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14. ABSTRACT
This epidemiologic study utilizes both existing datasets and newly collected survey data to examine the prevalence and patterns of GWI symptoms, diagnosed medical conditions, reproductive health, birth outcomes and other health issues among women who served during the Gulf War. The study will utilize data from multiple studies in order to establish a GWWC. In studies for which it is feasible to re-contact subjects, current data will be collected on women's symptoms and medical conditions and adverse reproductive outcomes (still births, ectopic pregnancies, birth defects), using postal survey questionnaires and telephone interviews. In this new data collection, the projected number of completed surveys is 200. Re-analyses of existing data will focus on health outcomes specifically affecting women. Female-to-male differences in GWI will be examined to determine whether GWI manifests differently in women. The number of women who will be included in the study is anticipate to be 955-1,420 women GW veterans and an additional 680-854 women veterans who were not deployed. The project will provide a comprehensive picture of the health of women GW veterans. This includes assessment of current health status, changes in health symptoms and conditions over time, and possible differences in health outcomes associated with specific experiences and exposures during the war. It will allow for an assessment of GWI symptom patterns that may be specific to women veterans and a determination of diagnosed medical conditions.

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1. **INTRODUCTION:** Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.

This epidemiologic study utilizes both existing datasets and newly collected survey data to examine the prevalence and patterns of GWI symptoms, diagnosed medical conditions, reproductive health, birth outcomes, and other health issues among women who served during the Gulf War. The study utilizes data from multiple studies in order to establish a Gulf War Women's Health Cohort. In new data collection, the projected number of completed surveys is 200.

2. **KEYWORDS:** Provide a brief list of keywords (limit to 20 words).

Birth defects; Gulf War veterans; reproductive outcomes; women's health

3. **ACCOMPLISHMENTS:** The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer whenever there are significant changes in the project or its direction.

What were the major goals of the project?

Coordinate with sites for IRB protocol submission; coordinate with sites for Augusta University IRB review; coordinate with sites for military 2nd level IRB review (ORP/HRPO).
Hire and train staff.
Assemble the GWWC from previous study data; develop and finalize data use agreements.
Conduct a pilot of survey questionnaire.
Implement quality assurance measures for data collection and data management.

What was accomplished under these goals?

Year three activities have carefully followed the Statement of Work. These activities have included obtaining final IRB approval at VA Boston Healthcare, Augusta University, and ORP/HRPO.

A major accomplishment in year three was the analysis of data from the CDC Air Force Study, Ft. Devens Study, and CSP 585 Gulf War Survey and Biorepository survey data in support of collaborative manuscripts. Another major accomplishment in year two was publication of four key

journal articles. These publications are included in the Appendices. A fourth manuscript is under review by the Journal of Women's Health.

Dr. Beth Unger at the Centers for Disease Control and Prevention (CDC) in Atlanta provided archived records from the CDC Air Force Study, which included women. The study data, which contain no personal identifiers or biological specimens, have been made available to Augusta University for use in the proposed collaborative study. In November 1994, the VA, DoD, and the Pennsylvania Department of Health requested that CDC investigate a report of unexplained illnesses among members of an Air National Guard unit who were GW veterans. After an initial investigation of 59 GW veterans, which involving standardized interviews and physical examinations, a larger sample of GW veterans (n=3,927) were surveyed in 1995, who were members of the index unit and three comparison units in Pennsylvania and Florida. After excluding 204 who were younger than 17 years during the GW, 1,163 (31.2%) were GW veterans and 2,560 (68.8%) had not been deployed. In addition to general health history, the respondents were asked about the frequency, duration, and severity of 35 symptoms and possible exposures during deployment. Birth outcomes were not asked about. In all units, the prevalence of each of 13 chronic symptoms was significantly greater ($p<0.05$) among persons deployed to the GW than among those not deployed.

In addition to the CDC Air Force study and extending data collection among participants in the Ft. Devens Cohort, we are proposing to include data from VA's Cooperative Studies Program (CSP) 585 Gulf War Biorepository and Health Survey pilot study (which ended in May 2016) [1, 20]). Veterans were eligible to participate in the VA's Cooperative Studies Program (CSP) 585 Gulf War Biorepository and Health Survey pilot study if they had served in the U.S. Uniformed Services during the period from August 1990-July 1991, regardless of deployment or combat status. The stratified recruitment panel was obtained from the Department of Defense Manpower Data Center (DMDC) and was drawn from a total population of 4,966,117 veterans who served during August 1990-July 1991. A subset of only the 301 women CSP 585 veterans (291 DMDC and 10 self-nominated) were included for the current proposed study. A data usage agreement was finalized with the principal investigator of the CSP 585 pilot study, Dr. Dawn

Provenzale at the VAMC in Durham, NC, and Dr. Coughlin at Augusta University.

Dr. Sullivan is currently the PI and leader of a DoD funded Gulf War Illness Consortium (GWIC) that brings together diverse experts from 9 institutions to study the pathobiology and treatment development for GWI. GWIC clinical studies include data collection from three study sites in Boston, Central Texas and Miami. Clinical study co-investigators include Drs. Nancy Klimas, Lea Steele and Maxine Krengel. The GWIC cohort will include study surveys of 300 GW veterans (about 20% 196 women) that will be shared for use in the currently proposed study.

Taken overall, the minimum sample size expected for this study is 6,835 male and female veterans. The number of women who will be included in GWWC is anticipated to be 560 to 800 women GW veterans and an additional 680 to 959 women veteran who were not deployed to the Persian Gulf. This includes 1,290 Army GW veterans from the Ft. Devens Cohort, 300 GW veterans from the Boston GWI Consortium (20% women), over 1,318 GW veterans from CSP 585 pilot study (23.7% women), 3,927 GW veterans from the CDC USAF study (which included about 522 women).

New data collection for the GWWC will involve telephone interviews and postal surveys of women (with a projected 200 completed surveys), including questions on women's health previously utilized in surveys conducted by the investigators at VA, VA Boston Healthcare system, and Boston University. De-identified data will be compiled and analyzed by Augusta University investigators in collaboration with the other study sites.

Boston University Data Coordinating Center Staff (Emily Sisson and others) and Vahe Heboyan and Steve Coughlin at Augusta University have continued the process of quality assurance of data management and data collection. This includes documenting data files and verifying n's of key variables included in existing datasets.

What opportunities for training and professional development has the project provided?

Dr. Benjamin Ansa is working under the mentorship of Drs. Coughlin and Heboyan. His doctoral dissertation at Augusta University will utilize data from the Gulf War Women's Health Cohort Study. Dr. Ansa completed a Study Protocol manuscript which has been accepted for publication.

How were the results disseminated to communities of interest?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Three abstracts were presented at professional conferences, detailing results from the Gulf War Women's Health Cohort Study.

What do you plan to do during the next reporting period to accomplish the goals?

Hire and train additional staff at subsites; continue quality assurance measures; undertake postal survey and telephone interviews of women Veterans included in Ft. Devens Study; code postal survey questionnaire/telephone interview responses; continue to prepare manuscripts and present finding at professional and scientific meetings.

4. **IMPACT:** Describe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:

What was the impact on the development of the principal discipline(s) of the project?

The Gulf War Women's Health Cohort Study will provide a comprehensive picture of the health of women GW veterans. This includes assessment of current health status, changes in health symptoms and conditions over time, and possible differences in health outcomes associated with specific experiences and exposures during the war. It will allow for an assessment of GWI symptom patterns that may be specific to women veterans and a determination of diagnosed medical conditions. The study will generate data that will improve our understanding of GWI in women veterans who served in the Gulf War, women GW veteran's health, and adverse reproductive outcomes.

What was the impact on other disciplines?

Nothing to report

What was the impact on technology transfer?

Nothing to report

What was the impact on society beyond science and technology?

Nothing to report

5. **CHANGES/PROBLEMS:** The Project Director/Principal Investigator (PD/PI) is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:

Changes in approach and reasons for change

Nothing to report

Actual or anticipated problems or delays and actions or plans to resolve them
Describe problems or delays encountered during the reporting period and actions or plans to resolve them.

There has been a delay in releasing funds from Augusta University to Boston VA Healthcare and the Boston University School of Public Health. This has led to a delay in initiating the survey of women Veterans in the Ft. Devens Study. Sponsored Research at Augusta University is actively working to resolve the delay in release of funds.

Changes that had a significant impact on expenditures

Nothing to report

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

Nothing to report

Significant changes in use or care of vertebrate animals.

Not applicable

Significant changes in use of biohazards and/or select agents

Not applicable

6. **PRODUCTS:** List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."

- **Publications, conference papers, and presentations**
  Report only the major publication(s) resulting from the work under this award.

Journal publications.

Coughlin SS, Heboyan V, Sullivan K, Krengel M, Wilson C, Iobst S, Klimas N. Cardiovascular disease among Female Veterans of the 1991 Gulf War Era: Results from the Cooperative Studies Program 585 Gulf War Era Cohort and Biorepository. Environ Health Sci 2019;2019;5:24-25.
Heboyan V, Krengel MH, Sullivan K, Klimas N, Wilson C, Coughlin SS. Gender differences in Gulf War Illness: a re-analysis of data from the CDC Air Force Study using CDC and Kansas case definitions. Journal of Occupational and Environmental Medicine 2019;61:610-6.

Sullivan K, Krengel M, Heboyan V, Wilson C, Iobst S, Klimas N, Coughlin SS. Prevalence and Patterns of Symptoms of Symptoms among Female Veterans of the 1991 Gulf War Era: 25 years later. Journal of Women's Health 2020, in press.
Ansa BE, Sullivan K, Krengel MH, et al. The Gulf War Women's Cohort Study: Study Design and Protocol. International Journal of Environmental Research and Public Health 2020, in press.

Books or other non-periodical, one-time publications.

Nothing to report

Other publications, conference papers, and presentations.

Heboyan V, Krengel MH, Sullivan K, Klimas N, Wilson C, Coughlin SS. Gender differences in Gulf War Illness: a re-analysis of data from the CDC Air Force Study using CDC and Kansas case definitions. Society for Epidemiologic Research annual meeting, Minneapolis, MN, June 2019

Iobst S, Coughlin SS, Heboyan V, Sullivan K, Krengel M, Wilson C, Klimas N. Frequency of Symptoms among Female and Male Veterans of the 1991 Gulf War Era: Results from the Cooperative Studies Program 585 Gulf War Era Cohort and Biorepository. Military Health System Research Symposium, Kissimmee, FL, August, 2019

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

Nothing to report

- **Technologies or techniques**
  Identify technologies or techniques that resulted from the research activities. In addition to a description of the technologies or techniques, describe how they will be shared.

Nothing to report

- **Inventions, patent applications, and/or licenses**

Nothing to report

- **Other Products**

Nothing to report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Steven Coughlin, PI, 2.4 person months, overseeing all aspects of the study
Vahe Heboyan, Co-I and study biostatistician, 2.4 person months, analysis of data and assisting with manuscripts
Maxine Krengel, Co-I, contributing to all aspects of the study, surveying GW women included in Ft. Devons Study
Kimberly Sullivan, Co-I, contributing to all aspects of the study
Emily Sisson, overseeing Boston University Data Coordinating Center activities
Stacy Iobst, Co-I, contributing to all aspects of the study
Col Candy Wilson, Co-I, contributing to all aspects of the study

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Nothing to report

What other organizations were involved as partners?

Nothing to report

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: For collaborative awards, independent reports are required from BOTH the Initiating PI and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to **https://ers.amedd.army.mil** for each unique award.

QUAD CHARTS: If applicable, the Quad Chart (available on https://www.usamraa.army.mil) should be updated and submitted with attachments.

9. APPENDICES:

Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.

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Cardiovascular Disease among Female Veterans of the 1991 Gulf War Era

Steven S. Coughlin[1,2,*], **Vahe Heboyan**[3], **Kimberly Sullivan**[4], **Maxine Krengel**[5], **Col Candy Wilson**[6], **Stacey Iobst**[7], **Nancy Klimas**[8,9]

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[3]Department of Interdisciplinary Health Sciences, College of Allied Health Sciences, Augusta University, Augusta, GA

[4]Boston University School of Public Health, Boston, MA

[5]VA Boston Healthcare System, Boston, MA

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[9]Institute for Neuro-Immune Medicine, Dr. Kiran C. Patel College of Osteopathic Medicine, Nova Southeastern University, Fort Lauderdale, FL

Introduction

Recent clinical studies have identified exercise-induced transient postural tachycardia and abnormal heart-rate variability in patients with Gulf War Illness (GWI) (Rayhan et al. 2013; Garner et al. 2018; Blanchard et al. 2018). Altered heart rate variability may reflect autonomic dysfunction and atrophy in the cardio-regulatory regions of the brainstem (Rayhan et al. 2013). However, the long-term cardiovascular effects of abnormal autonomic nervous system functioning in patients with GWI are unknown (Blanchard et al. 2018). In additional clinical research studies, veterans with GWI have been found to have higher levels of cytokines such as interleukins (Coughlin 2017), which are inflammatory factors associated with increased risk of coronary heart disease and other chronic diseases (Lampert et al. 2006).

Using data from the Veterans Affairs (VA) Cooperative Studies Program 585 Gulf War Era Cohort and Biorepository (Khalil et al. 2018), this study examined the prevalence of

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cardiovascular disease among female veterans who served during the Gulf War or Gulf War Era. A total of 301 women veterans participated in the survey. Mean ages in 2016 were 53 years among women who were deployed and 54 years among women who were not deployed. About one-fifth of the participants were > 60 years of age. About three-quarters of the participants were white, 17–20% were Black or African American, and the remainder were American Indian/Alaska Native, Asian/Pacific Islander, or other race. About 6–8% of the participants were Hispanic or Latino. The majority of the participants had completed some college or received a college degree. In this sample, 12–13% of the participants were current cigarette smokers, 35% self-reported high blood pressure, and 40–41% self-reported high cholesterol. Compared to women veterans not deployed to the Gulf, deployed women veterans were not more likely to report cardiovascular disease (heart attack, coronary artery disease, congestive heart failure, stroke, or peripheral vascular disease). About 6.9% percent of the women who were deployed to the Gulf reported cardiovascular disease as compared to 11.2% of the women who were not deployed (odds ratio = 0.6, 95% confidence interval 0.3–1.4, $P < 0.2$).

Twenty-seven years after the 1990–1991 Gulf War, women veterans who were deployed to the Gulf continue to report similar levels of cardiovascular disease risk factors (cigarette smoking, high blood pressure, high cholesterol) as non-deployed women veterans who served during the Gulf War era. Women veterans deployed to the 1990–1991 Gulf War do not appear to be at increased risk of cardiovascular disease, although studies with longer duration of follow-up and larger sample sizes are needed.

Acknowledgements:

The views expressed are those of the authors and do not necessarily reflect the official policy or position of the Air Force, the Department of Defense, the Department of Veterans Affairs, or the U.S. Government. This work was supported by the Office of the Assistant Secretary of Defense for Health Affairs, through the Gulf War Illness Research Program under Award No. W81X-WH-16-1-0774. The authors thank the VA Cooperative Studies Program (CSP) and Cooperative Studies Program 585 Gulf War Era Cohort and Biorepository investigators and staff for providing the data used in this study.

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Sex Differences in Gulf War Illness

A Reanalysis of Data From the CDC Air Force Study Using CDC and Modified Kansas Case Definitions

Vahé Heboyan, PhD, Maxine H. Krengel, PhD, Kimberly Sullivan, PhD, Stacey Iobst, PhD, RN, Nancy Klimas, MD, Candy Wilson, PhD, APRN, WHNP-BC, and Steven S. Coughlin, PhD

Objective: Estimate and compare the prevalence of Gulf War Illness (GWI) in male and female Gulf War veterans using Centers for Disease Control and Prevention (CDC) and modified Kansas case definitions. **Methods:** Data from the landmark CDC Air Force Study of GW Air Force veterans is used. **Results:** Nearly half of the deployed veterans met the GWI CDC case definition compared with 14% of non-deployed veterans. Only 29% met the definition using the modified Kansas criteria compared with 8% of non-deployed veterans. Deployed veterans and female veterans exhibited significantly higher GWI risk. Female GW veterans had higher rates of severe and mild-to-moderate cases of GWI. **Conclusion:** Results suggest increased GWI rates based on CDC and modified Kansas criteria among deployed and female veterans. Further research is needed to examine the chronic health outcomes of female GW veterans independently.

Keywords: epidemiology, gulf war illness, gulf war veterans, sex differences, symptoms

Gulf War Illness (GWI) is the leading health issue affecting Gulf War (GW) veterans .[1] At least 25% of the 700,000 US veterans who served in the 1990 to 1991 GW suffer from GWI,[1] which is characterized as a chronic multisymptom illness (CMI) not explained by medical diagnosis and standard laboratory tests. These symptoms usually manifest as a combination of cognitive and mood problems, persistent headache, fatigue, widespread pain, gastrointestinal, respiratory, and skin problems.[1,2] At present there are two main diagnostic case definitions for GWI, including the more specific Kansas criteria and the more sensitive CDC criteria of CMI.[3,4] A recent review[5] of the literature on the health of 1991 GW veterans indicates that the majority of reviewed studies, using alternative GWI case definitions, have found the excess rates of GWI among veterans to be 25% to 32%, while three studies using more narrow definitions, have reported lower estimates of GWI. The inconsistencies in these findings not only make it difficult for researchers and clinicians to understand the prevalence of this disabling condition, but make it difficult to determine the nature of the illness to target effective treatments. It is therefore imperative to more thoroughly compare case criteria and definitions and provide separate criteria for men and women where necessary.

Over 27 years have passed since the GW, but GWI still remains one of the most critical health challenges facing GW veterans. Researchers and medical practitioners still have not identified a single etiology that causes GWI nor have they found a single effective treatment. Furthermore, the research community at large still has not developed an objective diagnosis or a single validated case definition.[6] An Institute of Medicine (IOM)[7] study tasked by the US Department of Veterans Affairs (VA) was completed to develop a case definition for CMI. It was concluded that it could not establish a consensus case definition due to lack of uniform symptoms measured and the extended onset and long duration of these symptoms. The absence of a consensus case definition not only weakens GWI research but also results in a considerable uncertainty about the diagnosis in the clinical setting, which may result in misdiagnosis and limit the ability of healthcare providers to effectively treat GWI. Given these limitations and challenges, the committee also recommended that researchers utilize existing data and the two widely used case definitions for GWI (Kansas[4] and CDC[3]) to expand knowledge about GWI. Another recommendation was to separately study the apparent sex differences given the likelihood of differences in symptoms between men and women.

Women comprised almost 7% of the nearly 700,000 military personnel who served in the 1990 to 1991 GW and represented the largest proportion of US women serving in a war zone in US military history up to that point in time.[8] Expanded military roles for women increased their exposure to more intense levels of combat and toxicants.[9] Multiple studies have looked at rates of symptoms, GWI, and psychiatric conditions in female versus male GW veterans.[4,9–12] Results from some studies, but not all, suggest that GWI is more common in women GW veterans than their male counterparts.[4,11,12] However, in the 28 years since the war, few studies have been designed to specifically evaluate GWI and other medical outcomes in deployed women veterans of the 1991 GW[10,12] and original large scale datasets where compiled before relevant current criteria were provided. A small number of studies completed to date that examined women's symptoms have suggested excess rates of diabetes and women's health problems, for example, breast cysts, abnormal Pap smears, yeast infections, having difficulty getting pregnant and bladder infections, as compared with women who were not deployed to the Persian Gulf.[10–13] However, there is no consistency in findings in sex-specific rates of symptoms.

Given the increased focus on GWI case definition,[14,15] lack of consensus on case definition, and the need to better understand the mortality, morbidity, and symptomology[15] among GW veterans, it is essential to study the sex differences in GWI and its symptoms utilizing the two most widely used case definitions. The objective of

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this study was therefore to (1) conduct a comparative analysis of defining GWI cases based on CDC and Kansas criteria and (2) extend the study by Fukuda et al[3] of the health of US Air Force GW veterans by conducting a more in-depth comparative analyses of the prevalence of GWI and chronic illnesses in male and female veterans separately using case definitions from both criteria. We hypothesized that the prevalence of GWI and chronic illnesses would be greater among female GW veterans than their male counterparts as was the case with studies above.

This study makes important contributions to the scientific literature. First, it provides estimates for the sex differences in GWI and its symptoms, which, to the best of our knowledge, has not been previously studied in the CDC Air Force study population. Second, we provide comparative estimates for GWI case definition and its severity using both CDC and Kansas criteria in this important CDC cohort. Overall, this study fills the literature gap by enriching our knowledge about GWI sex disparities and makes a valuable contribution to the information on the comparability of the GWI case definition for CDC and Kansas criteria. Furthermore, this study provides new extensive analyses of the CDC Air Force Study data since the publication of the seminal article by Fukuda et al[3] over two decades ago.

METHODS

Data

In November 1994, the Department of Veterans Affairs, Department of Defense, and the Pennsylvania Department of Health requested that the CDC investigate a report of unexplained illnesses among members of an Air National Guard (ANG) unit who were GW veterans. We used shared data from the resultant CDC Air Force Study[3,16] of the health of GW veterans. The original data were collected during January to March of 1995 among the members of an ANG stationed in the south-central Pennsylvania (Unit A) and three comparison units (units B, C, and D) in Pennsylvania and Florida. The latter were selected for similarity in mission responsibility. After an initial investigation of 59 GW veterans, which involved standardized interviews and physical examinations, a larger sample of veterans who served during GW ($n = 3927$) were surveyed during January to March 1995.[3,16] After excluding 204 who were younger than 18 years during the GW, 1163 (31.2%) were GW veterans and 2560 (68.8%) had not been deployed.[3,16] All members, regardless of their health status or participation in the GW, were invited to anonymously complete a questionnaire of general health history, socio-demographic information, and symptom report, including the frequency, duration, and severity of the 35 symptoms most commonly mentioned, and used to verify and characterize GWI in the initial study that examined GW veterans from the ANG.[17]

Chronic Multisymptom Illness (CMI) Criteria

Definitions of GWI have varied across studies of GW veterans. The CMI criteria, also known as the ''CDC criteria'' was defined in Fukuda et al[3] based on 10 case-defining symptoms. A GWI case is defined as having one or more chronic symptoms for over 6 months from at least two out of following three categories: (1) fatigue, (2) mood and cognition (symptoms of feeling depressed, difficulty remembering or concentrating, feeling moody, feeling anxious, trouble finding words, or difficulty sleeping), and (3) musculoskeletal (symptoms of joint pain, joint stiffness, or muscle pain). A case is considered severe if each case-defining symptom was rated as severe; otherwise, the case is classified as mild-to-moderate. For a more detailed discussion of data collection and case definition, please refer to Fukuda et al[3] and CDC publications.[16,17]

Fukuda et al[3] reported that in all units the prevalence of each of 13 chronic symptoms was significantly greater ($P < 0.05$) among persons deployed to the GW than among those not deployed. The prevalence of mild-to-moderate and severe CMI cases was 39% and 6%, respectively, among GW veterans compared with 14% and 0.7% among non-deployed veterans. About 14% of the participants in the CDC study were women.

Modified Kansas Criteria (MKC)

The Kansas GWI case definition was developed for a population based survey of over 2000 Kansas veterans who were deployed to the Persian Gulf during the 1990 to 1991 GW. Steele[4] has proposed the Kansas definition for the presence of 29 moderate to severe health symptoms, which were empirically identified based on the patterns that distinguished veterans who were deployed to the Persian Gulf from those who were not. Symptoms are scored on a three point scale from mild (1) to severe (3) and a case is defined as having a total score of 2 or greater in at least three of six case defining domains: fatigue, pain, neurological and/or cognitive and/or mood, skin, gastrointestinal, and respiratory. This definition excluded veterans who had one or more medical conditions (cancer other than non-melanoma skin cancer, diabetes, heart disease other than high blood pressure, chronic infectious disease, liver disease, lupus, multiple sclerosis, stroke, bipolar disorder, schizophrenia) or who had been hospitalized since the GW for depression, posttraumatic stress disorder, or alcohol or drug dependence[11]. In this study, a modified Kansas criteria was used based on available symptom criteria from the 1995 CDC Air Force survey which included 20 of the 29 Kansas symptoms. The missing symptoms included some of the least commonly reported symptoms (ie, eyes very sensitive to light, blurred or double vision) so the lack of this information likely did not measurably affect Kansas GWI rates. The full modified Kansas criteria is listed in Appendix Table A1, http://links.lww.com/JOM/A566.

Statistical Analyses

We start our analyses by describing the Air Force Study data and computing the prevalence of the 35 most common symptoms reported by GW veterans by deployment. We estimated the rates of current symptom and symptoms lasting for more than 6 months for male and female veterans separately and used Chi-square and Fisher Exact tests (as applicable) to test for statistical difference in reported symptoms among male and female veterans. Then, to apply the Kansas criteria, we matched symptoms across six categories (fatigue, pain, neurological/cognitive/mood, skin, gastrointestinal, respiratory) to the symptoms available in the CDC Air Force database and were able to match 20 symptoms. Table A1, http://links.lww.com/JOM/A566 lists symptoms matched. To assess the comparability of the CDC and MKC, for the deployed veteran subsample, we computed GWI cases defined by both criteria and tested if there was a statistical difference in the rates in the overall sample and by sex. Finally, using both criteria, we constructed multinomial logistic regression models to estimate the multivariate associations of categorical socio-demographic variables and deployment status with GWI case severity for the whole sample and for male and female veterans separately. We reported the relative risk ratio (RRR) and corresponding 95% confidence intervals (CI). RRR is similar to the odds ratio (OR) and indicates the risk of the outcome occurring in the comparison group compared with the risk of the outcome occurring in the referent group changes with the variable in question. All analyses were conducted using STATA 14 (StataCorp LP, College Station, TX).

RESULTS

Demographic, Military, and Health Characteristics

Our sample of GW Air Force veteran data consisted of 3723 participants, which excludes respondents who were less than

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TABLE 1. Demographic, Military, and Health Characteristics of All Subjects ($N = 3723$) by Sex and Deployment Status (Percent)

Characteristics	Overall (Percent)			Deployed (Percent)			Not Deployed (Percent)		
	Male	Female	All	Male	Female	All	Male	Female	All
Age, median, yr	35*	33	34	37	33	36	33	33	33
Male			86			94			82
White	88	75	86	91	79	90	86	74	84
Married	72	55	69	76	49	75	69	55	66
Less than college education	31	22	30	34	33	34	30	21	29
Employed full-time	90	81	89	92	87	92	89	80	87
Deployed to Persian Gulf	34	13	31						
Current enlisted rank	86	90	86	83	84	83	87	91	88
Years on active duty									
<1	6	16	8	6	14	6	7	16	9
1–10	69	71	69	67	72	67	70	70	70
>11	25	14	23	28	13	27	23	14	21
Years in guard or reserve									
<1	43	36	42	38	34	37	46	37	45
1–10	28	41	30	25	31	25	30	43	32
>11	28	23	28	38	35	38	24	21	23
Self-assessed health									
Excellent	25	26	25	19	12	18	28	29	28
Very good	41	45	42	40	37	40	42	46	43
Good	29	24	28	32	35	33	28	22	27
Fair	4	4	4	9	9	9	2	4	2
Poor	0.5	1	0.5	0.7	7	1	0.3	0	0.3
Current smoker	22	24	23	25	30	25	21	23	21
Average No. of alcoholic drinks/wk									
None	34	50	37	32	46	33	35	51	38
1–3	36	37	36	37	39	37	36	37	36
>4	30	13	27	31	14	30	29	12	26

*All numbers in the table are percentages except for "Age, median, year" which is the median age in years.

18 years of age or not members of the units surveyed. Table 1 reports demographic, military, and health characteristics of GW veterans by sex. Male veterans comprised 86% of the sample. The median age of male veterans were 35 years (mean 36 years; range, 21–60) and of female veterans were 33 years (mean 33 years, range, 21–56); 88% of male and 75% of female veterans were white; 90% of male and 81% of female veterans were employed; at the time of survey 72% of male and 55% of female veterans were married; and 34% of male and 13% of female veterans were deployed to the Persian Gulf. Female veterans had fewer years on active duty and in guard or reserve. Also, a larger percentage of females reported having excellent or very good health, smoking, and consuming moderate amounts of alcoholic drinks (less than 4 drinks per week). Compared to non-deployed veterans, a large percentage of deployed veterans were male, white, and married. They also had less short-term (<10 years) active duty and National Guard or reserve experience and reported being less healthy with higher rates of smoking, especially among female deployed veterans.

Prevalence of Symptoms

Almost all veterans ($n = 3701$, 99%) participating in the survey reported at least one symptom as a current health problem. Compared with the veterans not deployed to the Gulf War, both male and female GW veterans reported significantly ($P < 0.05$) higher prevalence of all current symptoms and symptoms lasting more than 6 months except for hay fever or allergies, which were higher among non-deployed female veterans (Table 2 and Fukuda et al[3]). GW female veterans, compared with their male counterparts, reported the same or higher prevalence of all symptoms except joint stiffness, hay fever or allergies, diarrhea, and nasal sores for current symptoms and nasal sores, chemical sensitivity, and unintended weight loss for symptoms lasting more than 6 months. Of these higher reported current symptoms rates, most were statistically significant. However, only few significant differences were reported among male and female deployed or not deployed military personnel for symptoms lasting more than 6 months (Table 2).

Prevalence of Gulf War Illness

Appendix Table A2, http://links.lww.com/JOM/A566 reports results of GWI case definitions based on the CDC and modified Kansas Criteria (MKC) and Table 3 reports the results of defining GWI cases among male and female GW veterans using both CDC and modified-Kansas criteria.

CDC Criteria (Table A2, Part A, http://links.lww.com/JOM/A566). Overall, 3675 veterans provided data on all 10 case defining symptoms. About 25% of all veterans ($n = 889$; 753 men, 129 women, 7 unknown) met CDC's GWI definition, of which, about 10% ($n = 86$; 69 men, 17 women) were classified as severe. The prevalence of severe GWI among female veterans was 20% compared with 14% of mild-to-moderate cases. Among GW deployed veterans ($n = 1155$) who provided data on all 10 case defining symptoms, 517 (45%) veterans (476 men, 39 women, 2 unknown) met the CDC GWI definition. In comparison, only 14% ($n = 372$) of not deployed veterans met the CDC GWI definition.

Modified-Kansas Criteria (MKC) (Table A2, Part B, http://links.lww.com/JOM/A566). Of all deployed and non-deployed veterans ($n = 3723$), about 15% ($n = 540$; 450 men, 88 women, 2 unknown) met modified-Kansas GWI case definition, of which, about 11% ($n = 60$; 41 men, 19 women) were classified as severe. The prevalence of severe GWI among female veterans was 32%

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TABLE 2. Prevalence (Percent) of 35 Current and Longer-Term Symptoms Among Gulf War Veterans ($n = 1163$) and Non-Deployed Military Personnel ($n = 2538$) by Sex

	Current Symptoms (%)						Symptoms Lasting More than 6 months (%)					
	Veterans			Non-Deployed Military Personnel			Veterans			Non-Deployed Military Personnel		
Characteristics	**M**	**F**	**All**	**M**	**F**	**All**	**M**	**F**	**All**	**M**	**F**	**All**
Sinus congestion	51	61	52	37	47*	39	46	55	46	29	38	31
Headache	49	74*	50	36	59*	40	43	68	44	28	45	31
Fatigue	42	62*	43	15	26*	17	40	52*	40	11	21	13
Joint pain	36	38	36	13	13	13	33	36	33	11	11	11
Difficulty remembering or concentrating	34	42	35	9	7	9	31	39	32	8	5	8
Joint stiffness	31	29	30	12	9	11	28	28	28	9	8	9
Difficulty sleeping	27	39*	28	11	18*	12	24	36	25	8	13	9
Gas, bloating, cramps, or abdominal pain	25	46*	27	12	25*	15	24	42	25	9	19	11
Trouble finding words	26	32	26	8	9	8	24	28	24	7	8	8
Moody or irritable	25	35*	25	8	13†	9	24	33	24	7	9†	7
Rash or sores	23	30	23	6	7	6	21	29	21	5	5	5
numbness or tingling	20	29*	21	7	10†	8	19	22*	19	4	7	5
Muscle pain	20	20	20	8	8	8	18	19	18	6	6	6
Hay fever or allergies*	19	17†	19	18	21	18	18	17	18	16	19	16
Feeling depressed	17	30*	18	8	17*	10	16	28	16	6	13	8
Diarrhea (>3 loose stool samples per 24 hour)	18	17	18	4	4	4	16	17	16	3	2	3
Sore throat	17	29*	17	9	15*	10	15	25	15	6	10	6
Cough	16	25	17	11	11†	11	13	23†	14	6	6	6
Feeling anxious	16	28*	17	6	9*	7	15	26	15	4	7	5
Unintended weight gain >10 lb	16	30*	17	7	11*	7	14	29	15	5	8	5
Shortness of breath	16	17	16	6	6	6	14	16	14	4	5	4
Chest pain	15	20	15	7	8	7	13	17	13	5	6	5
Decreased interest in sex	14	26*	14	5	9*	6	12	23	13	3	6	4
Dizziness or trouble maintaining balance	13	28*	14	3	6*	4	11	20*	12	2	3	2
Night sweats that soak bed sheets	13	14	13	4	4	4	12	12†	12	3	2*	2
Fatigue lasting 24 hours after exertion	12	28*	13	2	4*	2	11	26	12	2	3	2
Nasal sores	11	9	11	5	6	5	10	7	9	3	4	4
Swollen lymph nodes	9	22*	10	2	9*	4	8	15†	8	1	5	2
Milk intolerance	7	13*	7	4	8*	5	6	13	7	4	7	4
Episodes of disorientation	6	13*	7	1	2	1	5	12	5	1	1	1
Nausea or vomiting	6	17*	6	2	4*	2	5	13	6	1	3	1
Wheezing	6	7	6	3	3	3	5	6	5	2	3	2
Chemical sensitivity	5	6	5	2	5*	2	5	3*	5	1	4	2
Fever	5	9	5	2	2	2	4	7	4	1	1	1
Unintended weight loss >10 lb	3	3	3	1	1	1	2	1	2	1	1	1

*Indicates statistically significant difference between male and female service members at 5% using a chi-square test to detect statistical difference between two categorical variables.

†Indicates statistically significant difference between male and female service members at 10% using a chi-square test to detect statistical difference between two categorical variables.

compared with 14% of mild-to-moderate cases. Whereas, among male veterans, mild-to-moderate cases were more prevalent using both CDC and MKC criteria. Among GW deployed veterans ($n = 1163$) that provided data, 334 (29%) veterans (306 men, 27 women, 1 unknown) met the MKC GWI case definition. In comparison, only 8% (n = 206) of not deployed veterans met the MKC GWI definition.

Comparative Analysis

A primary objective of the study was to compare GWI case definition using two distinct criteria. Table 3 reports tabulated GWI case definition by both criteria for deployed GW veterans. Table 3 tabulates GWI case definitions using both criteria. Results indicate that there is a statistical difference across criteria. The MKC identified only about half (302 out of 517) of GWI cases that were defined by CDC criteria, while also defining 31 GWI cases that were not defined by the CDC criteria. A similar relationship was evident when examining GWI case definition by sex. Table 4 cross-tabulates case severities using both criteria. Results showed that the majority of case mismatch were in the mild-to-moderate severity category for the overall sample as well as sex-specific. Over half of mild-to-moderate GWI cases defined by CDC criteria were classified as "non-case" by the MKC and these differences were statistically significant. We replicated these comparative analyses for the entire sample that involves both deployed veterans and not deployed military personnel (Table A3, http://links.lww.com/JOM/A566). Results were similar.

Table 5 reports results from the multivariate analyses of predicting GWI case severity (non-case, mild-to-moderate, severe) by CDC and MKC criteria using multinomial logistic regression models. Results showed that GWI was more likely among veterans that served in the Gulf War and among female veterans. More specifically, these who served in the 1990 to 1991 Gulf War were at about four times higher risk of being diagnosed with a mild-to-moderate GWI case (compared with not having GWI) than those who did not serve in the Gulf War. Moreover, female veterans were

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TABLE 3. Comparison of Gulf War Illness Case Identification among Deployed Gulf War Veterans by CDC and Modified† Kansas Criteria

CDC Criteria	Kansas Criteria		
Case Versus Non-case	**GWI Case**	**Non-case**	***P*-Value***
Overall			
GWI case	302	215	0.000
Non-case	31	607	
Male			
GWI case	278	198	0.000
Non-case	28	574	
Female			
GWI case	24	15	0.000
Non-case	3	25	

*Chi-squared or Fisher Exact test for group differences between CDC and Modified Kansas Criteria.
†Original criteria proposed by Steele (2000)[4] was modified due to lack of certain symptoms tracked in the CDC Air Force study.

at about 1.6 times higher risk of being diagnosed with a mild-to-moderate GWI case (compared with not having GWI). Results for the mild-to-moderate GWI were similar in models for both CDC and MKC case definitions.

Using the CDC GWI case definition, the risk associated with having a severe case (compared with non-case) of GWI was 15.2 times higher among Gulf War deployed veterans in the overall sample and 14.9 and 18.6 times higher among deployed male and female veterans, respectively. Female veterans were at three times higher risk of having a severe case of GWI (compared with non-case). These results were different when using the modified-Kansas GWI case definition. More specifically, in the model based on modified-Kansas criteria, female veterans were at a 5.5 times higher risk of having a severe case of GWI. Compared with the results from the models based on CDC criteria the risk ratios of having GWI were relatively lower for the overall model (RRR = 9.6) and female deployed veterans (RRR = 5.1) and slightly higher for male deployed veterans (RRR = 16.0). The relative risks of having GWI was also higher among those who were current smokers, had less than college education, were 40 to 49 years of age (compared with being <30 years of age), and enlisted.

We also estimated alternative multivariate regression models (not reported) where we included an interaction term that controls for being a female deployed veteran. We hypothesized that being both a female and deployed GW veteran might be associated with higher risks of having GWI. However, results did not show any statistically significant relationship.

DISCUSSION

We reanalyzed data collected in 1995 from the landmark CDC Air Force Study[3] to estimate the prevalence of GWI and its severity among 1990 to 1991 GW deployed and non-deployed veterans. We extended the seminal study by Fukuda et al[3] to examine the GWI differences by sex. We also used CDC and MKC, two of the most widely used GWI case definitions, to study the comparative differences in GWI case and severity and estimate socio-demographic and deployment factors affecting GWI. We applied both criteria to the entire sample and male and female veterans separately. The key conclusion from our study was that, regardless of GWI case definition criteria, veterans who were deployed in the GW exhibited statistically significantly higher risks of having GWI with women having higher rates than men. Furthermore, female GW veterans also had higher rates of severe GWI cases compared with male GW veterans.

Our study also found that 45% of GW veterans met the GWI case definition by CDC criteria, but only 29% met the definition using the modified-Kansas criteria. Rate of CDC criteria in non-deployed veterans was 14% and rate of Kansas criteria in non-deployed veterans was 8%. Excess prevalence of GWI is calculated by the subtraction of the percentage of GWI in GW veterans from the percentage of GWI in non-deployed veterans. This suggests an excess prevalence of 31% for CDC criteria and 21% for Kansas GWI criteria in our study. These results correspond well with rates listed in the 2008 VA Research Advisory Committee for Gulf War Veterans' Illnesses (RAC) report and that of other studies using similar case criteria with 25% to 32% excess prevalence of GWI in GW veterans.[1,3–6,13,18]

Our results also echo those of Dursa et al,[6] where they found inherent differences in GWI case definitions using CDC and modified-Kansas(modification to the Kansas[4] criteria by Dursa et al[6] is different from our modification due to differing study populations and symptom tracking) criteria in the large VA National Survey of 30,000 GW veterans conducted in 1995 where they reported an excess prevalence of 33% for CDC criteria and 23% for MKC. However, Dursa et al,[6] reported slightly higher rates of GWI in GW veterans at 50% for CMI and 40% for Kansas criteria in GW veterans and 17% in non-deployed veterans for both case criteria. The difference for this increased prevalence is likely reflected in the fact that Dursa et al's,[6] modified-Kansas criteria did not include severity of health symptoms in their reanalysis due to limitations of their original survey questions. Our study builds on and expands this prior work by comparing rates of severe and mild-moderate GWI in the original CDC cohort. Our results suggest that risk of severe GWI symptoms was dramatically higher in deployed GW veterans at 15.2 times greater risk for CDC criteria and 9.6 times greater risk for Kansas criteria.

Collectively, these results also confirm prior findings that the CDC criteria are more sensitive and the MKC are more specific for GWI in GW veterans. In fact, our GWI rates for deployed and non-deployed veterans are remarkably similar to those from the original Kansas cohort where Steele[4] found rates of 34% GWI in GW deployed veterans and 8% GWI in non-deployed veterans. These results confirm prior suggestions including those of the National Academy of Sciences that the greater sensitivity of the CDC criteria could be used for clinical case criteria and service connected health

TABLE 4. Comparison of Gulf War Illness Case Severity among Deployed Gulf War Veterans by CDC and Modified† Kansas Criteria

CDC Criteria	Kansas Criteria			
Case Severity	**Severe**	**Mild-Moderate**	**Non-Case**	***P*-Value***
Overall				
Severe	32	34	2	0.000
Mild-moderate	9	227	213	
Non-case	2	34	607	
Male				
Severe	26	30	2	0.000
Mild-moderate	8	214	196	
Non-case	2	26	574	
Female				
Severe	3	4	0	0.000
Mild-moderate	1	13	15	
Non-case	0	3	25	

*Chi-squared or Fisher Exact test for group differences between CDC and Modified Kansas Criteria.
†Original criteria proposed by Steele (2000)[4] was modified due to lack of certain symptoms tracked in the CDC Air Force study.

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TABLE 5. Multivariate Associations* With Mild-to-Moderate and Severe Gulf War Illness by Sex†

	Mild-to-Moderate Cases									Severe Cases								
	All			Male			Female			All			Male			Female		
Variables	**RRR**	***P*>*z***	**95% CI**	**RRR**	***P*>z**	**95% CI**	**RRR**	***P*>z**	**95% CI**	**RRR**	***P*>*z***	**95% CI**	**RRR**	***P*>*z***	**95% CI**	**RRR**	***P*>*z***	**95% CI**
CDC criteria																		
Gulf War Veteran (ref. No)	4.0	0.000	3.4–4.9	4.0	0.000	3.4–4.9	4.5	0.000	2.5–8.3	15.2	0.000	8.6–27.2	14.9	0.000	7.7–29	18.6	0.000	5.9–59.3
Age (ref. <30 years old)																		
30–39	1.1	0.242	1.0–1.5	1.1	0.388	0.9–1.5	1.3	0.311	0.8–2.3	1.2	0.587	0.7–2.2	0.9	0.713	0.5–1.8	3.7	0.107	0.8–18.3
40–49	2.0	0.000	1.6–2.7	2.0	0.000	1.6–2.7	2.5	0.004	1.4–4.8	1.3	0.441	0.7–2.8	1.2	0.572	0.6–2.7	1.8	0.588	0.3–14.7
≥50	1.6	0.010	1.2–2.3	1.5	0.033	1.1–2.2	2.9	0.116	0.8–11.2	1.5	0.378	0.7–3.7	1.4	0.457	0.6–3.6	0.0	0.984	
Current enlisted rank (ref. other units)	1.5	0.000	1.3–1.9	1.6	0.000	1.4–2.1	0.8	0.547	0.5–1.6	1.4	0.223	0.9–2.4	1.2	0.568	0.7–2.3	1.9	0.289	0.6–6.4
Current smoker (ref. No)	1.3	0.004	1.1–1.7	1.3	0.009	1.1–1.7	1.4	0.211	0.9–2.4	2.0	0.005	1.3–3.3	1.8	0.024	1.1–3.2	2.3	0.146	0.8–7.4
Race (ref. non-White)	1.2	0.198	1.0–1.6	1.0	0.856	0.8–1.4	2.0	0.019	1.2–3.7	0.6	0.051	0.4–1.1	0.5	0.026	0.3–1.0	0.9	0.879	0.3–3.3
Marital status (ref. not-married)	1.2	0.085	1.0–1.5	1.2	0.075	1.0–1.6	1.0	0.903	0.7–1.7	1.1	0.821	0.7–1.8	1.0	0.945	0.6–1.9	1.2	0.730	0.5–3.7
Education (ref. less than college education)	0.8	0.039	0.7–1.0	0.8	0.027	0.7–1.0	1.0	0.884	0.7–1.8	0.7	0.166	0.5–1.2	0.6	0.063	0.4–1.1	1.7	0.444	0.5–6.8
Gender (ref. male)	1.6	0.000	1.3–2.1							3.0	0.001	1.7–5.8						
Constant	0.1	0.000	0.1–0.2	0.1	0.000	0.1–0.2	0.1	0.000	0.1–0.2	0.0	0.000	0.1–0.1	0.0	0.000	0.1–0.1	0.0	0.000	0.1–0.1
Modified Kansas criteria																		
Gulf War Veteran (ref. No)	4.2	0.000	3.4–5.3	4.3	0.000	3.4–5.4	4.0	0.000	2.1–7.5	9.6	0.000	5.1–18.1	16.0	0.000	6.1–41.9	5.1	0.003	1.8–15.0
Age (ref. <30 years old)																		
30–39	1.1	0.551	0.8–1.4	1.0	0.863	0.8–1.4	1.3	0.352	0.7–2.5	1.1	0.762	0.6–2.3	0.8	0.537	0.3–1.8	2.0	0.259	0.6–7.1
40–49	1.5	0.006	1.1–2.1	1.5	0.016	1.1–2.1	1.5	0.273	0.7–3.4	1.0	0.915	0.4–2.5	0.7	0.433	0.2–1.9	2.4	0.253	0.5–10.2
≥50	1.4	0.149	0.9–2.0	1.3	0.236	0.8–2.0	1.9	0.450	0.4–10.0	1.4	0.538	0.5–4.1	1.0	0.934	0.3–3.3	0.0	0.985	
Enlisted in index unit (ref. Other units)	1.2	0.131	0.9–1.6	1.2	0.650	0.9–1.6	1.1	0.707	0.6–2.2	1.5	0.182	0.8–2.8	1.7	0.154	0.8–3.6	1.1	0.857	0.3–3.6
Current smoker (ref. No)	1.5	0.001	1.2–1.9	1.5	0.002	1.2–1.9	1.5	0.152	0.9–2.8	1.7	0.074	1.0–3.0	1.5	0.307	0.7–3.0	2.4	0.088	0.9–6.8
Race (ref. non-White)	1.1	0.686	0.8–1.5	0.9	0.779	0.7–1.4	1.6	0.203	0.8–3.2	0.6	0.178	0.3–1.2	0.7	0.415	0.2–1.8	0.6	0.359	0.2–1.7
Married (ref. not-married)	1.3	0.026	1.0–1.7	1.4	0.013	1.1–1.9	1.0	0.939	0.6–1.7	1.1	0.715	0.6–2.0	1.1	0.840	0.5–2.3	1.0	0.924	0.4–2.8
College and above education (ref. less than college education)	0.8	0.044	0.6–1.0	0.7	0.010	0.6–0.9	1.5	0.266	0.7–3.0	0.6	0.081	0.3–1.1	0.6	0.140	0.3–1.2	0.6	0.370	0.2–1.8
Gender (ref. male)	1.7	0.000	1.3–2.3	..						5.5	0.000	2.9–10.6						
Constant	0.1	0.000	0.0–0.1	0.1	0.000	0.0–0.1	0.0	0.000	0.0–0.1	0.0	0.000	0.0–0.0	0.0	0.000	0.0–0.0	0.0	0.000	0.0–0.1

RRR is similar to the odds ratio (OR) and indicates how the risk of the outcome falling in the comparison group compared with the risk of the outcome falling in the referent group changes with the variable in question.

*Relative risk ratios (RRR) are in comparison to the non-case.

†We have also estimated alternative multivariate regression models (not reported) where we included an interaction term that controls for being a female deployed veteran. We hypothesized that being both a female and deployed GW veteran might be associated with higher risks of having GWI. However, results did not show any statistically significant relationship.

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care at VA hospitals while the more specific Kansas criteria should be considered for use in biomarker and treatment trial efficacy studies of GWI.[7]

Our results also agree with those obtained by Wolfe et al[19] in a study of CMI among US Army veterans of the GW where women veterans were found to have 1.7 times higher risk of GWI than their male counterparts. Correspondingly, the original Kansas cohort found that women GW veterans had 1.5 times higher risk of GWI than male GW veterans.[4] More recently, Dursa et al,[6] also showed higher rates of GWI in female veterans. Several factors may account for the observed sex differences in GWI and individual symptoms including sex-differences in susceptibility to neurotoxicant exposures in theatre and/or higher exposures among female personnel. In addition, sex hormones may modulate the proinflammatory cytokine immune response.[20]

As with all studies, this study has several strengths and limitations. First, this study was a reassessment of data collected in 1995 and thus does not represent the current health of GW veterans. The study was done with Air Force veterans only and may not be representative of all Gulf War veterans. However, the results do correlate with other studies and estimates of excess prevalence among deployed GW veterans from all military branches which seems to indicate that branch of service may be less important with regard to GWI than particular exposures encountered during the war.

There may be confounding variables that could lead to symptoms that were not addressed in this study. This study also did not account for comorbid conditions that may be associated with symptoms of GWI. However, considering that this dataset was obtained only 4 years after the war when many veterans were still quite young and had qualified to be healthy enough for military service just 4 years prior, it is unlikely that many comorbid conditions were present at the time of this study with the exception of potential mental health diagnoses including PTSD. However, given the relatively short duration of the Gulf War compared with more recent conflicts, less than 10% of GW veterans have been diagnosed with PTSD while nearly a third have been diagnosed with GWI.[1,5] This suggests that mental health comorbidities do exist in this cohort but at a much lower rate than the most recent conflicts in Iraq and Afghanistan and certainly not enough to account for the higher rates of GWI in this cohort. There were also no additional analyses possible based on exposures during the war as the original CDC dataset did not provide this information for analysis. Also, given the small number of severe cases in some instances, the relative risk results should be viewed with caution and validated in other study samples. Nonetheless, this study provides a previously unprecedented ability to reassess the two major case criteria in GWI in early time points after the war in a seminal cohort of GW veterans. This also allowed for reassessment of sex and symptom severity comparisons in GWI in this cohort.

In conclusion, there is a need for additional studies of sex-differences in the frequency of GWI and individual symptoms, including longitudinal studies and studies of more recent GW veteran cohorts. The current results showed that surveys from 1995 revealed increased rates of both CDC and Kansas GWI criteria in male and female GW veterans with excess rates that were highly comparable to other large seminal studies in the field including that of the original Kansas criteria cohort. This study confirms the recommendations of the IOM that the CDC criteria is best suited for clinical case criteria and health care at VA hospitals while the Kansas criteria is better suited for biomarker and treatment trial efficacy research studies where greater diagnostic specificity is required. In addition, increased prevalence and severity of GWI symptoms in female veterans indicates that further research is needed to examine the chronic health outcomes of female GW veterans independently from their male counterparts.

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Original Article

Prevalence and Patterns of Symptoms Among Female Veterans of the 1991 Gulf War Era: 25 Years Later

AU2 ▶ Kimberly Sullivan, PhD,[1] Maxine Krengel, PhD,[2] Vahe Heboyan, PhD,[3] Samantha Schildroth, MPH,[1] Col Candy Wilson, PhD, APRN,[4] Stacey Iobst, PhD, RN,[5] Nancy Klimas, MD,[6,7] and Steven S. Coughlin, PhD[8,9]

Abstract

Background: A new national cohort of Gulf War (GW) veterans of 1,318 participants was created from the Veterans Affairs Cooperative Studies Program 585 Gulf War Era Cohort and Biorepository (GWECB) pilot study. However, female veteran health outcomes have not been reported separately for those deployed versus nondeployed to the 1990–1991 GW.
Methods: Using data from the cooperative studies program (CSP) #585 GWECB, this study examined whether excess prevalence and patterns of Gulf War Illness (GWI) symptoms were present among female veterans who served during the GW compared with female veterans who did not deploy to the GW (GW-Era).
Results: A total of 301 women veterans participated in the survey (203 GW, 98 GW-era). Mean ages in 2016 were 53 years among GW women veterans and 54 years among GW-era women. Participant groups did not differ by age, race, ethnicity, or education, but GW women were more likely to have served in the army or navy and less likely to have served in the air force. Compared with GW-era women, GW-deployed women were significantly more likely to report 7 out of 34 symptoms related to cognitive, neurological, and mood problems and respiratory complaints when controlling for age, race, GW deployment, branch of service, and smoking status in logistic regression analyses. Ordered logistic regression was also used to estimate the association between the total number of self-reported symptoms and deployment status, age, race, branch of service, and smoking status. Results showed deployed GW veterans to have a nearly twofold risk of reporting more symptoms than GW-era women, with younger, nonwhite, army-enlisted GW women significantly more likely to report more total symptoms.
Discussion: Twenty-five years after the war, GWECB women GW veterans continued to report a wide variety of symptoms at a significantly higher excess frequency prevalence than GW-era women. Our results showed at least a 14% excess frequency prevalence in all seven significantly different symptoms encompassing two out of the six Kansas GWI criteria, including neurological/mood/cognition, and respiratory domains. These results suggest that further study of these symptom domains is warranted in GW women veterans.

Keywords: Gulf War veterans, symptoms, veterans, women, Gulf War Illness

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AU3 ► **Introduction**

Women comprised 7% of the nearly 700,000 military personnel who served in the 1990–1991 Gulf War (GW)[1] and represented the largest proportion of U.S. women serving in a war zone in U.S. military history to that point in time. This equates to nearly 50,000 GW women veterans, many of whom seek medical care at Veterans Affairs (VA) facilities. In fact, this influx of women veterans seeking care for health problems after the GW resulted in the creation of specialty clinics for women veterans at VA hospitals across the country. Nevertheless, emerging evidence indicates that women veterans still have significant barriers to health care access with an estimated 19% of women veterans having delayed or unmet health care needs.[2] This problem may be due to expanded military roles for women increasing their exposure to more intense levels of combat and to toxicant exposure requiring even more types of specialty care for women veterans.[1]

Research on health symptoms in women veterans suggests higher rates of poor sleep quality, fatigue, and insomnia; chronic pain including headache and musculoskeletal complaints; respiratory problems; skin problems; as well as cognitive and mood-related complaints in women veterans from the Vietnam era to Operation Iraqi Freedom/Operation Enduring Freedom (OIF/OEF).[3–13] Specifically, OIF/OEF-deployed women had higher rates of musculoskeletal complaints, depression, and skin disorders compared with their male counterparts.[8] While women veterans who were nonwhite and younger tended to have more severe insomnia compared with other women veterans with insomnia.[5] In addition, OIF/OEF women veterans were significantly more likely to have respiratory symptoms and asthma than OIF/OEF-deployed men or nondeployed women veterans.[11,12]

Additional research suggests that the 1990–1991 GW women veterans may have chronic health issues and conditions specific to their cohort that are more frequent than among other cohorts of women veterans or among age-matched nonveteran women.[14] Although multiple studies have examined health symptoms in GW veterans,[15–22] few studies have specifically reported on symptoms among female veterans of the 1990–1991 GW.[21–23] A small number of studies with women veterans suggested excess rates of health problems, for example, breast cysts, abnormal Papanicolaou (Pap) smears, yeast infections, and bladder infections, but few have reported on more general health symptoms.[23,24]

In a study of 236 GW veterans from the United Kingdom, Unwin et al.[23] compared gender differences in 50 self-reported symptoms. Women veterans reported higher rates of headaches, fatigue, constipation, stomach cramps, urinary frequency, and nausea compared with male GW veterans. In another study of 2,301 U.S. GW veterans,[25] women veterans reported significantly more headaches, aches/pains, and upset stomach than their male counterparts. An earlier comparison of air force women veterans, including 900 GW-deployed and 900 GW-era veterans showed that GW women were significantly more likely to report symptoms related to Gulf War Illness (GWI), including fatigue, joint pain, forgetfulness, concentration problems, gastrointestinal difficulties, and skin rash.[24] However, these findings need to be validated in GW women from all military branches. A more recent study comparing chronic conditions in GW women from the Ft. Devens Cohort (FDC) compared with nonveteran women from the general population from the same years using the National Health and Nutrition Examination Survey (NHANES) showed that GW women were 2.8 times more likely to report a doctor diagnosis of diabetes than age-matched NHANES women.[14] They were also three times less likely to report hypertension and two times less likely to report high cholesterol than FDC men.[14] As these studies have suggested that women GW veterans are likely to show different symptoms than their male counterparts and different from a nonveteran women comparison sample, it was essential to conduct a study of recently reported health symptoms in GW-deployed women veterans from all military branches.

In a recently published article describing a cohort from a VA cooperative studies program (CSP) of GW-deployed and nondeployed (GW-era) men and women, it was reported that health symptoms that most frequently self-reported included joint pain and stiffness, problems getting to sleep and feeling unrested after sleep, fatigue, and muscle pain. This report was the most common symptoms in the total 1,318 participants.[26] This initial article of the cohort described the overall CSP #585 Gulf War Era Cohort and Biorepository (GWECB) sample but did not assess health symptom outcomes by GW deployment and gender, leaving important questions unanswered. The current analysis was designed to assess this large new cohort of GW-deployed and GW-era veterans, specifically focusing on women veterans' outcomes.

The objectives of the current study were therefore to examine the frequency and patterns of health symptoms 25 years postdeployment in GW-deployed and GW-era women veterans from all military branches. It was hypothesized that those symptoms associated with the diagnostic pattern of GWI, including fatigue, chronic pain, and cognitive complaints, would be higher in GW veterans. The study utilized and further examined a recently collected, large existing, deidentified data set—VA Cooperative Studies Program #585 GWECB pilot study to examine the prevalence and patterns of GWI symptoms among female veterans who served during the GW or GW Era.

Methods

The methods used for the GWECB have previously been detailed.[26] Briefly, veterans were eligible to participate in the GWECB if they had served in the U.S. Uniformed Services during the period from August 1990 to July 1991, regardless of deployment or combat status. The pilot study recruitment sample was based on a stratified random sample of 90,000 veterans from the 1990 to 1991 GW era. The stratified recruitment panel was obtained from the Department of Defense Manpower Data Center (DMDC) and was drawn from a total population of 4,966,117 veterans who served from August 1990 to July 1991. Veterans were selected for inclusion in the pilot study recruitment sample ($n = 10{,}042$) according to vital status, availability of valid contact information, and geographic location within the contiguous United States. Of this sample contacted, 1,275 consented to participate. Veterans meeting eligibility criteria could also self-nominate for participation; these 76 veterans (10 women, 66 men) heard about the GWECB via social media, local events, word of mouth, and other channels. In total, 2,062

women veterans were invited to participate through DMDC mailings and the 296 who chose to participate from the mailings indicated a 14.4% response rate from the mailings of DMDC-identified women veterans. Of the 296 DMDC-identified women, five participants did not answer the question, ''What is your gender,'' and so, these five participants were not included in the current study leaving 291 DMDC-identified women participants. As part of the Gulf War Women Cohort Study (W81X-WH-16-1-0774), a subset of only the 301 women GWECB veterans (291 DMDC and 10 self-nominated) were included for the current analysis. The Augusta University Institutional Review Board (IRB) determined that this analysis was exempt from IRB review.

Data collection

In 2015–2016, 25 years after the conflict had ended, veterans in the pilot recruitment sample and those who volunteered were mailed an invitation packet that included the GW-era veterans' survey, informational and consent documents, and an opt-out postcard as reported in Khalil et al.[26]

Survey instrument

As described by Khalil et al.,[26] the GW-era veterans' survey was developed in collaboration with several researchers and clinicians experienced in conducting studies with veterans from the 1990 to 1991 GW era. The survey assessed military service history; lifestyle and other behaviors; and physical and mental health, including health symptoms in the past 6 months. When available, validated instruments and other measures previously used in GW research[16] were chosen.

Statistical analysis

After cross-tabulations and exploratory analyses of the survey were completed, stepwise logistic regression methods were used to compare groups of GW women veterans and nondeployed GW-era women with respect to frequency of symptoms. In addition, ordered logistic regression was used to estimate the association between the total number of self-reported symptoms and deployment status. Deployment status was included in the models as a predictor variable and age, race, branch of service, and smoking status were adjusted for in the analyses. Ninety-five percent confidence intervals (CIs) were obtained for adjusted odds ratios (ORs) and adjustments were not made for multiple comparisons. The goodness-of-fit of each model was examined using the log-likelihood ratio tests.[27] Excess prevalence was determined by subtracting the percent of GW symptom responders from GW-era responders.[16] Cross-tabulations of the data were performed using STATA. In general, we had sufficient power to detect an OR of 2.0 when the proportion of exposed individuals was in the range of 0.30–0.50.

Results

Demographics

In total, 291 women veterans from the DMDC mailings were included in the current study. Those agreeing to participate were not significantly different on any demographic outcomes from those who chose not to participate from the DMDC mailing list for available demographics, including sex, race, military branch and deployment status ($p > 0.05$). Forty-four percent of the GWECB women veterans were VA ◀ AU4 treatment seekers. As might be expected, significantly more GW-deployed women participated in the study compared with nondeployed GW-era women (56.3% vs. 67.6%; $p < 0.01$) (Table 1). ◀ T1

A total of 301 women veterans (291 DMDC, 10 self-nominated) participated in the survey. Of these, 203 were deployed to the GW and 98 were not deployed to the war. Demographic data are shown in Table 2. Single-digit frequency results were suppressed to protect participant confidentiality (CMS Cell Size, 2017). ◀ T2 Deployed and nondeployed groups did not significantly differ by age, education, race, ethnicity, or cigarette smoking, but they did differ with respect to the military branch ($p < 0.05$). Their mean age in 2016 was 53 years for GW-deployed and 54 years for GW-era women. About one-fifth of the participants in both groups were ≥60 years of age. In both groups, about three-quarters of the participants were white, slightly less than a quarter were black or African American, and the remainder were other race (including American Indian/Alaska Native, Asian/Pacific Islanders). In both groups, <10% of the participants were Hispanic or Latino. Importantly, the participants were from all branches of military service (Table 2). GW-deployed veterans were more likely to be army or navy veterans and less likely to be air force veterans (Table 2). The majority of

Table 1. Characteristics of Women Veterans Invited to Participate in the Gulf War Era Cohort and Biorepository Survey in the Pilot Mailing and Those Who Completed the Gulf War Era Cohort and Biorepository Survey ◀ AU9

	Pilot mailing		*Completed survey*	
Female DMDC data	n	%	n	%
Race				
White	1,486	72.07	227	76.69
Black	510	24.73	63	21.28
American Indian	2	0.1	0	0
Asian	3	0.15	0	0
Other	56	2.72	5	1.69
Unknown	5	0.24	1	0.34
Branch				
Army	1,002	48.59	143	48.31
Navy	423	20.51	59	19.93
Air Force	519	25.17	74	25
Marine Corps	110	5.33	19	6.42
Coast Guard	8	0.39	1	0.34
Service component				
Active duty	1,094	53.06	145	48.99
Reserve	782	37.92	130	43.92
National Guard	186	9.02	21	7.09
Theater				
Yes	1,160	56.26	200	67.57
No	902	43.74	96	32.43

No significant differences were found between the pilot mailing and completed survey cohorts, except for those who served in theater were significantly higher in the completed survey group ($p < 0.01$).

DMDC, Defense Manpower Data Center veteran lists were used for pilot mailing survey.

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Table 2. Characteristics of Women Veterans in the Gulf War Era Cohort and Biorepository Survey by Deployment Status, 2014–2016, ($N = 301$)

Variables	*Deployed to Gulf* n	*Deployed to Gulf* %	*Not deployed to Gulf* n	*Not deployed to Gulf* %	p-*value chi-squared or Fisher's exact test*
Age at time of survey completion					
Mean age (years, in 2016)	53		54		
Age group, years (in 2016)					
≤49	84	42	27	28	0.061[a]
50–59	81	40	49	50	
≥60	37	18	22	22	
Race					
White	145	72	73	74	0.774[a]
Black/African American	42	21	17	17	
Other	15	7	8	8	
Ethnicity					
Not Spanish, Hispanic, or Latino	184	92	90	94	0.687[a]
Spanish, Hispanic, or Latino	15	8	6	6	
Service branch					
Army	94	47	37	38	0.021[b]
Navy	44	22	16	16	
Air Force	29	14	30	31	
Marine Corps	16	8	4	4	
National Guard	18	9	10	10	
Highest level of education completed					
High school/GED or less	9	4	1	1	0.478[b]
Bachelor's degree or some college	136	67	71	72	
Master's, professional, or doctoral degree	53	26	24	24	
Missing data	4	2	2	2	
Cigarette smoking					
Current smoker	25	12	13	13	0.177[a]
Former smoker	53	26	15	15	
Never smoked	106	52	62	63	
Missing data	18	9	8	8	

[a]Chi-square test.
[b]Fisher's exact test.
AU10 ▶ GED.

the participants in both groups had completed some college or received a college degree. About 13% of the participants in both groups were current cigarette smokers, while GW-deployed veterans showed a slightly higher but nonsignificantly different rate of former smokers (26% vs. 15%).

Self-reported health symptoms

T3 ▶ Results of the 34 different symptoms are shown in Table 3. GW-deployed GWECB women veterans were significantly more likely to report seven symptoms consistent with GWI, including low tolerance for heat or cold, difficulty breathing or shortness of breath, frequent coughing when not having a cold, difficulty concentrating, difficulty remembering recent information, feeling down or depressed, and feeling anxious (Table 3). In addition, GW-deployed women had an excess prevalence for 33 out of the 34 total health symptoms with trending significance for 4 symptoms and significant differences for 7 symptoms. All 7 symptoms showed an excess prevalence of 14% or more in GW women veterans (Table 3).

Table 4 shows the total number of symptoms self-reported ◀ T4 by GW-deployed and GW-era women veterans. Forty percent of the GW-deployed women reported over 20 symptoms compared with 21% of the GW-era women. That is, GW women had a 19% excess prevalence (40%–21%) in reporting 20 or more symptoms compared with GW-era women. When these results were further compared by ordered logistic regression to estimate the association between the number of self-reported symptoms and deployment status, age, race, branch of service, and smoking status, results showed that GW-deployed veterans were nearly twice as likely to report more total symptoms (OR = 1.87, 95% CI: 1.18–2.97, $p = 0.008$). In addition, nonwhite other racial groups, including American Indian/Alaska Native or Asian/Pacific Islander women, were nearly four times more likely to report more symptoms than white women (OR = 3.97, 95% CI: 1.57–10.05, $p = 0.004$). While older women veterans were less likely to report more symptoms when compared with younger women veterans (OR = 0.39, 95% CI: 0.21–0.72, $p = 0.003$). Finally, branch of service comparisons showed that air force (OR = 0.23, 95% CI: 0.20–0.69, $p = 0.002$)- and navy (OR = 0.43, 95% CI: 0.23–0.78, $p = 0.005$)-enlisted women were significantly less likely to report more symptoms than army-enlisted women.

Discussion

The results of this study indicate that, when surveyed 25 years after the 1990–1991 GW, women veterans from all branches of the military who were deployed to the GW continued to report a wide variety of symptoms at a higher frequency than GW-era women. This was evident by GW women veterans showing higher symptom reporting for 33 out of 34 total health symptoms and significantly different excess prevalence for 7 out of 34 health symptoms related to cognitive and mood problems and respiratory complaints. In addition, GW women veterans had nearly twice the risk of reporting over 20 total symptoms, a symptom burden that would be expected to negatively impact quality of life and require medical evaluation and intervention.[28,29] This was ◀ AU5 especially true for younger, nonwhite army-enlisted women veterans who were significantly more likely to report more total symptoms. Correspondingly, a recent article on these women GWECB veterans reported excess chronic medical outcomes, compared with GWECB male veterans, showing higher asthma, thyroid problems, migraine headaches, irritable bowel syndrome (IBS), osteoporosis, and mood-related disorders in the GWECB women.[30]

Notably, many of the symptoms that were higher in the current GWECB cohort fit into the current case definitions of GWI, including the Kansas criteria, requiring symptoms in three out of six symptom domains (fatigue, neurological/cognitive/mood, pain, respiratory, gastrointestinal, and skin).[16] Specifically, GW women reported at least 14% higher excess prevalence in all seven significantly different

Table 3. Prevalence and Association of Health Symptoms with Gulf War Deployment Status in the Gulf War Era Cohort and Biorepository Women Veteran Participants

AU11 ▶ Symptoms	*Deployed to Gulf (N = 202)* n	%	*Not deployed to Gulf (N = 98)* n	%	*Excess prevalence (%)*	*OR*	*95% CI*	*c-stat*
Fatigue	140	69	60	61	8	1.50	0.84–2.71	0.68
Feeling unwell after physical exercise or exertion	81	40	31	32	8	1.46	0.82–2.57	0.67
Problems getting to sleep or staying asleep	144	71	59	60	11	1.61	0.89–2.91	0.67
Not feeling rested after you sleep	145	72	62	63	9	1.56	0.84–2.88	0.64
Pain in your joints	148	73	72	73	0	1.10	0.56–2.16	0.67
Stiffness in your joints	149	74	71	72	1	0.94	0.49–1.80	0.69
Pain in your muscles	123	61	55	56	5	1.22	0.69–2.14	0.67
Body pain, where you hurt all over	95	47	35	36	11	1.72	0.97–3.04	0.70
Headaches	129	64	48	49	15	1.69	0.96–2.96	0.70
Feeling dizzy, lightheaded, or faint	92	46	35	36	10	1.65	0.94–2.90	0.68
Eyes very sensitive to light	96	48	40	41	7	1.25	0.73–0.17	0.66
Blurred or double vision	63	31	27	28	4	1.07	0.59–1.96	0.69
Numbness or tingling in your extremities	122	60	51	52	8	1.39	0.80–2.41	0.66
Tremors or shaking	37	18	13	13	5	1.56	0.73–3.34	0.72
Low tolerance for heat or cold	108	53	36	37	17	1.88[a]	1.07–3.31	0.70
Night sweats	99	49	41	42	7	1.34	0.77–2.34	0.66
Having physical or mental symptoms in response to certain smells or chemicals	59	29	19	19	10	1.44	0.74–2.77	0.72
Skin rashes	70	35	23	23	11	1.82	0.96–3.44	0.63
Other skin problems	63	31	18	18	13	1.05	0.58–1.89	0.61
Diarrhea	60	30	27	28	2	1.09	0.62–1.96	0.60
Nausea or upset stomach	81	40	32	33	7	1.12	0.63–1.99	0.68
Abdominal pain or cramping	85	42	32	33	9	1.33	0.75–2.35	0.68
Difficulty breathing or shortness of breath	78	39	19	19	19	2.62[b]	1.37–5.00	0.71
Frequent coughing when you do not have a cold	68	34	19	19	14	2.26[a]	1.18–4.31	0.68
Wheezing in your chest	38	19	12	12	7	1.54	0.71–3.34	0.67
Sore throat	66	33	23	23	9	1.62	0.89–2.96	0.65
Tender lymph nodes in your neck or armpits	47	23	16	16	7	1.43	0.72–2.85	0.67
Difficulty concentrating	127	63	45	46	17	1.94[a]	1.12–3.37	0.70
Difficulty remembering recent information	124	61	44	45	16	1.85[a]	1.07–3.19	0.68
Trouble finding words when speaking	116	57	45	46	12	1.44	0.84–2.49	0.68
Feeling down or depressed	122	60	39	40	21	2.57[b]	1.47–4.48	0.70
Feeling irritable or having angry outbursts	111	55	45	46	9	1.27	0.72–2.24	0.72
Feeling moody	120	59	49	50	9	1.34	0.77–2.35	0.71
Feeling anxious	110	54	37	38	17	1.90[a]	1.10–3.29	0.65

Adjusted for age, race, smoking status, and service branch.
[a]<5%.
[b]<1%.
CI, confidence interval; OR, odds ratio.

symptoms compared with GW-era women. These seven symptoms overlap with two of the six domains for the Kansas GWI criteria, including neurological/cognitive/mood and respiratory domains.[16] These results correspond with previously reported higher excess prevalence rates in GW women from Pierce, where 29 out of 48 total symptoms were higher in 900 air force GW women veterans.[24,31] However, 10% higher excess prevalence of symptoms was reported by Pierce[24,31] for six symptoms encompassing the neurological/cognitive/mood and fatigue domains of the Kansas GWI criteria. Our results, 20 years later, show seven symptoms encompassing neurological/cognitive/mood and respiratory domains of the Kansas GWI criteria indicating that GW women are showing increased frequency of symptom reporting over time that is over and above that expected in normal aging. This is evident by the increased prevalence rates we find compared with age-matched GW-era women veterans in these domains. In fact, we also found that younger women were more likely to report more total symptoms than older women in this cohort. This also corresponds with recent findings reported by the FDC of GW women veterans, where GW veterans showed higher rates of chronic medical conditions than the general population of nonveteran NHANES women.[14]

A sizeable percentage of the women GW veterans reported neurological symptoms and over half of the women GW

Table 4. Number of Self-Reported Symptoms over the Past 6 Months Among Women Veterans in the Gulf War Era Cohort and Biorepository Survey by Deployment Status, 2014–2016

No. of Symptoms	*GW deployed* n *(%)*	*Not GW deployed* n *(%)*	*Excess prevalence (%)*
0–5	26 (13)	23 (23)	10
6–10	34 (17)	19 (19)	2
11–20	62 (31)	35 (36)	5
21–34	80 (40)	21 (21)	19
Variables	*OR*	p	*95% CI*
Deployed (ref. not deployed)	1.81	0.014	1.13–2.90
Age (ref. <49 years of age)			
50–59	0.81	0.402	0.49–1.33
Older than 60	0.50	0.034	0.27–0.95
Race (ref. white)			
Black	1.22	0.492	0.69–2.14
Other	1.02	0.004	1.56–10.38
Smoking status (ref. former smoker)			
Current Smoker	1.08	0.842	0.51–2.28
Never smoker	0.90	0.702	0.53–1.53
Branch of service (ref. Army)			
Navy	0.43	0.005	0.23–0.78
Air Force	0.38	0.002	0.20–0.69
Other	1.09	0.795	0.57–2.07

We used ordered logistic regression to estimate the association between the number of self-reported symptoms and deployment status, age, race, and smoking status by testing for the statistical differences in the cut-points above.

GW, Gulf War.

veterans reported low tolerance for heat or cold. Sixty-four percent of the women GW veterans reported headaches indicating a 15% excess prevalence rate when compared with GW-era women. An association between deployment status and headache was also observed in the study of U.K. GW women veterans by Unwin et al.[23] and in the study of U.S. GW veterans by Wagner et al.[25] In addition, a recent GWECB article by Brown et al.[30] showed higher rates of migraine headaches in GWECB women compared with GWECB men.

In this study, strong associations were observed between deployment status and respiratory symptoms. Thirty-nine percent of the women GW veterans reported difficulty breathing or shortness of breath resulting in a 19% excess prevalence rate compared with GW-era women veterans. These results were also higher than the 6% excess prevalence for GW-deployed women reported by Pierce,[24,31] many years prior in air force women. About one-third of the women GW veterans reported frequently coughing when they did not have a cold. These results also correspond with a 9% excess prevalence rate for GW women reported by Pierce.[24,31] Although the pathogenesis of respiratory symptoms in GWI is unknown, many of the GW women veterans may have been exposed to deployment-related pulmonary hazards such as smoke from oil well fires and toxic fumes from burn pits used to incinerate wastes. It would be important to examine exposure data in relation to these health symptom findings. In addition, these results also correlate with the recent article showing higher asthma rates in GWECB women compared with GWECB men.[30]

In previous studies, veterans suffering from GWI have commonly reported cognitive symptoms.[22,32–34] In the present study, almost two-thirds of the women GW veterans reported difficulty remembering recent information and difficulty concentrating, resulting in an excess prevalence of 16% and 17%, respectively, compared with GW-era women. Associations between deployment status and forgetfulness and loss of concentration were also observed in the study of U.K. GW women veterans compared with male GW veterans by Unwin et al.[23] These associations were also reported in air force GW-deployed women by Pierce,[24,31] where a 16% and 8% excess prevalence rate was reported, respectively, compared with GW-era women. This suggests an increase in this cohort of twice the rate of concentration problems 20 years later in GWECB GW-deployed women veterans from all military branches.

A majority of the women GW veterans reported psychiatric symptoms, which may be due or more likely contribute to cognitive changes. Sixty percent of the women GW veterans reported feeling down or depressed showing a 20% excess prevalence rate with GW-era veterans. This was higher than the 8% excess prevalence rate previously reported by Pierce[24,31] in GW-deployed air force women. This also corresponds with GW-deployed women having twice the risk of depression and 1.5 times the risk of anxiety and/or panic disorder in the recent GWECB article reported by Brown et al.[30] The high symptom burden observed in this study (neurological, respiratory, cognitive), and diminished quality of life, is likely to partly account for psychiatric symptoms such as depression and anxiety, although the mechanisms by which physical and cognitive problems occur (central nervous system involvement) also largely contribute to mental health issues. For example, exposures to pesticides during the GW have been correlated with mood outcomes suggestive of a causal link.[34] In addition, other research has shown that physical stressors, including the hormone cortisol, can exacerbate the effects of pesticides and other chemical exposures on the central nervous system and behavioral outcomes in a multiple-hit model.[35–37] However, it is clear that these higher rates of mental health symptoms should be addressed and treated in women GW veterans regardless of the etiology.

With respect to limitations, the current study is cross sectional in nature. Information about symptoms was also self-reported and not verified by physician diagnosis. There was also no distinction by exposures during deployment in this analysis, which could vastly underreport symptom burden in exposed groups by combining them with unexposed groups. In addition, response bias is a possibility due to the low response rate in the GWECB pilot study at 13%.[26] Selection bias is also a possibility due to the inclusion of a small group of participants who were self-nominated. However, the study also has several strengths. For example, the generalizability of the study findings is enhanced by the national sample of GW and GW-era veterans, the inclusion of veterans who do and do not receive VA health care services, and the inclusion of veterans from all branches of the military. A further strength of the current study is that the symptom inventory developed for the GWECB was informed by decades of research on GWI and improved upon symptom checklists and inventories used in previous studies.

Significant differences were found between GW-deployed and GW-era women veterans in symptoms that define current GWI case criteria, including CDC and Kansas criteria.[15,16] These symptoms specifically include the following: cognitive impairment, neurological and mood concerns, and respiratory problems. A recent reanalysis of the seminal CDC cohort that determined the CMI/GWI criteria of Fukuda et al.[15] found that women GW veterans were at three times higher risk for meeting Fukuda criteria and 5.5 times higher risk of meeting the modified Kansas GWI criteria than men in that cohort.[38] Notably, those results correspond with the current study where GWECB women showed higher rates of respiratory symptoms, which would make GW women more likely to meet the additional Kansas criteria of respiratory conditions than their male counterparts. Given the increase in women in the military and women with these chronic health symptoms, future planning of women's clinics at VA hospitals should be expanded to include more aggressive screenings for women veterans for headaches and other neurological symptoms, respiratory problems, and sleep-related disorders.

In conclusion, women veterans who were deployed to the GW continue to report a wide variety of symptoms at a higher frequency than nondeployed women veterans who served during the GW era. This suggests that GW women have poorer health than their nondeployed counterparts. This is especially true of younger, nonwhite, army-enlisted veterans in this cohort who report a significantly higher total symptom burden than their older counterparts from other military branches. This corresponds with higher rates of chronic conditions in women veterans for diabetes, osteoporosis, thyroid problems, asthma, and IBS found in this and other GW cohorts.[14,30] The high symptom burden is likely to negatively impact quality of life and to require medical intervention such as treatment for specific symptoms or clusters of symptoms.[28,29] The symptoms observed with excess prevalence in GW women from all military branches in this study related to neurological, cognitive, mood, and respiratory complaints, which are all relevant to GWI and appear to be increasing since early reports by Pierce[24,31] reported them in air force women. Additional research is needed to identify specific biological markers of GWI and effective treatments for this debilitating condition that may be gender specific with regard to health symptom domains.

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AU6 ▶ ### Author Disclosure Statement

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Protocol

The Gulf War Women's Health Cohort: Study Design and Protocol

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Abstract: Military service and deployment affect women differently than men, underscoring the need for studies of the health of women veterans and their receipt of health care services. Despite the large numbers of women who served during the 1990–1991 Gulf War, few studies have evaluated Gulf War illness (GWI) and other medical conditions specifically as they affect women veterans of the 1991 Gulf War. The objectives of the Gulf War Women's Health Cohort study are: (1) to establish the Gulf War women's cohort (GWWC), a large sample of women veterans who served in the 1990–1991 Gulf War and a comparison group of women who served in other locations during that period; and (2) to provide current, comprehensive data on the health status of women who served during the 1990–1991 Gulf War, and identify any specific conditions that affect Gulf War women veterans at excess rates. The study will utilize both existing datasets and newly collected data to examine the prevalence and patterns of Gulf War Illness symptoms, diagnosed medical conditions, reproductive health, birth outcomes and other health issues among women who served during the Gulf War. The Gulf War Women's Health Cohort study will address the need for information about the comprehensive health of women veterans who were deployed to the Gulf War, and other wars during the Gulf War era.

Keywords: Gulf War; Gulf War illness; chronic multisymptom illness; veterans; women

1. Introduction

Increased prevalence of reported health conditions and symptoms in musculoskeletal, neurological, pulmonary, gastrointestinal, and dermatological systems have been acknowledged among deployed veterans of the 1991 Gulf War (GW) era, when compared with veterans who did not deploy to the war [1–5]. These health conditions and symptoms, commonly known as Gulf War illness (GWI), are referred to by the Department of Veterans Affairs as "chronic multisymptom illness" [6].

Among the nearly 700,000 military personnel who served in the 1991 Gulf War, almost 7% (49,000) were women [7,8]. Military service and deployment affect women differently than men, underscoring

the need for studies of the health of women veterans and their receipt of health care services across their lifespan [7,9]. Although in nearly three decades since the war, some studies have investigated the rates of GWI in female vs. male GW veterans, with results suggesting that GWI is more common in women GW veterans than their male counterparts [10,11], few studies have evaluated GWI and other medical conditions specifically as they affect women veterans of the 1991 Gulf War.

A small number of studies suggested excess rates of women's health problems, e.g., breast cysts, abnormal pap smears, yeast infections, and bladder infections [7]. Several studies have identified significantly elevated rates of birth defects and adverse reproductive outcomes among GW veterans. Increased risks of ectopic pregnancies and spontaneous abortions were observed in some studies [12]. Overall, however, findings have varied with different study designs and sample sizes, with some studies showing elevated risks of stillbirths, miscarriages, and/or birth defects [13–18]. There remains a need to evaluate birth outcomes specifically among women GW veterans, in appropriate subgroups, e.g., by time-period of birth, by parental exposures and by other deployment characteristics.

Studies that have investigated the mental health of veterans revealed that the proportions of females with major depressive disorder, post-traumatic stress disorder, and anxiety disorder were higher among Gulf War veterans (35%, 23.7% and 17.1% respectively), compared to Gulf War era veterans (27.1%, 12.3% and 17.0% respectively) [9,19].

Theories about the pathobiology of GWI focus on neurological, immune, and endocrine mechanisms, which may be differentially altered in women by life course events from pregnancy to menopause. Menopause has effects on a number of organ systems including the cardiovascular, skeletal, nervous, and genitourinary systems. In addition, pregnancy complications, including pre-eclampsia and gestational diabetes can result in later life health effects, including cardiovascular disease and adult onset diabetes in at-risk women. Given that many female veterans who were deployed to the Gulf region are now middle-aged, they may be at risk for these later lifespan health outcomes. These outcomes have been poorly studied to date and thus more research on this topic is needed.

Based on the reasons enumerated above, there remains a paramount need to evaluate the health status across the life course of women GW veterans in appropriate subgroups, e.g., by hazardous and risky exposures, and by other deployment characteristics. The objectives of this study are: (1) to establish the Gulf War women's cohort (GWWC), a large sample of women veterans who served in the 1990-1991 Gulf War and a comparison group of women who served in other locations during that time period; and (2) to provide current, comprehensive data on the health status of women who served during the 1990-1991 Gulf War, and identify any specific conditions that affect GW women veterans at excess rates.

The specific aims include: (1) to assemble the GWWC using data collected from 955 to 1420 women GW veterans and an additional 680 to 854 women veterans who were not deployed to the Persian Gulf, who participated in previous and ongoing population studies of 1990–1991 Gulf War era veterans. (2) To conduct a multimodal health survey to provide data on the current health status of the subset of previously surveyed GW era women veterans who are eligible to be re-contacted (with a projected 200 completed surveys) and comparisons between GW deployed veterans and non-deployed GW era veterans. (3) To provide comprehensive data on veteran-reported pregnancy and birth outcomes among GW and GW era women veterans. (4) To evaluate GWI and other high interest health outcomes in women veteran subgroups, including subgroups identified by (a) veterans' deployment characteristics (e.g., locations and exposures, branch of service), and (b) veterans' age and menopausal status (e.g., pre-, peri-, and post-menopause subgroups). (5) Where possible, to provide a longitudinal assessment of changes in GW era women veterans' health over time, using baseline data collected in the original population studies from which the current cohort sample is drawn. (6) To examine sex differences in GWI including female to male differences in the frequency of symptoms associated with GWI and the overall prevalence of GWI among GW female and male veterans.

2. Materials and Methods

2.1. Study Design

The study involves the reanalysis of existing data from epidemiologic studies of the health of Gulf War veterans and a survey of women included in the Ft. Devens Cohort Study.

2.2. Study Sites

The lead site is Augusta University. VA Boston Healthcare and the Boston University School of Public Health Data Coordinating Center will be collecting survey data. All required Institutional Review Board (IRB) approvals will be obtained at each site before project implementation. The study team holds monthly conference telephone calls, and all non-compliance and/or unanticipated problems associated with the study protocol or applicable requirements will be reported in accordance with local policy.

2.3. Study Participants and Inclusion Criteria

All of the study participants served during the 1991 Gulf War and participated in previously conducted epidemiologic studies of the health of Gulf War veterans. Participants will be located using their last known mailing address, with contact information updates using information from multiple sources, including the U.S. Postal Service and commercial locating services. The VA Boston Healthcare System is responsible for contacting women veterans who previously participated in the Ft. Devens Cohort (FDC) Study. The Ft. Devens, MA Cohort of GW veterans is one of the few longitudinal cohorts of GW veterans and is the longest running cohort of GW veterans [18]. 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).

2.4. Procedure

The study will utilize both existing datasets (Specific Aim 1) and newly collected data (Specific Aim 2) to examine the prevalence and patterns of GWI symptoms, diagnosed medical conditions, reproductive health, birth outcomes (Specific Aim 3), and other health issues across the lifespan, including hypertension, cardiovascular risk and diabetes among women who served during the Gulf War. The project will provide a comprehensive picture of the health of women GW veterans. This includes assessment of current health status, changes in health symptoms and conditions over time, and possible differences in health outcomes associated with specific experiences and exposures during the war (Specific Aim 4). It will allow for an assessment of GWI symptom patterns that may be specific to women veterans, a determination of diagnosed medical conditions among women veterans, and an evaluation of changes in women's health over time, including changes potentially associated with menopause and early reproductive complications and subsequent risk for increased age-related health outcomes (Specific Aim 5). The proposed study will utilize data from multiple studies in order to establish the GWWC. In studies that have retained personal identifiers and for which it is feasible to obtain IRB permission to re-contact subjects, current data will be collected on women's current health symptoms, GWI (defined by both Kansas and CDC CMI criteria) [20], diagnosed medical conditions, and reproductive outcomes and complications (e.g., still births, ectopic pregnancies, birth defects, pre-eclampsia, gestational diabetes). For all studies, re-analyses of existing data will be conducted to focus on health outcomes specifically affecting women. This will allow for the frequency and nature of GWI symptoms to be better characterized among women veterans. Female to male differences in GWI will be examined in some of the studies, in order to determine whether GWI manifests differently in women (Specific Aim 6).

In the study, a re-survey of a longitudinal cohort will be included (Ft. Devens cohort (FDC) Reunion Survey). Dr. Maxine Krengel at the VA Boston Healthcare System and Boston University School of Medicine, and Dr. Kimberly Sullivan at the Boston University School of Public Health,

recently conducted a follow-up survey of male and female Army veterans who were deployed to the Persian Gulf and participated in the Ft. Devens cohort Study. Through the use of longitudinal data, where health symptoms were first measured one year after deployment and then repeatedly over the past 19 years, they are examining symptom trajectories, i.e., patterns of change over time. The use of longitudinal data allows consideration of relapsing, remitting, and late-emerging symptoms, in order to refine case definitions of GWI and for a clearer understanding of the potential causes for these symptom trajectories (i.e., genetic predisposition, environmental exposures, prior treatment efficacy). Several questions related to women's health have been asked in surveys of the cohort, including difficulty conceiving, number of births, whether a child was born with a birth defect, stillbirths, uterine or ovarian tumors, hysterectomy, menopause, amenorrhea, vaginal yeast infections, premenstrual symptoms, pain during intercourse, difficulty achieving orgasm, Depo-Provera shots, and breast disease. The most recent survey of this cohort ended by September 2016.

In 1991, a total of 1290 subjects from the Ft. Devens cohort participated in a postal survey, in which the prevalence of 52 symptoms and risk factors for reported symptoms were examined. The survey questionnaire included questions about background and demographic variables, GW duty service (active, reserve/National Guard, military rank), health outcomes (health functioning, general symptoms, medical conditions, and symptoms associated with multiple chemical sensitivity), numerous environmental exposures associated with GW deployment, and alcohol use. About 60% of the respondents met the CDC criteria for chronic multisymptom illness (CMI). Female gender, lower levels of education, self-reported use of a medical clinic in the Gulf, ingestion of anti-nerve gas pills, anthrax vaccination, tent heaters, and exposure to oil fire smoke, and chemical odors were related to CMI in logistic regression analyses [7]. Women from this cohort will be resurveyed as part of the GWWC. The Ft. Devens cohort was one of the first studies to report a 1.8 times higher risk of GWI in women veterans [9].

Dr. Beth Unger at the Centers for Disease Control and Prevention (CDC) in Atlanta provided archived records from the CDC Air Force Study, which included women. The study data, which contain no personal identifiers or biological specimens, have been made available to Augusta University for use in the proposed collaborative study. In November 1994, the VA, DoD, and the Pennsylvania Department of Health requested that CDC investigate a report of unexplained illnesses among members of an Air National Guard unit who were GW veterans. After an initial investigation of 59 GW veterans, which involved standardized interviews and physical examinations, a larger sample of GW veterans (n = 3927) were surveyed in 1995, who were members of the index unit and three comparison units in Pennsylvania and Florida. After excluding 204 who were younger than 17 years during the GW, 1163 (31.2%) were GW veterans and 2560 (68.8%) had not been deployed. In addition to general health history, the respondents were asked about the frequency, duration, and severity of 35 symptoms and possible exposures during deployment. Birth outcomes were not asked about. In all units, the prevalence of each of 13 chronic symptoms was significantly greater ($p < 0.05$) among persons deployed to the GW than among those not deployed.

In addition to the CDC Air Force study and extending data collection among participants in the Ft. Devens Cohort, we are proposing to include data from VA's Cooperative Studies Program (CSP) 585 Gulf War Biorepository and Health Survey pilot study (which ended in May 2016) [1,21]). Veterans were eligible to participate in the VA's Cooperative Studies Program (CSP) 585 Gulf War Biorepository and Health Survey pilot study, if they had served in the U.S. Uniformed Services during the period from August 1990–July 1991, regardless of deployment or combat status. The stratified recruitment panel was obtained from the Department of Defense Manpower Data Center (DMDC) and was drawn from a total population of 4,966,117 veterans who served during August 1990–July 1991. A subset of only the 301 women CSP 585 veterans (291 DMDC and 10 self-nominated) was included for the current proposed study. A data usage agreement was finalized with the principal investigator of the CSP 585 pilot study, Dr. Dawn Provenzale at the VAMC in Durham, NC, and Dr. Coughlin at Augusta University.

Dr. Sullivan is currently the PI and leader of a DoD funded Gulf War Illness Consortium (GWIC) that brings together diverse experts from 9 institutions to study the pathobiology and treatment development for GWI. GWIC clinical studies include data collection from three study sites in Boston, Central Texas and Miami. Clinical study co-investigators include Drs. Nancy Klimas, Lea Steele and Maxine Krengel. The GWIC cohort will include study surveys of 300 GW veterans (about 20% women) that will be shared for use in the currently proposed study.

Taken overall, the minimum sample size expected for this study is 6,835 male and female veterans. The number of women who will be included in GWWC is anticipated to be 560 to 800 women GW veterans and an additional 680 to 959 women veterans who were not deployed to the Persian Gulf. This includes 1290 Army GW veterans from the Ft. Devens Cohort, 300 GW veterans from the Boston GWI Consortium (20% women), over 1318 GW veterans from CSP 585 pilot study (23.7% women), 3927 GW veterans from the CDC USAF study (which included about 522 women).

New data collection for the GWWC will involve telephone interviews and postal surveys of women (with a projected 200 completed surveys), including questions on women's health previously utilized in surveys conducted by the investigators at VA, VA Boston Healthcare system, and Boston University. De-identified data will be compiled and analyzed by Augusta University investigators in collaboration with the other study sites.

2.5. Survey Questionnaire Design

A survey questionnaire was developed based upon questionnaires used in previous surveys (Ft. Devens Cohort and Kansas study). Questions are included about a variety of topics including marital status, employment status, educational attainment, general health status, symptoms, medical conditions diagnosed or treated by a physician, use of health care services, and reproductive outcomes and complications. The respondents will be asked about the frequency, duration, and severity of a comprehensive list of about 40 symptoms, partly to ensure that both the CDC and Kansas criteria for GWI can be used in the analysis. They will also be asked if they had ever been diagnosed or treated by a physician for any of about 25 medical and psychiatric conditions, and when each reported condition had developed. An open-ended question will also be included about additional medical or psychiatric conditions they may have had diagnosed or been treated for. Data will be collected on gender-specific symptoms and medical conditions that occur in women and about adverse reproductive outcomes and complications (spontaneous abortions, stillbirths, ectopic pregnancies, pre-term births, birth defects, pre-eclampsia and gestational diabetes).

For women veterans, questions will be included about the use of hormone replacement therapy, whether they ever had an abnormal Pap smear (and when), whether they have had a hysterectomy, whether they were pregnant or nursing in the past year, and whether they had menstrual periods in the past year. An open-ended question will also be included about additional gynecological problems they may have had.

The survey will take about 30 to 45 min to complete and will be carefully pilot tested in a small sample of veterans before use.

2.6. Interviewing Process

All subjects will be assigned a participant ID number. Following institutional review board (IRB) approval, the veterans will be sent an advance letter signed by the PI that describes the study, requests their participation, and lets them know that, if they agree to participate, they will have the option of being interviewed by telephone or by filling out and returning a postal survey questionnaire. The letter will include a copy of the IRB-approved consent form. A postcard will be included to allow them to opt out of the survey.

New data collection for the GWWC will involve postal surveys and telephone surveys (CATI telephone survey questionnaires) of women from the Ft. Devens Study (with a projected 200 completed surveys). Web-based data collection will be undertaken if a high response rate is not achieved using

telephone and postal surveys. The questions and content of the online survey questionnaire would be identical to the postal survey.

2.6.1. Computer-assisted Telephone Interviews

Veterans who do not opt out will be contacted by telephone, in order to invite them to complete the survey and obtain their informed consent. Computer-assisted telephone interviews will be used for this purpose. Attempts will be made to reach the veterans, calling at different times on different days of the week. Once a potential respondent is reached by telephone and their identity is verified by the interviewer, the consent form will be read to the veteran and, if they agree to be interviewed, the interviewer will proceed with the survey questions using predetermined prompts and procedures. Telephone interview responses will be captured by a REDCap electronic questionnaire.

2.6.2. Postal Surveys

For respondents who have not opted out or who cannot be reached by telephone or for whom a telephone number is unavailable, data will be collected using postal survey questionnaires developed in a TELEForm optical character recognition system. All subjects will have an assigned participant ID number. A sequential mailing protocol will be followed using a modified Dillman method. A letter, signed by the principal investigator, will be sent to each veteran that requests their participation and includes two copies of a consent form, a postal survey questionnaire, and a pre-addressed, stamped return envelope. Three weeks after the survey mailing, a postcard thank you/reminder card will be sent. After 6 weeks, veterans who have not completed and returned the questionnaire or refused consent will be sent a second mailing with a cover letter, consent form, questionnaire, and return envelope, followed by a postcard thank you/reminder card. After 12 weeks, veterans who have not completed and returned the questionnaire or refused consent will be sent a second mailing with a cover letter, consent form, questionnaire, and return envelope, followed by a postcard thank you/reminder card. Paper questionnaires will include a scannable barcode identifying the veteran and whether it was from the first, second, or third wave of the survey.

Survey responses will be checked for completeness and then coded and scanned using Teleform software for entry into an electronic database. All electronic data will be stored on a secure server with access controlled by unique login names and passwords; paper forms will be stored in a locked cabinet in the principal investigator's locked office. Personal identifiers needed for tracking purposes will be stored separately from the research data, whether electronic or paper. All investigators and staff who have access to patient information will be required to complete required human subjects research ethics training. The research team will conduct annual evaluations for quality assurance and data integrity purposes.

2.6.3. Web-Based Survey

If a high response rate is not achieved using telephone and postal surveys, web-based surveys will be undertaken, using methods previously used by the Boston University School of Public Health Data Coordinating Center to survey veterans in the Ft Devens Reunion Survey [18]. In collecting information from the respondents, personally identifying information is kept separate from health information and the records are only linked with the subjects' unique study identification number. Veterans who have not participated in the Gulf War Women Health Cohort Study telephone or postal survey, and who have not refused consent, will be sent a letter inviting them to complete the online survey. They will be provided with a unique web personal identification number and the website URL. The online survey will begin by asking them to read the consent form. The questions that are included in the online survey (if the survey is undertaken) will be identical to those in the postal survey questionnaire.

2.7. Quality Assurance

All survey data collected as part of the proposed study will be carefully monitored for completeness. If a veteran returns two copies of the questionnaire, the most complete questionnaire will be selected for inclusion. A scannable bar code will identify the veteran and whether the questionnaire was from the first, second, or third wave. The quality of the data will be maximized through pre-coded responses and computerized internal consistency checks and range checks of specified values. The use of CATI interviews and barcodes and Teleform software for scanning paper questionnaires will maximize the accuracy of computer databases. Any information from paper questionnaires that requires manual entry into computer databases (e.g., information from open-ended responses) will be entered twice, in order to check for data entry errors and to resolve any discrepancies. Personally identifying information, such as names and addresses, will be kept separate from survey responses and will be kept under lock and key.

2.8. Type of Data Collected

Information will be collected about self-reported symptoms, medical conditions, and military deployment-related exposures.

2.9. Outcomes Measures

The main outcomes of interest include GWI defined using the CDC and Kansas criteria. Other outcomes of interest include self-reported health status (excellent, very good, good, fair, or poor), functional status, individual symptoms and medical conditions, including those that are gender-specific and only occur among women. Table 1 provides a list of self-reported medical conditions diagnosed or treated by a doctor that will be examined in the proposed study, including their date of onset (before 1990 or after 1990).

Table 1. Medical conditions that will be examined in the Gulf War Women's Cohort study.

Asthma	Stomach or intestinal problem (and what type)
Allergies	Skin cancer
High blood pressure	Any other cancer (and what type)
High cholesterol	Depression
Migraine headaches	Alcohol or drug dependence
Seizures	Fibromyalgia
Arthritis (and what type)	Bladder infections
Any skin condition (and what type)	Chronic fatigue syndrome
Chronic bronchitis	Post-traumatic stress disorder
Lung disease (and what type)	Fertility problems
Heart disease (and what type)	Hysterectomy (women only)
Diabetes	Menopausal status (women only)
Thyroid problem (and what type)	Breast lumps or cysts (women only)
Gestational diabetes	Yeast infections (women only)
Pre-eclampsia	Abnormal Pap smear (women only)
Cerebrovascular disease	Lupus
Peripheral vascular disease	

Other outcomes of interest that will be examined in the analysis include spontaneous abortions, stillbirths, ectopic pregnancies, pre-term births, and birth defects. A large number of individual symptoms will be examined in the proposed study, including their severity (mild, moderate, or severe) and date of onset (before 1990 or after 1990), and whether they have been a problem in the past six months or past year.

2.10. Risk Factors, Potential Confounding Variables, and Effect Modifiers

Gender is a key risk factor in this study. Gender may also modify the effect of other risk factors such as exposures during military deployment. Several variables will be examined as risk factors, potential confounding variables or effect modifiers including age, marital status, educational attainment, military rank (officer, enlisted), branch of service, and component (active, reserves, National Guard). In analyses of data for women, additional variables that will be examined in the analysis include use of hormone replacement therapy and menopausal status.

2.11. Statistical Analysis

Cross-tabulations will be used to analyze data on the frequency and patterns of veteran reported chronic symptoms and medical conditions diagnosed by healthcare providers (Specific Aim 2a). Chi-square and Fisher's exact tests will be performed to examine the statistical significance of observed associations. Prevalence odds ratios will be obtained with 95% confidence intervals. Additional analyses will be stratified on branch of service, component, or study cohort. Logistic regression will be used to obtain the prevalence odds ratios associated with chronic symptoms and medical conditions. These outcomes will be assessed in relation to military, deployment, and demographic characteristics using stratified analyses and included in multivariable models as appropriate. Military characteristics (GW deployment status, rank) and demographic variables (age category, sex, education) will be included in the models. Analyses of medical conditions and symptoms will be repeated while focusing on conditions that began after 1990.

The prevalence of GWI defined by the CDC and Kansas criteria (Specific Aim 2b) will be examined by obtaining proportions of veterans who have combinations of symptoms that meet the criteria, along with 95% confidence intervals. This will be done separately for GW and GW era veterans. Prevalence odds ratios will then be obtained in which GWI is the dichotomous dependent variable and the covariates include age categories, sex, deployment status, military rank, and study cohort. Two or more design variables will be used for nominal variables that have three or more categories (for example, branch of service, component). In determining whether the Kansas criteria for GWI are met, cases will be excluded if the veterans had one or more medical conditions (cancer other than non-melanoma skin cancer, diabetes, heart disease other than high blood pressure, chronic infectious disease, liver disease, lupus, multiple sclerosis, stroke, bipolar disorder, schizophrenia) or had been hospitalized since the Gulf War for depression, post-traumatic stress disorder, or alcohol or drug dependence.

The prevalence of female-specific health symptoms and medical conditions (Specific Aim 2c) will be examined by obtaining proportions of women veterans who have combinations of symptoms that meet the criteria, along with 95% confidence intervals. This will be done separately for GW and GW era veterans. Additional analyses will be stratified on branch of service, component, or study cohort. Prevalence odds ratios will then be obtained, in which GWI is the dichotomous dependent variable; and covariates include age categories, deployment status, branch of service, component, military rank, and study cohort.

Analyses of general health and functional status, use of healthcare services, and hospitalizations (Specific Aim 2d) will consist of descriptive analyses (frequency distributions and cross-tabulations) of the data performed using SAS. Additional analyses will be stratified by deployment status and sex. Both chi-square and Fisher's exact tests will be used to examine the statistical significance of observed associations. In order to adjust for age and study cohort, the Mantel–Haenzel procedure will be used.

Analyses of veteran-reported pregnancy and birth outcomes among GW and GW era women veterans (Specific Aim 3) will also consist of frequency distributions and cross-tabulations of the data, stratified by deployment status. Additional analyses will be stratified on branch of service, component, or study cohort. Further analyses will be stratified by whether or not the veteran met criteria for GWI using the CDC and Kansas case definitions. The Mantel–Haenzel procedure and logistic regression methods will be used to adjust for age, study cohort, and other potential confounding variables.

The prevalence of GWI in women veteran subgroups (Specific Aim 4) will be examined by obtaining proportions of veterans who have combinations of symptoms that meet the CDC and Kansas criteria of GWI, along with 95% confidence intervals. This will be done separately for GW and GW era veterans. Stratified analyses will be completed in order to examine subgroups of women defined by deployment characteristics (location, exposures, branch of service). Similar analyses will be completed while stratifying on age, menopausal status, (pre-, peri-, and post-menopause subgroups), and study cohort. The Mantel–Haenzel procedure and logistic regression methods will be used to adjust for study cohort and other potential confounding variables.

Changes in GW and GW era women veterans' health over time (Specific Aim 5) will be examined using baseline and follow-up data obtained from women veterans in the Ft. Devens cohort and Kansas study. These analyses will be limited to women veterans who participated in both the baseline and follow-up surveys. Cross-tabulations of the data will initially be performed. Chi-square and Fisher's exact tests will be used to examine the statistical significance of observed temporal associations. Prevalence odds ratios associated with chronic symptoms, GWI, and other chronic medical conditions will be obtained using logistic regression. Military characteristics (deployment status) and demographic variables (age at baseline, education) will be included in the models as appropriate.

To examine sex differences in the frequency of symptoms associated with GWI and in the prevalence of GWI and other chronic medical conditions among female and male veterans (Specific Aim 6), cross-tabulations of the data will be completed, together with chi-square and Fisher's exact tests, to examine the statistical significance of observed associations. Additional analyses will be stratified on GW deployment status, sex, branch of service, component, rank, or study cohort. Prevalence odds ratios associated with chronic symptoms and medical conditions will be obtained using logistic regression. Effect modification by sex will initially be examined in exploratory cross-tabulations of the data and then by including interaction terms in the models. Log-likelihood ratio tests will be used to determine levels of statistical significance. Military characteristics (GW deployment status, rank) and demographic variables (age category, sex, education) will be included in the models. Analyses of medical conditions and symptoms will focus on conditions that began after 1990.

After female veterans in the Ft. Devens Study have been resurveyed, it will be possible to conduct longitudinal analyses from two time points to determine whether the scores on a variable increased or decreased over time. The changes in scores ($Y_{2\text{-}1}$) will be calculated using the longitudinal modeling with logistic regression. One score will be subtracted from another, where the score at the first time point (Y_1) is subtracted from the score at the second time point (Y_2): $Y_{2\text{-}1} = Y_2 - Y_1$.

Pooled analyses of data from two or more study cohorts will be completed to examine data collected at about the same time period, and the outcome and explanatory variables are measured in a similar fashion. When pooled analyses are undertaken, results will first be examined for each study cohort separately so that the heterogeneity of study results can be assessed. Survey data collected from veterans included in the Ft. Devens Cohort will allow for pooled analyses, because the procedures for collecting new data via postal questionnaire or telephone interview are identical.

Power Analysis

Sample size calculations were based upon an array of assumptions, taking into account likely response rates and attrition. Based upon literature review, the proportion of GW women who have GWI were estimated to be 35–40%, taking into account branch of service and differences across studies. The percentage of women who report a history of other medical conditions of interest will likely vary

widely between 5–50%, depending upon the current prevalence of common chronic conditions, such as hypertension, overweight, and obesity. Based upon a type I error rate of 5% and statistical power of 0.80, a sample of 800 GW women veterans and an equal number of non-deployed women veterans would allow for the detection of a 20% difference in the proportion of women who have CMI, high blood pressure, or overweight/obesity (Specific Aim 1). Based upon a type I error rate of 5%, and power of 0.80, a sample of 800 GW female veterans and a substantially larger sample of male GW veterans will allow for the detection of a 10% difference in the proportions of women and men who have GWI (Specific Aim 6).

Additional sample size calculations were carried out for a two-tailed test on proportions (P1, P2). For a two-tailed test on proportions, with a type I error rate of 5%, power of 0.80, and where P1 = 0.15 and P2 = 0.30, 134 women per group (or 268 women total) would be needed to detect this difference (Specific Aims 2–5). For ordinal variables, the statistical power to detect meaningful differences across groups will be greater.

3. Ethical Considerations

This study protocol has been reviewed and approved by the Augusta University IRB and the IRBs at other participating institutions. There are no known risks to participants in this survey, other than potential, minor psychological distress. The research team will be cognizant of participants' response/reactions to questions and medical diagnoses and will provide more detailed information and/or support if and when necessary. Potential risks due to breaches of confidentiality will be minimized by strict adherence to measures for protecting the confidentiality of the data.

Personally identifying information will be kept separate from survey responses under lock and key, and only members of the study team will have access to the data. Study data and PDF files of scanned survey questionnaires (without personal identifiers) will be transmitted to the Boston University School of Public Health Data Coordinating Center (BU DCC) using the BU DCC's secure STP transfer site. Personal identifiers will not be included in data files or PDF files sent to the BU DCC using the secure server. A BU DCC secure transfer site will be used to transfer the overall study data set (analytic file) from BU to Augusta University and the other participating institutions for statistical analysis.

Personally identifying information from the Ft. Devens Study will only be available to Dr. Maxine Krengel at the VA Boston Healthcare System and her research assistant, and will not be shared with other study investigators. Personally identifying information from the CSP 585 pilot study is not being provided to GWWC Study investigators, only de-identified data. The other existing datasets that are being assembled to create the GWWC consist of de-identified data.

The potential benefits of the study include increased knowledge of the prevalence of GWI and symptoms among GW female veterans, factors associated with symptoms, and female/male differences in GWI. There is no direct benefit to participants in this study.

4. Conclusions

The Gulf War Women's Health Cohort Study will address the need for information about the comprehensive health of women veterans that were deployed to the Gulf War, and other wars during the Gulf War era. The study is likely to contribute importantly to the understanding of key women veterans' health concerns related to deployment during the Gulf War. A broad range of women's health issues will be addressed, including adverse reproductive outcomes and complications (spontaneous abortions, stillbirths, ectopic pregnancies, pre-term births, birth defects, pre-eclampsia and gestational diabetes).

The study will provide important information about changes in physical and mental health as women veterans advance in age. A particular goal of the study is to establish a cohort of women veterans who can be invited to participate in IRB approved clinical research studies. Potential topics for these studies include symptom-based conditions, such as Gulf War illness and chronic fatigue

syndrome; chronic pain, headache, traumatic brain injury, and other neurological conditions; and chronic conditions that are prevalent in both veteran and non-veteran populations as people reach middle age or older age (for example, diabetes, cardiovascular disease, rheumatoid arthritis, chronic pulmonary conditions).

Results from some studies related to this project have been published. A recent study of the rates of chronic medical conditions in 1991 Gulf War veterans using the Ft. Devens cohort revealed that female GW veterans had lower odds of developing high blood pressure and higher odds of developing diabetes when compared with age-matched females from the 2013–2014 National Health and Nutrition Examination Survey (NHANES) [22]. An analysis of the CDC Air Force Study revealed that the prevalence of mild-to-moderate and severe cases of CMI was 39% and 6%, respectively, among GW veterans, compared with 14% and 0.7% among 2520 non-deployed veterans. Although no physical examination, laboratory, or serologic findings identified cases, veterans who met the case definition had significantly diminished functioning and well-being [23]. Results to date from the re-analysis of the Cooperative Studies Program 585 Gulf War Era Cohort and Biorepository indicate that GW women showed significantly increased symptom reporting in 7 of the 34 symptoms queried, compared with non-deployed GW-era women veterans ([24], in press). The GW deployed women were also significantly more likely to report more total symptoms than the GW-era women, with more than half of the GW women reporting more than 21 total current health symptoms. Younger and non-white GW women veterans were particularly likely to report more total health symptoms.

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