDC reporting more chronic conditions than NHANES men. The FDC excess prevalence for these conditions ranged from 9.0 to 17.9% (Table 3). The odds of FDC men reporting chronic bronchitis was 3.94 times higher than the

NHANES men. There was no significant association between cohort and the seven other chronic conditions in this age group ($p > 0.05$).

For males in their 60s, the non-restricted analyses indicated significant associations between cohort and high cholesterol, stroke, cancer, asthma, arthritis, and chronic bronchitis ($p < 0.05$), with the FDC reporting higher prevalence. In the restricted analyses, there was a significant association between cohort and two chronic conditions including stroke and chronic bronchitis ($p < 0.05$) with FDC reporting higher rates than NHANES men. The excess prevalence was 12.1 and 10.5% respectively (Table 3). The odds of FDC men reporting stroke and chronic bronchitis were 5.69 and 4.83 times higher respectively than the NHANES men.

Non-restricted and restricted male age comparison results of prevalence and odds ratios are summarized in Table 3. Due to the small number of women in the FDC, female age grouping analyses did not yield sufficient power, and thus are not reported.

3.4. Chronic Conditions and Toxicant Exposures in the Ft. Devens Cohort

For the comparison of chronic medical conditions and toxicant exposures in the FDC, the same 9 chronic conditions were assessed as in the prior FDC and NHANES comparisons. There was a significant association between self-reported chemical/biological weapons (CBW) exposure and 4 chronic conditions ($p < 0.05$), with CBW-exposed veterans reporting higher prevalence rates of HBP, diabetes, arthritis and chronic bronchitis (Table 4). The excess prevalence of these conditions ranged from 10 to 21% higher prevalence. CBW-exposed veterans had greater than 4 times the odds of reporting diabetes in unadjusted analyses and 3 times the odds in adjusted analyses compared with unexposed veterans.

There was also a significant association between PB pill usage during the war and 2 chronic conditions ($p < 0.05$) with PB exposed veterans reporting higher prevalence rates of heart attack and diabetes ($p < 0.05$). The excess prevalence for these two conditions were 10% and 12.5% respectively. PB-exposed veterans had 11 times the odds of reporting a heart attack in unadjusted analyses and 12 times the odds in adjusted analyses than the non-PB-exposed FDC veterans (Table 4).

3.5. Direct Comparison of Prevalence of Chronic Conditions in Men and Women within the Ft. Devens Cohort

When rates of the 9 chronic conditions were directly compared between men and women in the FDC, gender was significantly associated with 3 outcomes: HBP, for which FDC men had nearly 3.5 times the odds of reporting compared to FDC women (OR = 3.45); high cholesterol, for which FDC men had more than 2 times the odds of reporting compared to FDC women (OR = 2.25); and diabetes, for which FDC men had decreased odds of reporting compared to FDC women (OR = 0.38). Gender was not associated with any of the other chronic conditions (Table 5).

Table 4. Rates of medical conditions for exposed and unexposed Ft. Devens veterans.

Condition	Exposed % (n = 178)	Unexposed % (n = 139)	Excess Prevalence	p-Value	OR [CI]	Adjusted OR [CI]
Chemical/Biological Warfare (CBW)						
Self reported doctor diagnosed medical conditions						
High Blood Pressure	54.0%	42.0%	12.0%	0.040	1.621 [1.033–2.544]	1.601 [1.012–2.533]
High Cholesterol	56.8%	53.4%	3.4%	0.633	1.145 [0.717–1.827]	1.084 [0.674–1.742]
Heart Attack	11.0%	5.5%	5.5%	0.161	2.147 [0.796–5.795]	2.013 [0.742–5.464]
Diabetes	29.9%	8.9%	21.0%	0.000	4.340 [2.055–9.165]	3.242 [1.647–6.382]
Stroke	4.1%	3.7%	0.4%	1.000	1.122 [0.293–4.288]	1.116 [0.289–4.310]
Cancer	17.5%	11.4%	6.1%	0.204	1.643 [0.785–3.439]	1.494 [0.722–3.090]
Asthma	18.5%	10.3%	8.2%	0.094	1.987 [0.919–4.296]	1.940 [0.896–4.201]
Arthritis	43.4%	23.9%	19.5%	0.002	2.446 [1.403–4.265]	2.199 [1.261–3.834]
Chronic Bronchitis	16.0%	5.7%	10.3%	0.020	3.175 [1.225–8.229]	3.997 [1.426–11.202]
Chronic Fatigue Syndrome (CFS)	15.2%	2.8%	12.4%	0.002	6.131 [1.717–21.889]	5.957 [1.664–21.321]
Irritable Bowel Syndrome (IBS)	24.8%	8.7%	16.1%	0.003	3.439 [1.529–7.734]	3.401 [1.502–7.699]
Pyridostigmine Bromide (PB) Pills						
	% (n = 247)	% (n = 112)				
Self reported doctor diagnosed medical conditions						
High Blood Pressure	50.2%	40.9%	9.3%	0.109	1.456 [0.923–2.299]	1.542 [0.969–2.453]
High Cholesterol	58.4%	51.0%	7.4%	0.226	1.351 [0.840–2.174]	1.305 [0.807–2.110]
Heart Attack	11.5%	1.1%	10.4%	0.003	11.348 [1.501–85.798]	12.141 [1.601–92.054]
Diabetes	23.7%	11.2%	12.5%	0.015	2.452 [1.172–5.128]	2.175 [1.107–4.273]
Stroke	4.6%	1.1%	3.5%	0.280	4.193 [0.516–34.067]	4.673 [0.572–38.192]
Cancer	15.3%	10.1%	5.2%	0.265	1.606 [0.723–3.567]	1.443 [0.666–3.124]
Asthma	12.5%	11.5%	1.0%	0.845	1.100 [0.496–2.438]	1.127 [0.507–2.505]
Arthritis	36.4%	31.4%	5.0%	0.494	1.249 [0.725–2.152]	1.223 [0.711–2.105]
Chronic Bronchitis	13.1%	8.0%	5.1%	0.227	1.751 [0.720–4.255]	1.664 [0.678–4.085]
Chronic Fatigue Syndrome (CFS)	10.9%	2.4%	8.5%	0.037	4.885 [1.094–21.809]	5.076 [1.132–22.760]
Irritable Bowel Syndrome (IBS)	20.9%	8.6%	12.3%	0.017	2.791 [1.175–6.627]	2.662 [1.112–6.372]

* Actual N of each medical condition may vary due to missing data. Adjusted ORs control for Gender and Current Smoking.

Table 5. Direct comparison of medical condition prevalence in men & women of the Ft. Devens cohort.

Medical Condition	Men	Women	p-Value	OR [CI]	* Adjusted OR [CI]
High Blood Pressure	52.9%	22.2%	0.000	3.933 [1.895–1.895]	3.454 [1.622–7.353]
High Cholesterol	59.5%	37.2%	0.006	2.484 [1.291–4.777]	2.249 [1.127–4.488]
Heart Attack	9.2%	2.5%	0.224	3.961 [0.523–30.024]	3.253 [0.415–25.466]
Diabetes	20.9%	37.2%	0.021	0.447 [0.227–0.881]	0.378 [0.182–0.782]
Stroke	4.4%	0.0%	0.246	N/A	N/A
Cancer	14.4%	12.2%	0.815	1.215 [0.450–3.277]	1.099 [0.390–3.100]
Asthma	15.3%	9.5%	0.363	1.712 [0.581–5.050]	1.570 [0.527–4.679]
Arthritis	35.9%	29.3%	0.485	1.354 [0.662–2.769]	1.296 [0.592–2.835]
Chronic Bronchitis	10.7%	17.1%	0.289	0.580 [0.236–1.426]	0.460 [0.179–1.182]

* Adjusted ORs control for Age, Race, Education, and Current Smoking.

4. Discussion

More than 25 years post-deployment, GW veterans continue to report more chronic health symptoms and chronic medical conditions than non-deployed veterans [1,4,9,10,12–14,22,23,30]. A recent meta-analysis of chronic health symptoms in deployed GW veterans versus non-deployed GW-era veterans showed that GW veterans had higher odds of reporting mood-cognition, fatigue, musculoskeletal, gastrointestinal, and dermatological symptoms compared with non-deployed veterans when 21 studies encompassing 129,000 veterans were compared [4]. The meta-analysis suggested that the symptom categories encompassed in the Kansas GWI criteria are appropriate for determining the multi-symptom disorder called GWI [1]. In addition to GWI, as veterans age, they continue to develop chronic medical conditions and diseases of aging, as would be expected in the general population. Chronic illness is common in aging individuals, and an estimate in 2000 reported that 45% of Americans had chronic conditions, with over 20% having multiple chronic conditions [31]. In general, non-veteran women report more increased chronic conditions than men and one report suggested that GW veteran women may show increased rates of chronic conditions that have been used as exclusionary medical conditions for the Kansas GWI criteria [32]. This raises the question of whether the exclusionary criteria currently used for GWI case criteria are still appropriate in an aging population of veterans, and whether these GW veterans are showing the same age-related rates in chronic health conditions as the general population, or are showing unique age- and gender-related patterns of development of chronic medical conditions. To our knowledge, the current study is the first to compare GW veterans' health status to that of the general public by comparing the Ft. Devens Cohort (FDC) with the NHANES cohort and thus builds upon and extends prior GW studies comparing chronic health conditions.

Results showed that male GW veterans have significantly greater odds of developing chronic conditions including HBP, high cholesterol, heart attack, diabetes, stroke, arthritis, and chronic bronchitis. Specifically, FDC men in their 40s have 27 times higher odds of reporting a heart attack compared to the NHANES cohort of the same age. Rates of chronic conditions such as arthritis and chronic bronchitis also appear to be significantly higher in FDC males in their 50s and stroke risk is five times higher in the 60s age range compared to the NHANES cohort. These results correspond with prior accelerated aging cognitive patterns previously noted in the FDC veterans [27]. The fact that heart attack risk is significantly higher in the 4th decade, but not later in the 5–6th decades, in the FDC males suggests that GW veterans may be at increased risk for cardiovascular insults earlier than the general population. The additionally higher risk of stroke in the 6th decade of FDC males appears to suggest earlier cerebrovascular disease risk as well. These results also correspond with reports of increased prevalence over a 10-year period (1995–2005) for arthritis, hypertension, heart disease and diabetes in a large National Survey of Gulf War veterans [14]. Significant new onset of chronic conditions including hypertension, coronary heart disease, and arthritis was also reported by Li et al. (2011) in GW veterans when compared with non-deployed era veterans [14]. However, these studies did not specifically assess gender differences.

Important gender differences were also observed in this study. Male GW veterans had significantly higher odds of developing seven out of the nine chronic conditions assessed when compared with age-matched NHANES males. Conversely, female GW veterans had lower odds of developing HBP and higher odds of developing diabetes when compared with age-matched NHANES females. The FDC was one of the first studies to report a 1.8 times higher risk of GWI in women veterans [26]. Although there were trends for higher odds of developing medical conditions for women in this study, statistical differences were not found in this latest FDC survey, which showed that women veterans have at least the same rate of GWI than their male counterparts. In addition, prior studies in other GW veteran cohorts have reported increased chronic conditions and/or exclusionary medical conditions for GWI in women GW veterans [32]. The current study found fewer chronic conditions in women veterans compared with the general population, while the male veterans showed more chronic conditions than the general population sample of men. When FDC men and women were directly compared for rates of chronic conditions, men had higher rates of HBP and high cholesterol and lower rates of diabetes compared to FDC women. Therefore, it is clear that the trajectory of chronic conditions in male and female GW veterans is different and therefore, their treatment planning should be considered based on these different risk patterns [33,34]. Specifically, men should be aggressively screened and treated for HBP and high cholesterol and women should be screened for diabetes to reduce further potential heart disease and cardiovascular events.

GW veterans' chronic medical conditions were also compared by exposure status. Results indicated that neurotoxicant exposures during deployment were associated with higher rates of chronic conditions, compared to unexposed FDC veterans. In several prior studies, CBWs including sarin and cyclosarin were associated with GWI, as well as with altered brain imaging outcomes and other chronic illnesses including brain cancer [19,20,35–38]. PB has been associated with increased risk of GWI in the FDC and other cohorts as well as with other health outcomes including symptom severity, cognitive decrements and altered neuroendocrine function [5–8,26,30,39,40]. Although prior studies have reported these chronic medical conditions to be higher in GW veterans, this is the first study that we are aware of to report these toxicant exposures to be related to increased prevalence of these chronic conditions.

Collectively, these results indicate that toxic wounds from GW deployment related exposures appear to be associated with more than the chronic health symptoms of GWI but also with chronic conditions of aging. These results are similar to those observed in aging Vietnam veterans who were also shown to have increased risk of developing HBP, diabetes and multiple types of cancer if they were exposed to Agent Orange, the signature toxic wound during the Vietnam era [25,41]. Further assessment of chronic conditions and their causes in other confirmatory cohorts of GW veterans and reconsideration of some Kansas GWI exclusionary criteria is warranted given the current findings. The chronic conditions identified in this study are of importance for future studies of GW veterans and the impact of potential accelerated aging and development of age-related neurodegenerative conditions. While the biological mechanisms for possible accelerated aging in GW veterans are unknown, recent studies in human research participants and laboratory animals have implicated mitochondrial dysfunction and chronic neuroinflammation in GWI [42–45]. Additionally, understanding prevalence rate differences or excess prevalence of these chronic conditions is important not only to devise appropriate inclusion and exclusion criteria for GWI in an aging population, but also to assess the impact of prior toxicant exposures on GWI pathology.

Strengths and Limitations

The strengths of the current study are that it includes comparisons of chronic conditions in two population-based cohorts including a cohort of deployed GW veterans who were followed within a week after their return from the Gulf War and the well-designed general population cohort called the National Health and Nutrition Examination Surveys (NHANES). Both cohorts were designed as population-based survey study cohorts. The limitations of the current study are the relatively low

response rate of the current FDC survey (35%), which could have introduced some response bias, where sicker veterans responded to the survey. However, recent other longitudinal cohorts of GW veterans including the National Survey of Gulf War veterans have reported almost identical response rates on recent surveys with no response bias when prior participant rates were compared suggesting this may be less of an issue with population-based GW veteran cohorts [24]. In addition, although the FDC men were reporting increased rates of chronic conditions compared to NHANES men, the FDC women veterans actually showed lower prevalence of most chronic conditions when compared with the NHANES cohort. These results suggest against response bias in that sicker GW women veterans were not in fact responding to the FDC cohort in this latest FDC survey. Additionally, the FDC includes a large number of National Guardsmen and Reservists, and thus may not be representative of all Gulf War veterans. Furthermore, the small number of women may have limited the analyses and added some uncertainty to the results. Due to demographic differences between cohorts, restricted analyses were performed that limited the sample to White/Caucasians with at least a high school education. This limits the generalizability of our findings to not only other Gulf War veterans but to Gulf War veterans of different gender, races, and education levels.

Lastly, in splitting the samples by age, the sample was smaller for each age group, which may have introduced statistical power issues. Future work is needed to replicate these findings with larger cohorts.

5. Conclusions

In summary, GW veterans in the FDC cohort had significantly increased odds for reporting chronic conditions including high blood pressure, high cholesterol, heart attack, diabetes, stroke, arthritis and chronic bronchitis compared with the NHANES general population cohort. This was true for comparison of males in the two cohorts with heart attack being higher in the FDC 4th decade and chronic bronchitis and arthritis being higher in the FDC 5th decade and the addition of stroke risk being higher in the 6th decade. Female comparisons showed a different pattern with FDC women veterans having significantly lower odds of high blood pressure and significantly higher odds of diabetes when compared with NHANES women. Direct comparisons of male and female FDC showed male veterans had higher odds for reporting HBP and high cholesterol and lower odds of reporting diabetes than FDC women veterans. Gulf War-related exposures, including self-report of chemical weapons, was associated with significantly higher odds of HBP, diabetes, arthritis and chronic bronchitis and self-report of PB exposure was associated with higher risk of heart attack and diabetes. Results indicate that GW veterans are at higher risk of chronic conditions than the general population and these risks are associated with self-reported toxicant exposures. These results should be considered when assessing the functionality of exclusionary criteria for currently used GWI case definitions.

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