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PRINCIPAL INVESTIGATOR: Steven S. Coughlin, PhD

CONTRACTING ORGANIZATION: Augusta University Research Institute, Augusta, GA

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14. ABSTRACT 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 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 are: 1) To assemble the GWWC from data collected from women veterans who participated in previous and ongoing population studies of GW era veterans; 2) To conduct a multimodal health survey to provide data on the current health status of women who served during the 1991 GW era 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 (i) deployment characteristics.					
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1. INTRODUCTION:

This epidemiologic study utilized 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 utilized data from multiple studies in order to establish a Gulf War Women's Health Cohort.

2. KEYWORDS:

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

3. ACCOMPLISHMENTS:

What were the major goals of the project?

Coordinate with sites for IRB continuing review and approval; coordinate with sites for Augusta University IRB continuing review and approval; coordinate with sites for military 2nd level IRB review (ORP/HRPO).
Hire and train staff.
Analyze data from epidemiologic studies of women veterans.
Conduct a survey of women veterans included in the Ft. Devens Cohort.
Implement quality assurance measures for data collection and data management.

What was accomplished under these goals?

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

A major accomplishment in year five was the analysis of data from the CSP 585 Gulf War Survey and Biorepository survey in support of collaborative manuscripts. Another major accomplishment in year five was publication of a key journal article. These publications are included in the Appendices.

New data collection for the GWWC involved a postal survey of women included in the Ft. Devens Study, 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 were 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 Steven 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 worked under the mentorship of Drs. Coughlin and Heboyan. His doctoral dissertation at Augusta University utilized data from the Gulf War Women's Health Cohort Study. Dr. Ansa examined health conditions reported by women included in the CDC Air Force Study and the Ft. Devens Study.

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?

This is the final report for the Gulf War Womens Health Cohort Study. Although all of the aims of the study have been accomplished, we plan to continue to prepare manuscripts and present findings at professional and scientific meetings.

4. IMPACT:

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

The Gulf War Women's Health Cohort Study provides a comprehensive picture of the health of women GW veterans. This included an assessment of current health status, changes in health symptoms and conditions over time, and differences in health outcomes associated with specific experiences and exposures during the war. The study allowed for an assessment of GWI symptom patterns that may be

specific to women veterans and a determination of diagnosed medical conditions. The study generated data that improves 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:

Changes in approach and reasons for change

Nothing to report

Actual or anticipated problems or delays and actions or plans to resolve them

There had 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 successfully resolved the delay in release of funds. The survey of women veterans included in the Ft. Devens study was completed in the Summer of 2021.

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:

- **Publications, conference papers, and presentations**

Journal publications.

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

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

Coughlin SS, Krengel M, Sullivan K, Pierce PF, Heboyan V, Wilson C. A review of epidemiologic studies of the health of Gulf War women veterans. Journal of Environment and Health Science 2017;3.

Coughlin SS. Physical activity among Gulf War veterans (editorial). Annals of Translational Medicine and Epidemiology 2016;3(1). pii: 1010.

Coughlin SS. Reproducing Epidemiologic Research and Ensuring Transparency. American Journal of Epidemiology 2017;186:393-4.

Coughlin SS. A Neuroimmune Model of Gulf War Illness. Journal of Environment and Health Science 2017;3:1-6.

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. Environ Health Sci 2019;5:24-5.

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.

Zundel CG, Krengel MH, Yee MK, Grasso CM, Janulewicz Lloyd PA, Coughlin SS, Sullivan K. Rates of Chronic Medical Conditions in 1991 Gulf War Veterans Compared to the General Population. International Journal of Environmental Research and Public Health 2019;16:949.

Krengel M, Sullivan K, Heboyan V, Zundel CG, Wilson C, Klimas N, Coughlin SS. Neurotoxicant exposures and rates of Chronic Multisymptom Illness and Kansas Gulf War Illness Criteria in Gulf War deployed women veterans, submitted for publication.

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

Nothing to report

Other publications, conference papers, and presentations.

Coughlin SS, Sullivan K, Krengel M, Heboyan V, Iobst S, Wilson C. Gulf War illness and deployment-related exposures among women Gulf War veterans. 2020 Virtual Gulf War Illness (GWI)-State of the Science Conference, August 18-19, 2020.

- **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, contributed to all aspects of the study, surveying GW women included in Ft. Devons Study
Kimberly Sullivan, Co-I, contributed to all aspects of the study
Emily Sisson, oversaw Boston University Data Coordinating Center activities
Stacy Iobst, Co-I, contributed to all aspects of the study
Col Candy Wilson, Co-I, contributed 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?

Consortium Sites:
Boston University Medical Center, Co-I: Kimberly A. Sullivan, PhD - 1.2 calendar months effort/year
Subaward funds total for 09/30/2016 - 09/29/2021: \$334,912

Boston VA Research Institute, Inc., Co-I: Maxine Krengel, PhD - 1.44 calendar months effort per year
Subaward funds total for 09/30/2016 - 09/29/2021: \$117,640

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS:

QUAD CHARTS:

9. APPENDICES:



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_{2-1}) 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): $Y_{2-1} = Y_2 - Y_1$.

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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Editorial

Physical Activity and Chronic Illnesses among Gulf War Veterans

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Editorial

The prevalence of physical inactivity and obesity is a serious threat to the health of Americans, including those who are military veterans, because of the increased risk of cancer of the breast, colon, and other sites; diabetes; cardiovascular diseases; arthritis; sleep apnea; premature mortality; and other adverse health consequences [1]. Along with maintenance of normal weight and consumption of healthy food, physical activity contributes to individual health and wellbeing [2,3]. Physical activity, nutrition, and energy balance are important determinants of weight loss and maintenance of healthy weight. However, many US adults do not meet the national guidelines for engaging in regular physical activity. Based on data from the 2013 Behavioral Risk Factor Surveillance System (BRFSS), only half of US adults (50.2%) met guidelines for physical activity and an additional 11.7% only partially met the guidelines (Woo et al., unpublished). Approximately 35% of U.S. adults are obese [4,5].

Public health recommendations emphasize a lifestyle approach to increasing physical activity that includes brisk walking, climbing stairs, doing house work and yard work, and engaging in recreational activities [1]. Among persons living with chronic illness, physical activity and maintaining a healthy body weight can reduce the risk of disease progression or recurrence and improve quality of life.

Encouraging physical activity among middle-aged and older persons is essential, as they may suffer from one or more chronic illnesses and are at risk of declining physical fitness or unintended weight gain. The 2008 Physical Activity Guidelines for Americans emphasize that all adults should avoid inactivity [6]. Some physical activity is better than none, and adults who participate in any amount of physical activity gain some health benefits. For substantial health benefits, adults should do at least 150 minutes a week of moderate-intensity or 75 minutes a week of vigorous-intensity aerobic physical activity, or an equivalent combination of moderate- and vigorous-intensity aerobic activity. Such activity should be performed in episodes of at least 10 minutes and, preferably, spread throughout the week [6].

Studies have found that less than half of US veterans meet recommendation for physical activity and that the prevalence of

inactivity is particularly high among veterans who obtain their health care from Department of Veterans Affairs (VA) facilities [7]. Following military discharge, the percentage of former military service men and women engaging in moderate-to-vigorous physical activity declines substantially [8]. Substantial weight gain has also been associated with the time of military discharge [9]. Although active duty military personnel are more fit and less likely to be overweight or obese than civilians, no such differences have been observed in comparisons of veteran and non-veteran populations [9]. In an analysis of data collected in 2003-2005, Coughlin et al. [10] found that the percentages of Gulf War and Gulf Era veterans who were overweight (BMI 25 to $\leq$ 29.9), were 46.8% and 48.7%, respectively. The percentages who were obese (BMI $\geq$ 30) were 29.6% and 28.3%, respectively [10]. The prevalence of obesity is 37.4% in veteran patients seen at Veterans Health Administration medical centers [11].

Gulf War veterans who suffer from Gulf War Illness often experience chronic pain, fatigue, fatigue upon exertion, impaired cognition, and other debilitating symptoms. As a result, they are less likely to engage in regular moderate to vigorous intensity physical activity and are at risk of chronic conditions such as overweight, obesity, cardiometabolic diseases, and certain types of cancer. The VA Cooperative Study 470 Study Group conducted a randomized controlled trial from 1999 to 2001 among 1,092 Gulf War veterans who reported at least 2 of 3 symptom types (fatigue, pain, and cognitive) for more than 6 months [12]. The participants were randomized to receive usual care, cognitive behavioral therapy (CBT) plus usual care, exercise plus usual care, or CBT plus exercise plus usual care. The exercise sessions were 60 minutes for 12 weeks and were specifically designed to improve physical activity level by incorporating the patient's symptoms into the treatment regimen. The percentage of veterans with improvement in physical function at 1 year was 11.5% for usual care, 11.7% for exercise alone, 18.4% for CBT plus exercise, and 18.5% for CB alone. The participants were relatively noncompliant with both therapies, attending on average only 50% of the sessions [12]. About 13% - 15% did not attend any sessions. For secondary outcomes, exercise alone or in combination with CBT significantly improved fatigue, distress, and cognitive symptoms but not pain [12]. Predictors of compliance during treatment included less pain, greater age, and body mass index [13]. The results of the trial suggest that CBT and/or exercise can provide modest relief for some of the symptoms of Gulf War Illness. Cook et al. [14] found that GWI patients (n=15) who suffered from chronic musculoskeletal pain rate exercise as more painful and effortful and were more sensitive to heat-pain stimuli than healthy Gulf War veteran controls (n=17).

Additional research is needed to identify optimal physical activity regimens for veterans who suffer from GWI which take into account differences in patient symptoms (e.g., musculoskeletal pain), response

to moderate or vigorous intensity physical activity, comorbid health conditions, age, gender, and other factors. Published studies do not clarify what types of physical activity are most appropriate for patients suffering from GWI according to intensity level, duration, or frequency. As veterans who served during the 1991 Gulf War advance in age, they are at increasing risk of chronic conditions that are prevalent among men and women in the general US population including heart disease, diabetes, and common forms of cancer (e.g., colorectal cancer and breast cancer). Gaining additional scientific information about effective treatments for GWI and patient self-management techniques, such as tailored physical activity regimens, is essential for limiting disability and premature mortality in this important veteran population.

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Commentary

Reproducing Epidemiologic Research and Ensuring Transparency

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Measures for ensuring that epidemiologic studies are reproducible include making data sets and software available to other researchers so they can verify published findings, conduct alternative analyses of the data, and check for statistical errors or programming errors. Recent developments related to the reproducibility and transparency of epidemiologic studies include the creation of a global platform for sharing data from clinical trials and the anticipated future extension of the global platform to non-clinical trial data. Government agencies and departments such as the US Department of Veterans Affairs Cooperative Studies Program have also enhanced their data repositories and data sharing resources. The Institute of Medicine and the International Committee of Medical Journal Editors released guidance on sharing clinical trial data. The US National Institutes of Health has updated their data-sharing policies. In this issue of the *Journal*, Shepherd et al. (*Am J Epidemiol.* 2017;186:387–392) outline a pragmatic approach for reproducible research with sensitive data for studies for which data cannot be shared because of legal or ethical restrictions. Their proposed quasi-reproducible approach facilitates the dissemination of statistical methods and codes to independent researchers. Both reproducibility and quasi-reproducibility can increase transparency for critical evaluation, further dissemination of study methods, and expedite the exchange of ideas among researchers.

clinical trials; confidentiality; de-identification; privacy; reproducible research

In 2006, Peng et al. (1) noted that, as is the case in other scientific fields, epidemiologic evidence is strengthened when important findings are replicated by multiple independent investigators using independent data, methods, and instruments; however, in many instances, epidemiologic studies may not be fully replicable because of the time and expense involved. They argued that an attainable minimum standard in epidemiology is reproducibility, meaning that independent investigators are able to analyze the original data and interpret it on their own (1). Measures for ensuring reproducibility include making data sets and software available to other researchers so that they can verify published findings, conduct alternative analyses of the data, evaluate the sensitivity of the findings to modeling choices, and check for statistical or programming errors (1). Ideally, de-identified data from epidemiologic studies should be shared with qualified researchers with data-use agreements in place that protect participants from re-identification. In the 11 years that have elapsed since the publication of the article by Peng et al. (1), there have been several important developments related to the reproducibility of epidemiologic studies. These developments include the creation of a global platform

for sharing data from clinical trials and the anticipated future extension of the global platform to non-clinical trial data (epidemiologic, public health, surveillance, and genomic data) (2). Government agencies and departments such as the US Department of Veterans Affairs Cooperative Studies Program have also enhanced their data repositories and data-sharing resources. Both the Institute of Medicine and the International Committee of Medical Journal Editors have released guidance on sharing clinical trial data (3, 4). Ongoing efforts by the Clinical Data Interchange Standards Consortium address key questions, such as how to best protect the privacy of trial participants, how much data to share, and in what format data should be stored and accessed (i.e., standards for data and metadata) (5). The US National Institutes of Health has updated data sharing policies for studies they fund (6–8).

Ioannidis et al. (9) argued that there is inadequate emphasis on recording of research decisions and on reproducibility of research and that correctable weaknesses in the design, conduct, and analysis of biomedical and public health research studies can lead to misleading results. Despite the growing movement to encourage reproducibility and transparency

practices in epidemiology and the broader scientific community, including a call to provide open access to original data from published studies, a recent review of a random sample of 441 articles published in biomedical journals from 2000 to 2014 found that only 1 study provided a full protocol and none had open access to all of the raw data (10). Potential solutions include rewarding reproducibility practices with funding and academic or other recognition and monitoring both the proportion of research studies undergoing rigorous independent reproducibility checks and the proportion that were able to be reproduced (9).

In this issue of the *Journal*, Shepherd et al. (11) outline a pragmatic approach for reproducible research with sensitive data for studies in which data cannot be shared because of legal or ethical restrictions. Their proposed approach, which they refer to as quasi-reproducible, includes posting analysis code used in the published study on a publicly available website along with simulated data and results obtained by applying that code to the simulated data. The empirical example provided by Shepherd et al. (11) illustrates that legal and ethical considerations may prevent the public disclosure of cohort data on conditions such as human immunodeficiency virus infection even when the data have been de-identified. However, it is still possible to increase the transparency of methods used in epidemiologic studies. Their proposed approach, while not a perfect way to resolve the potential conflicts between legal and ethical concerns and achieve the attainable minimum standard of ensuring reproducible epidemiologic studies, facilitates the dissemination of statistical methods and code to independent researchers. Researchers may wish to check for statistical or programming errors or to apply the analysis code from a published paper to different studies.

Epidemiologic research interacts with many disciplines, using methods and collaborating with researchers from other sciences including genomics, informatics, economics, and psychology. Careful attention to study design, conduct, analysis, documentation, and reproducibility is needed (9). Minor corrections and clarifications after publication should not be a reason to stigmatize other researchers (12). Both reproducibility and quasi-reproducibility can increase transparency for critical evaluation, further dissemination of study methods, and expedite the exchange of ideas among researchers.

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Cardiovascular Disease among Female Veterans of the 1991 Gulf War Era

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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.

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A Review of Epidemiologic Studies of the Health of Gulf War Women Veterans

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Abstract

Introduction: In the 25 years since the 1990-1991 Gulf War (GW), studies have evaluated Gulf War Illness (GWI), sometimes referred to as medically unexplained multi symptom illness, and other medical and neurological conditions in women GW veterans.

Materials and Methods: In this article, we review epidemiologic studies of the health of women who served in the 1990-1991 GW based upon bibliographic searches in PubMed and CINAHL with relevant search terms through September 2015.

Results: A total of 56 articles were identified in the bibliographic searches. By screening abstracts or full-text articles, a total of 21 relevant studies were identified. Results from some studies, but not all, suggest that GWI is more common in women GW veterans than their male counterparts. Few studies of GW veterans focused on women's health. A small number of studies suggested excess rates of woman's health problems, e.g., breast cysts, abnormal Papanicolaou (Pap) smears, yeast infections, and bladder infections. Several studies have identified significantly elevated rates of birth defects and adverse reproductive outcomes among GW veterans. However, findings have varied with different study designs and sample sizes, with some studies showing elevated risks of stillbirths, miscarriages, and/or birth defects and others have not. In some studies, participants reported increased risks of ectopic pregnancies and spontaneous abortions.

Conclusion: Further research is needed to provide a comprehensive picture of the health of women GW veterans and to examine a broad range of women's health issues including adverse reproductive outcomes. Some deployment-related health problems only become apparent decades later and other conditions may worsen or improve over time. Assessments are needed 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. Future studies would be strengthened by assessing GWI symptom patterns that may be specific to women veterans, examine diagnosed medical conditions among women veterans, and evaluate changes in women's health over time, including changes potentially associated with menopause and age.

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Introduction

Women comprised almost 7 percent of the nearly 700,000 military personnel who served in the 1991 Gulf War and represented the largest proportion of U.S. women serving in a war zone in U.S. military history to that point in time. In addition, expanded military roles for women increased their exposure to more intense levels of combat and to toxicant exposures (Bond, 2004). Woman GW veterans, therefore, may have health issues specific to their cohort that are more frequent than among other cohorts of women veterans or among non-veteran women. Several studies have examined rates of Gulf War Illness (GWI) and rates of psychiatric illnesses by gender in GW veterans. GWI illness is sometimes referred to as medically unexplained multisymptom illness or chronic multisymptom illness (Wolfe, et al. 2002; Coughlin, et al. 2013).

Some results from (Wolfe, et al. 2002; Coughlin, et al. 2013) but not all (Unwin, et al. 2002) suggest that GWI is more common in women GW veterans than their male counterparts and additional studies have found no gender difference in the prevalence of GWI. A small number of studies suggested excess rates of woman's health problems, e.g., breast cysts, abnormal Papanicolaou (Pap) smears, yeast infections, and bladder infections (Pierce, 1997; Unwin, et al. 2002; Pierce, 2005). However, in the 25 years since the war, few studies have evaluated GWI and other medical and neurological conditions specifically in women GW veterans (Pierce, 1997). In addition to the lack of studies specific to gender, the original research that was conducted was more than 10 years ago and to our knowledge, follow-up studies have not been completed.

In this article, we review published epidemiologic studies on the health of GW women and identify gaps in our current understanding of the health of women who were deployed to the GW or who served elsewhere during that era. We also summarize published studies of adverse reproductive outcomes such as ectopic pregnancies, spontaneous abortions, stillbirths, and birth defects. Finally, we offer several recommendations for further research on the health of women GW veterans.

Methods

The present review is based upon bibliographic searches in PubMed and CINAHL and relevant search terms. Articles published in English from 1990 through September 2015 were identified using the following medical subject heading (MeSH) search terms and Boolean algebra commands: (Gulf War) and (veterans health) and ((women's health) or (women)). The searches were not limited to words appearing in the title of an article. Information obtained from bibliographic searches (title and topic of article, information in abstract, and key words) was used to determine whether to retain each article identified in this way. In addition, we reviewed the references of reports prepared by the Institute of Medicine and the Research Advisory Committee on Gulf War Illness Research and published review articles. A total of 56 article citations were identified in the bibliographic searches as detailed in Figure 1. After screening the abstracts or full texts of these articles, and examining the references of review articles and reports, 21 studies were identified for further review. This included one study that focused specifically on women GW veterans (Pierce, 1997; Pierce, 2005); a study

of women veterans from more than one era, in which results were reported separately by era (Washington, et al. 2013); 10 studies of both male and female GW veterans in which at least some results were reported separately for women (CDC, 1995; Fukuda, et al. 1998; Steele, 2000; Wolfe, et al. 2002; Kang, et al. 2005; Coughlin, et al. 2013; Smith, et al. 2013; Provenzale D, 2015); and 9 studies of adverse reproductive outcomes and birth defects (Cowan, et al. 1997; Araneta, et al. 2000; Kang, et al. 2001; Araneta, et al. 2003; Araneta, et al. 2004; Doyle, et al. 2004; Wells, et al. 2006; Kelsall, et al. 2007; Verret, et al. 2008). Several studies were also identified of mortality and cancer incidence among male and female GW veterans (Kang, et al. 1996; Macfarlane, et al. 2000; Kang, et al. 2001; Macfarlane, et al. 2003; Macfarlane, et al. 2005; Lincoln, et al. 2007). The present review extends upon the work of earlier authors (Pierce, 1997; Unwin, et al. 2002; Pierce, 2005) by including studies published in the last several years and by offering suggestions for further epidemiologic research on the health of women Gulf War veterans.

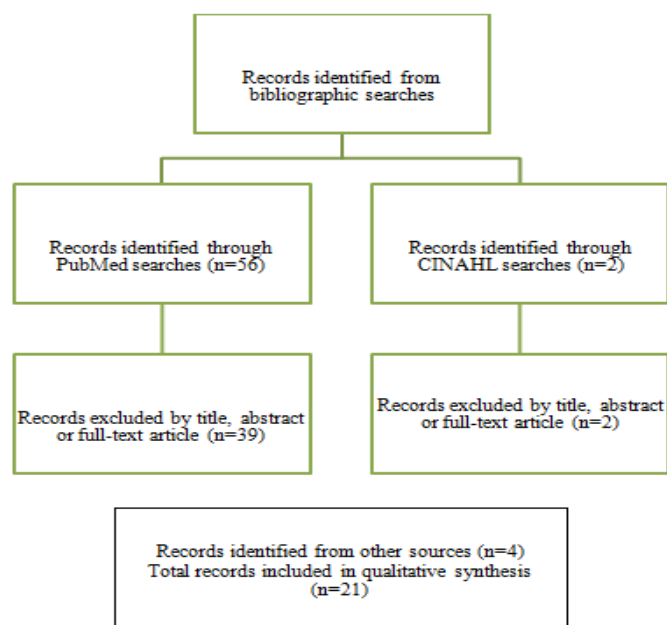


Figure 1: Summary of search and exclusion process.

Results

Epidemiologic surveys that have examined the health of women GW veterans are summarized in Table 1. Several questions related to women's health have been asked in surveys of the Ft. Devens, Massachusetts cohort including difficulty conceiving, whether a child was born with a birth defect, stillbirths, uterine or ovary tumors, hysterectomy, menopause, amenorrhea, vaginal yeast infections, premenstrual symptoms, pain during intercourse, difficulty achieving orgasm, and breast disease (Wolfe, et al. 2002). About 60% of the respondents met the Centers for Disease Control and Prevention (CDC) criteria for chronic multisymptom illness (CMI). In addition to female gender, positive associations were found for those with 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.

Table 1: Design characteristics of studies of U.S. veterans of the first Gulf War that provided information about the health of women veterans.

Study	Inception	Design	Administration	Population eligible to participate	Focus
Devens Cohort Study (Wolfe et al. 2002)	1991, 1995-1996, 1997, 2013 (ongoing)	Repeat cross-sectional surveys of established cohort	Initial re-adjustment survey, with follow-up surveys by mail or in-person	Deployed Army soldiers (84 units, n = 2,300) returning from GW through Ft. Devens, MA	Physical and psychological health, symptoms, reproductive history, adverse birth outcomes, women's health, domestic and military exposures
Longitudinal Health Study (Kang et al. 2000, 2009)	1993-1995	Cross-sectional survey of established cohort with follow-up surveys conducted in 2005 and 2012	Mail survey, telephone interviews; web-based survey added in 2012	National sample of GW (n=15,000) and GW era (n=15,000) veterans	Health status, health care use, physical and psychological health conditions, symptoms, military exposures. Questions on reproductive health outcomes were included in the 1995 survey. Questions on women's health were included in the 2012 follow-up survey
USAF (Pierce 1997, 2005)	1993	Cross-sectional survey and follow-up surveys conducted 2 and 4 years later	Mail surveys	Sample of 525 USAF women (expanded to 2,400 women for the second follow-up survey) who served in USAF, stratified on component (active, National Guard, or reserve), deployment (in the theater or deployed elsewhere), and parental status (parent or nonparent)	Physical and psychological health, symptoms, gender-specific health
Air Nat'l Guard (Fukuda et al. 1998; CDC 1995)	1994	Cross-sectional		GW veterans from a PA-based Air National Guard unit, two USAF reserve units (PA, FL) and an active duty USAF unit (FL) (n=3,927)	Physical health, symptoms, risk factors for illness
(Unwin et al. 2002)	Post-1997	Cross-sectional survey	Mail survey	Random sample of UK Armed Forces Personnel. 4,250 deployed to GW, 4,250 non-deployed, plus Bosnia cohort. Women (n=1,026) were over-sampled	Physical and psychological symptoms, medical disorders, military exposures
Kansas (Steele 2000)	1998	Cross-sectional study	Telephone survey	KS veterans or reserve members (n=2,030) who served on active duty between 8/90 and 7/91	Physical and psychological health, symptoms, military exposures
Millennium Cohort Study (Gray et al. 2002; Smith et al. 2014)	2001	Repeated cross-sectional surveys	Mail survey, telephone survey	Random sample of US military personnel serving in October 2000 (panel one). Random sample of military personnel with 1 to 2 years of service as of October 2003 (panel two), and more recent panels. Marines and women were over sampled in panel two	Health status, health care use, medical and psychological health, symptoms, military exposures
Iowa Gulf War Study (Carney et al. 2003)	1995-1996	Cross-sectional study	Telephone survey	Sample of 4,886 GW era veterans from Iowa (9.2% women) stratified on GW deployment and military status, age, gender, race, officer status, and branch of service	Health status, health care use, military preparedness and exposures
National Survey of Women Veterans (Washington et al. 2013)	2009	Cross-sectional survey of random sample of women veterans	Telephone survey	National sample of 3,611 women veterans	Healthcare delivery preferences, health care use, general health status, physical and psychological health conditions
Survey of GW veterans (Vogt et al. 2007, 2008; Smith et al. 2013)	Not stated	Cross sectional survey	mail survey	National sample of 495 GW veterans (25% women) from all branches of service and unit components	Combat experiences, perceived threat, difficult living and working environment, concerns about family/relationship disruptions, sexual harassment, psychological health conditions, physical symptoms

Table 2: Participant characteristics and findings of studies of U.S. veterans of the first Gulf War that provided information about the health of women veterans.

Study	Number of GW women who participated	Number of GW men who participated	Comparison group	Findings	Other Information
Devens Cohort Study (Wolfe et al. 2002)	Of 1,290 participants in the 1997 survey, 10.4% were women GW veterans	In 1997, 90.6% of 1,290 respondents were men	N/A	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 MSI in logistic regression analyses.	Additional analyses of data for women are planned.
National Health Study/ Longitudinal Health Study (Kang et al. 2000, 2005, 2009)	11,441 GW veterans, 19.7% women	9,476 non-deployed GW era veterans		Among GW veterans, the adjusted odds ratio for PTSD associated with a report of sexual assault was 5.41 (95% confidence interval [CI] 3.19-9.17) in female veterans and 6.21 (95% CI 2.26-17.04) in male veterans (19).	
USAF (Pierce 1997, 2005)	160 to 625	N/A	365 to 539 GW era women deployed elsewhere		Women deployed to the Gulf reported increased general health problems, skin rash, cough, depression, unintentional weight loss, insomnia, memory problems, breast lumps or cysts, and abnormal Pap tests than did women deployed elsewhere ($p < 0.05$).
Air Nat'l Guard (Fukuda et al. 1998; CDC 1995)	Of 3,723 participants, 14% were female, 47% were deployed to the Persian Gulf. The number of deployed women was not reported	About 86% were male, 47% were deployed; the number of deployed men was not reported	Air Nat'l Guard not deployed to the Persian Gulf		Additional analyses of data for women are planned.
(Unwin et al. 2002)	226 GW women		192 non-deployed GW era women, and 227 deployed to Bosnia	Women were significantly more likely than men to report 6 symptoms (headaches, fatigue, constipation, stomach cramp, passing urine more often, and nausea). Women deployed to the Persian Gulf had similar rates of ill health as their male counterparts. GW women veterans were about three times as likely to meet the CDC criteria for CMI than GW era women veterans, and as compared to women who were deployed to Bosnia.	
Kansas (Steele 2000)	216	1,331	482 non-deployed GW era veterans residing in KS		Questions about women's health (e.g., questions to assess menopausal status) were included in the survey questionnaire.

Millennium Cohort Study (Smith et al. 2014)	n=73,078, 74.0% deployed to the Persian Gulf, 21.6-33.4% women	n=73,078, 74.0% deployed to the Persian Gulf, 66.6-78.4% men		A higher prevalence of CMI was observed among GW veterans as compared with non-deployed veterans who had served during that same era. Women had a higher prevalence of CMI over time than men	
Iowa Gulf War Study (Carney et al. 2003)	129 GW women	3,695 GW men	206 non-deployed GW era women	Men and women had similar military experiences but men more often participated in combat. Men were more likely than women to report exposures to smoke, psychological stress, and lead. No significant gender differences were found in exposure to solvents/ petrochemicals, infectious diseases, neurotoxins, heat stress, trauma, or radiation. Compared with male GW veterans, GW women veterans had more outpatient and inpatient health care use 5 years after deployment.	
National Survey of Women Veterans (Washington et al. 2013)	780 GW era women veterans, deployment status not reported	N/A	WW II, Korea era, Vietnam era, and OEF/ OIF/ OND era women veterans	GW era women veterans (n=780) often cited cost of care as an important consideration.	
Survey of GW veterans (Vogt et al. 2007, 2008; Smith et al. 2013)	83 GW women	234 GW men		Several gender differences in exposure were observed along with gender-related differences in associations between deployment stressors and mental health outcomes. Among men and women combined, 33.8% met CDC criteria for CMI.	

The National Health Survey/Longitudinal Health Study of Gulf War Era Veterans (Kang, et al. 2000; Kang, et al. 2009) is one of the largest studies of the health of male and female GW and GW era veterans. A sample of 30,000 veterans (50% deployed to the Persian Gulf, 20% women) were initially invited to participate in 1995 and again in 2005 and 2012. Branch of service (Army, Navy, Air Force, and Marine Corps) and unit component (active, reserve, National Guard) were represented in both groups. A stratified random sampling method was employed to ensure that women and those who served in the reserve or National Guard were adequately represented. Although this study has provided a wealth of information about the health of GW veterans and non-deployed GW era veterans, most published analyses have controlled for gender rather than reporting gender-specific results. A notable exception is an article by Kang et al. 2005, on the role of sexual assault on the risk of PTSD among GW veterans. The adjusted odds ratio for PTSD associated with a report of sexual assault was 5.41 (95% confidence interval [CI] 3.19 - 9.17) in female veterans and 6.21 (95% CI 2.26 - 17.04) in male veterans (Kang, et al. 2005). Neither the CDC criteria for CMI nor the Kansas criteria for GWI have been used in published analyses of data from this study (Coughlin, et al. 2013). Results from the 2012 follow-up survey, which included questions about women's health, were recently reported.

Pierce, 1997, studied a stratified representative sample of GW and GW era military service women who served in the

USAF. The control group consisted of GW era women veterans who were deployed elsewhere. The study included a stratified sample of women who were interviewed about two years following the war and again in a follow-up study conducted two years later (Pierce, 1997). The sampling frame was stratified on component of the U.S. Air Force (USAF) (active, National Guard, or reserve), deployment (in the Persian Gulf theater or elsewhere), and parental status (parent or nonparent). Certain strata were over-sampled so that the sample consisted of 50% active duty, 25% reserve, and 25% guard, and 33% deployed to the theater of operations vs. 66% who served elsewhere during the same period of time. Of the 638 who were sampled, 525 (82%) women were located and, of those, 509 (97%) participated. Subsequent data collection included self-administered postal surveys that had response rates of 92% (n = 484) and 87% (n = 456), respectively (Pierce, 1997). Measures included items concerning general physical health and gender-specific health items. In addition to questions about general health status, survey items were included of 18 symptoms of gender-specific health problems and 17 medications for which medical treatment or health services were sought. Multiple statistical analyses were used to describe women's physical and emotional health at two time points following the war. Women deployed to the theater reported significantly more general health problems as well as gender-specific health problems than did women deployed elsewhere (p < 0.05). A cluster of common health problems includ-

ed: skin rash, cough, depression, unintentional weight loss, insomnia, and memory problems (Pierce, 2005). Women serving in the theater also reported a significant increase in gender-specific problems (i.e., lumps or cysts in the breasts, abnormal Pap tests) compared to women deployed elsewhere. In a further follow-up survey of this cohort of USAF women two years later, a total sample of 2,400 women were sampled (1,200 GW and 1,200 deployed elsewhere during the GW era) and 1,164 completed the survey (Pierce, 2005). About 45% of the initial sample responded. Women deployed to the theatre continued to report more health problems compared with women deployed elsewhere during the same period, after adjustment for age, education, smoking, and alcohol use ($p < 0.001$). An association with GW deployment was observed for 29 of 48 symptoms (Pierce, 2005).

In November 1994, the VA, DoD, and the Pennsylvania Department of Health requested that the 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 ($n = 3,927$) were surveyed in 1995, who were members of the index unit and three comparison units in Pennsylvania and Florida (CDC, 1995; Fukuda, et al. 1998). 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 (Fukuda, et al. 1998). In addition to general health history, the respondents were asked about the frequency, duration, and severity of 35 symptoms and possible exposures during deployment. 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 cases of CMI was 39% and 6%, respectively, among male and female GW veterans compared with 14% and 0.7% among 2,520 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 (Fukuda, et al. 1998). About 14% of the participants in the CDC study are women.

Unwin et al. 2002, conducted a cross-sectional mailed survey of a random sample of United Kingdom Armed Forces Personnel who were deployed to the GW, non-deployed controls and controls who were deployed to Bosnia. The GW cohort consisted of 4,000 deployed veterans plus an additional 250 women who were oversampled. The total sample size for the deployed cohort was 4,250 and the same number for the non-deployed cohort. The stratification variables were service (Royal Navy, Army, Royal Air Force), gender, age, service status (regular or reservist), rank (officer or other), and fitness (Army and Royal Air Force only). The questionnaire was completed by 645 women, 226 from the GW cohort, 227 from the Bosnia cohort, and 192 from the GW era cohort. The health of service women was compared with that of service men. The main outcome measures were physical symptoms and illnesses, functional capacity, and CMI defined using the CDC criteria. No gender differences were found for 32 of the 50 symptoms. Women were significantly more likely than men to report 6 symptoms (headaches, fatigue, constipation, stomach cramp, passing urine more often, and nausea). GW women had similar rates of ill health as their male counterparts (Unwin et al. 2002). GW women veterans were

about three times as likely to meet the CDC criteria for CMI as non-deployed GW era women veterans, and as compared to women who were deployed to Bosnia (Unwin et al. 2002).

In a study conducted in Kansas in 1998, Steele, (2000); used telephone interviews of 1,548 veterans who served in the GW and 482 who served elsewhere during the GW era. All of the subjects lived in Kansas at the time of the study. In addition to general questions about military service, the respondents were asked about the severity of 37 symptoms in the past year and when the symptoms first occurred. They were also asked if they had ever been diagnosed or treated by a physician for any of 16 medical and psychiatric conditions, or for any medical condition in 5 general areas, and when each reported condition had developed. GWI, defined as having chronic symptoms in 3 of 6 domains, occurred in 34% of GW veterans, 12% of non-deployed GW era veterans who reported receiving vaccines during the war, and 4% of non-deployed GW era veterans who did not receive vaccines (Steele, 2000). The prevalence of GWI was lowest among GW veterans who served on board ship (21%) and highest among those who were in Iraq and/or Kuwait (42%). Questions about women's health (e.g., questions to assess menopausal status) were included in the survey questionnaire. About 15.9% of the participants in the Kansas study are women. Additional analyses of data for women, and to compare female-to-male differences in risk of GWI and frequency of symptoms, are planned.

The Millennium Cohort Study (Gray, et al. 2002; Smith, et al. 2014) is one of the largest, ongoing studies of US military personnel and veterans. The study was launched in 2001 to examine deployment, demographic, behavioral, and occupational characteristics related to military service and various health outcomes. The first panel of participants invited to participate in the study was randomly selected from US military personnel who were serving in October 2000. Persons who had been deployed to Bosnia, Southwest Asia, or Kosovo between 1998 and 2000, Reserve and National Guard members, and women were oversampled. The second panel of invited participants was randomly selected from military personnel with 1 to 2 years of service as of October 2003. Marines and women were oversampled in the second panel. In an analysis of data from panels one and two ($n = 73,078$, 74.0% deployed to the Persian Gulf, 21.6-33.4% women), Smith et al. 2014, examined 18 symptoms that have been reported to be higher among GW veterans (severe headache; diarrhea; rash or skin ulcer; sore throat; night sweats; chest pain; unusual muscle pains; shortness of breath; trouble sleeping; unusual fatigue; sudden unexplained hair loss; being sleepy all the time; forgetfulness; stomach pain; pain in the arms, legs, or joints; cough; feeling down, depressed, or hopeless; and feeling nervous, anxious, or on edge or worrying about different things). The CDC criteria were used to assess CMI. A higher prevalence of CMI was observed among GW veterans as compared with non-deployed veterans who had served during that same era. Women had a higher prevalence of CMI over time than men (Smith, et al. 2014).

In a random sample of GW veterans from Iowa, Carney et al. 2003 compared the combat experiences, occupational and other service-related exposures, and health care use of GW male and female veterans. The sample ($n = 4,886$ potential subjects, 9.2% women) was stratified by GW deployment and military status (active duty, National Guard/reserve), age, gender, race,

officer status, and branch of service. Deployed women ($n = 129$) were more often in the Army, single, without children, college educated, and reported fewer vaccinations than deployed men ($n = 3,695$). Men and women had similar military experiences but men more often participated in combat. Women were less likely than men to report exposures to smoke, psychological stress, and lead. No significant gender differences were found in exposure to solvents/petrochemicals, infectious diseases, neurotoxins, heat stress, trauma, or radiation (Carney, et al. 2003). Compared with male GW veterans, GW women veterans had more outpatient and inpatient health care use 5 years after deployment.

The National Survey of Women Veterans (Washington, et al. 2013) is a nationally representative sample of 3,611 women veterans surveyed by telephone in 2009. Women who served during different eras (World War II, Korea, Vietnam, first GW, and Operations Enduring Freedom, Iraqi Freedom, New Dawn) are represented. Washington et al. 2013, examined the health-care delivery preferences and use (types of healthcare services and number of visits used, use of VA or non-VA healthcare services) of women veterans by military service era. GW era women veterans ($n = 780$) often cited cost of care as an important consideration.

Vogt et al. (2007; 2008) studied 495 GW veterans from across the U.S. Women were oversampled at 25%. Participants ($n = 317$, 26.2% women) deployed from active duty, reserve, and National Guard units and represented the Army, Navy, Air Force, Marines, and Coast Guard branches of the military. Several gender differences in exposure were observed along with gender-related differences in associations between deployment stressors and mental health outcomes. For example, as concerns about family/relationship disruptions increased, levels of anxiety increased for both women and men; however, the strength of the association was stronger for women than men. Using data from this same study, Smith et al. 2013 found that 33.8% met CDC criteria for CMI. The prevalence of CMI was not reported for men and women separately.

Several epidemiologic studies have examined reproductive outcomes among GW veterans (Cowan, et al. 1997; Araneta, et al. 2000; Kang, et al. 2001; Araneta, et al. 2003; Araneta, et al. 2004; Doyle, et al. 2004; Wells, et al. 2006; Kelsall, et al. 2007; Verret, et al. 2008). Several studies have identified significantly elevated rates of birth defects and adverse reproductive outcomes among GW veterans. This includes findings reported in 2001 from VA's large national survey of U.S. Gulf War veterans indicating that children born to women GW veterans had nearly three times the rate of "likely" birth defects as children of women veterans of the same period who did not serve in the Gulf War (Kang, et al. 2001). In the National Health Survey ($n = 15,000$ GW Veterans and $n = 15,000$ non-deployed GW era Veterans; 20% women), Kang et al. 2001, found that male GW veterans, compared with their non-Gulf Veteran controls, reported a significantly higher rate of miscarriage (odds ratio [OR] = 1.62; 95% confidence interval [CI] = 1.32-1.99). Female GW veterans also reported more miscarriages than their respective controls, although their excess was not statistically significant (OR = 1.35; CI = 0.97-1.89). Both men and women deployed to the Gulf Theater of operations reported significant excesses of birth defects among their live born infants. These excess rates also extended to the subset of "moderate to severe" birth defects [males: OR = 1.78 (CI = 1.19-2.66); females: OR = 2.80 (CI =

1.26-6.25)]. No statistically significant differences by deployment status were found among men or women for stillbirths, pre-term deliveries or infant mortality (Kang, et al. 2001). 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 (Kang, et al. 2001; Araneta, et al. 2003; Araneta, et al. 2004). Increased risks of ectopic pregnancies and spontaneous abortions have been observed in some studies (Araneta, et al. 2000; Araneta, et al. 2004).

Discussion

The results of this review indicate that there is currently a paucity of epidemiologic studies that have evaluated GWI and other high interest health outcomes in women veteran subgroups, e.g., subgroups identified by deployment characteristics (e.g. location, exposures, and branch of service). Studies often show differences, however, there are limitations in the research that need addressing, including limited numbers of women and variability in job and deployment times. Some, but not all studies adjusted for mental health conditions such as post-traumatic stress disorder when looking at physical health conditions. There may also have been residual confounding or unmeasured confounders in studies that compared male and female Gulf War veterans or in studies that compared Gulf War women veterans and controls. There is a need for additional studies of women veterans who served in the 1990-1991 Gulf War and comparison groups of women who served in other locations during that same time period. This should include extended analyses of existing datasets and new data collection. Much more is known now about the complex configuration of symptoms reported at the time of the 1990-1991 Gulf War. Current, comprehensive data are needed on the health status of women who served during the 1990-1991 Gulf War, and appropriate controls, in order to identify specific conditions that affect GW women veterans at excess rates. Some medical conditions (e.g., rheumatoid arthritis, chronic fatigue syndrome, migraine headache) are known to be more common among women than men, both among veteran and non-veteran populations. Among the questions of interest are: what is the prevalence of GWI among women GW veterans, defined by both the CDC and Kansas criteria (Fukuda, et al. 1998; Steele, 2000). What is the frequency and patterns of veteran-reported chronic symptoms and medical conditions diagnosed by healthcare providers? What is the prevalence of female-specific health symptoms and medical conditions? What are their general health and functional status and use of healthcare services including hospitalizations? Studies are needed to examine sex-differences in GWI including female-to-male differences in the frequency of symptoms that are associated with GWI and the overall-all prevalence of GWI among GW female and male veterans. In particular, longitudinal studies are needed to help separate out exposure outcomes from "normal" aging processes that occur over time. There is a need for longitudinal assessments of changes in GW era women veterans' health over time, using baseline data collected in the original population studies from which current cohort samples are drawn. Studies are also needed to provide comprehensive data on veteran-reported pregnancy and birth outcomes among GW and GW era women veterans.

Few epidemiologic studies that have evaluated GWI

and other high interest health outcomes in women veteran subgroups, by subgroups identified by age and menopausal status (e.g., pre-, peri- and post-menopause subgroups). Theories about the pathobiology of GWI focus on neuro-immune mechanisms and those mechanisms may be altered by menopause. Menopause has effects on a number of organ systems including the cardiovascular, skeletal, central nervous and genitourinary systems (Gameiro, et al. 2010; Sammaritano, 2012). Studies have shown that following menopause, women can experience an increase in pro-inflammatory serum markers such as IL-1, IL-6, and TNF-alpha (Gameiro, et al. 2010). Given that many women veterans who were deployed to the Gulf region may be in the midst of natural or surgically induced menopause, more research on this topic is important.

There remains a need to evaluate birth outcomes in appropriate subgroups, e.g., by time period of birth, by parental exposures and by other deployment characteristics (e.g., whether the women were later deployed to Operation Enduring Freedom or Operation Iraqi Freedom). There is a paucity of subgroup analyses assessing rates of birth defects and other reproductive outcomes by time period of birth and by parental exposures and other deployment characteristics. Although data from a large GW birth defect registry suggests there may have been significant increases in rates of some birth defects in the early years after the war, but that those differences leveled off over time, GW birth defect studies have not compared rates in GW vs. non deployed GW era veterans by birth year/time period, or by whether the parent veteran had GWI or experienced exposures that may be associated with birth outcomes. Higher diagnosis of birth defects and adverse reproductive outcomes in Gulf War women veterans compared to controls might be in part due to higher awareness, concerns about health issues related to the Gulf War, better access to health care and differential quality of care that veterans receive. Further research is needed to address these important issues.

In summary, further research is needed to provide a comprehensive picture of the health of women GW veterans and to examine a broad range of women's health issues including adverse reproductive outcomes (spontaneous abortions, still births, ectopic pregnancies, pre-term births, and birth defects). This includes assessments 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. Future studies would be strengthened by assessing GWI symptom patterns that may be specific to women veterans, examine diagnosed medical conditions among women veterans, and evaluate changes in women's health over time, including changes potentially associated with menopause and age. Such data would improve our understanding of GWI in women veterans who served in the Gulf War, women GW veteran's health, and adverse reproductive outcomes, and lay the groundwork for future research aimed at a short-term or longer-term improvement in clinical treatment of women veterans with GWI, and the definition and diagnosis of GWI in women.

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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

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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 review⁵ 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 (Kansas⁴ and CDC³) 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 symptomology¹⁵ 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 al³ 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 al³ 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 al³ 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 al³ and CDC publications.^{16,17}

Fukuda et al³ 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. Steele⁴ 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 dependence¹¹. 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

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 al³). 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%

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

Characteristics	Current Symptoms (%)						Symptoms Lasting More than 6 months (%)					
	Veterans			Non-Deployed Military Personnel			Veterans			Non-Deployed Military Personnel		
	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 >10lb	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 >10lb	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

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	GW Case	Non-case	P-Value*
Overall			
GW case	302	215	0.000
Non-case	31	607	
Male			
GW case	278	198	0.000
Non-case	28	574	
Female			
GW 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 Study³ 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 al⁵ 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 Kansas⁴ criteria by Dursa et al⁶ 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 Steele⁴ 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.

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

Variables	Mild-to-Moderate Cases						Severe Cases					
	All			Male			Female			All		
	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
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
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
≥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
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
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
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
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
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
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
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
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
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
≥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
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
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
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
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
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
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

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.

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 al¹⁹ 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 neurotoxic 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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A Neuroimmune Model of Gulf War Illness

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Abstract

Several studies have implicated immune system disruption in the pathophysiology of GWI. In addition, alterations in brain structure and functioning have been associated with specific exposures in theater, including pyridostigmine bromide and nerve gas agents. Recent studies conducted up to 25 years after the 1991 conflict have examined factors associated with the continuation or worsening of GWI.

Drawing upon published studies of neural and immune system abnormalities in veterans with GWI, this paper proposes a model of GWI that takes into account neurologic and immunologic pathways, neuroimmune mechanisms of disease pathophysiology, individual predisposition due to sex and genetic background, and comorbid factors including neurological conditions such as neuritis/neuralgia and epilepsy that may occur along a continuum with GWI.

The proposed neuroimmune model of GWI is likely to be useful for designing new research studies, clarifying factors involved in the continuation or worsening of GWI, and identifying biomarker screening algorithms for the illness. The proposed model goes beyond previously proposed frameworks for GWI by taking into account potential differences in risk based upon female vs. male sex, time elapsed since exposure to neurotoxins, duration and severity of illness, comorbid conditions, and genotype.

Keywords: Brain imaging; Cytokines; Gulf War syndrome; Gulf War veterans; Human leukocyte antigen; Humoral immunity; Neurocognitive; Serum biomarkers; Symptoms

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Introduction

An estimated 25% to 32% of the 700,000 military personnel who served in the 1991 Gulf War (GW) suffer from Gulf War illness (GWI) (White et al. 2016). GWI illness is sometimes referred to as medically unexplained multisymptom illness or chronic multisymptom illness. Although the cause of GWI is unknown, the most likely etiology is exposure to multiple neurotoxins such as organophosphate pesticides, sarin or cyclosarin nerve agents, and pyridostigmine bromide medication used as a prophylactic agent against chemical warfare attacks. Although the duration of the conflict was relatively short, the 1991 GW was unusual because of the numbers of chemical exposures experienced by military personnel, including extensive use of

pesticides, use of pyridostigmine bromide medication, and low-dose chemical warfare agents released by the destruction of Iraqi facilities (White et al. 2016). The 1991 GW is the only conflict in which pyridostigmine bromide was widely used to protect against the effects of possible nerve gas attacks (Golomb, 1999; White et al. 2016). Military personnel who were deployed to the Persian Gulf commonly experienced multiple exposures in different combinations; those who had some exposures were also much more likely to have additional toxic exposures (Cherry et al. 2001; Boyd et al. 2003; Steele et al. 2012; White et al., 2016). The potential interactive effects of these exposures have not been well-characterized in epidemiologic studies.



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Drawing upon published studies of neural and immune system abnormalities in veterans with GWI, including recently reported findings, this paper proposes a model of GWI that takes into account neurologic and immunologic pathways, neuroimmune mechanisms of disease pathophysiology, individual predisposition due to genetic background, and other factors. The proposed neuroimmune model of GWI goes beyond previously proposed frameworks for GWI by taking into account potential differences in risk based upon female *vs.* male sex, time elapsed since exposure to neurotoxins; duration and severity of illness, and comorbid factors. The latter include neurological conditions such as neuritis/neuralgia and epilepsy that may occur along a continuum with GWI, and chronic, comorbid conditions such as diabetes and cardiovascular disease that can cause fatigue and other symptoms and which become more prevalent as people advance in age.

Studies of humoral immunity

Several studies have implicated immune system disruption in the pathophysiology of GWI (O'Bryan et al. 2003; Skowera et al. 2004; Whistler et al. 2009; Broderick et al. 2011, 2012, 2013; Smylie et al. 2013; Moss 2013; Parkitney et al. 2015; James et al. 2016; Georgopoulos et al. 2016, 2017; Abou-Donia et al. 2017). Some studies of the role of humoral immunity in GWI have examined the frequency of human leukocyte antigen (HLA) alleles (O'Bryan et al. 2003; Georgopoulos et al. 2016). HLA Class II proteins are located in the Major Histocompatibility Complex MHC of chromosome 6 and are expressed on all nucleated cells. They play a role in immune recognition by presenting peptides from exogenous proteins to CD4⁺ helper T cells (Meuer et al. 1982). Georgopoulos et al. (2016) identified 144 unique alleles of Class I and II HA genes in 66 veterans with GWI (64 men, 2 women) and 16 without GWI (15 men, 1 woman). These investigators identified 6 Class II alleles that classified participants 84% correctly (56/66 GWI and 13/16 controls). The number of copies of the 6 alleles was significantly higher in the control group, suggesting that the HLA alleles conferred a protective effect for GWI. In support of this interpretation of the findings, overall symptom severity was inversely associated with the number of allele copies. On average, veterans who had larger numbers of allele copies had lower severity of neurological-cognitive-mood, pain, and fatigue symptoms (Georgopoulos et al. 2016). These results are consistent with the hypothesis that exposures of GW veterans served as environmental triggers that contributed to the development of GWI in genetically susceptible veterans who had lower frequencies of HLA alleles that conferred protection. This hypothesized mechanism may relate to both autoimmunity and inflammatory processes since HLA has a role in both (Trowsdale and Knight 2013). The very small number of female research participants precluded looking for sex differences.

James et al. (2016) extended this research by examining whether the effect of HLA allele frequency on GWI symptom severity is exerted by modulating the strength of neural synchronicity. The latter is an important aspect of brain function in health and disease (Singer 1999). Sixty-five GW veterans (63 men, 2 women) with GWI and 16 healthy controls (15 men, 1 woman) underwent a magnetoencephalography scan to assess the strength of brain synchronicity. They had previously undergone HLA genotyping to determine the number of copies of 6

protective alleles. The results demonstrated the presence of substantial, widespread HLA- and non-HLA-related neuronal influences on neurological-cognitive-mood, pain, and fatigue symptom severity in GWI (James et al. 2016). The study was limited by the small number of female research participants.

Georgopoulos et al. (2016) compared synchronous neural interactions between patients with GWI (*n* = 40) and seven other diseases (schizophrenia [*n* = 21], Alzheimer's disease [*n* = 66], posttraumatic stress disorder [*n* = 159], major depressive disorder [*n* = 10], relapsing-remitting multiple sclerosis [*n* = 43], Sjogren's syndrome [*n* = 32], and rheumatoid arthritis [*n* = 8]). All of the research participants underwent a resting-state magnetoencephalographic scan to calculate synchronous neural interactions. Synchronous neural interactions observed in patients with GWI differed significantly from those observed in patients with schizophrenia, Alzheimer's disease, posttraumatic stress disorder, and major depressive disorder but not from those in patients with relapsing-remitting multiple sclerosis, Sjogren's syndrome, and rheumatoid arthritis. Because GWI brain synchronicity did not differ significantly from that of the three immune-related diseases (relapsing-remitting multiple sclerosis, Sjogren's syndrome, and rheumatoid arthritis) but did differ significantly from that of the other diseases, these findings indicate that altered brain communication in GWI likely reflects immune-related processes (Georgopoulos et al. 2017; James et al. 2016). The number of female research participants was not reported.

Autoantibodies to neuronal and glial proteins

The cytoarchitecture of the central nervous system (CNS) is maintained by a complex cellular milieu that includes neuronal and glial cells that maintain proper communication if functioning properly. Abou-Donia et al. (2017) screened the serum of 20 veterans with GWI (8 males, females) and 10 non-veteran controls (4 males, 6 females) who had low-back pain for the presence of autoantibodies to neuronal and glial proteins (neurofilament triplet proteins, tubulin, microtubule associated tau proteins, microtubule associated protein-2, myelin basic protein, myelin associated glycoprotein, glial fibrillary acidic protein, calcium-calmodulin kinase II, and glial S-100B protein). Tau proteins are involved in the stabilization and assembly of axonal microtubules (Liliang et al. 2011). Myelin basic protein is produced by oligodendroglia in the (CNS) and Schwann cells in the peripheral nervous system (Abou-Donia et al. 2017). Glial fibrillary acidic protein plays an important role in maintaining the shape and motility of astrocytic processes and contributes to white matter architecture, myelination, and blood brain barrier integrity (O'Callaghan et al. 2015). In the study by Abou-Donia et al. (2017), veterans with GWI had significantly higher levels of autoantibody reactivity in all proteins examined except S-100B. If these findings are replicated in larger samples of veterans, serum autoantibodies may be useful as biomarkers of GWI. The presence of neuronal injury/gliosis in GW veterans is consistent with results from epidemiologic studies indicating that 25 years after the 1991 conflict, the health of many veterans with GWI is not improving and may be getting worse (Abou-Donia et al. 2017; White et al. 2016).

Immune network signaling

Whistler et al. (2009) conducted a pilot study involv-

ing 9 GWI cases and 11 sedentary control veterans who had not been deployed to the Persian Gulf. The cases and controls were matched on age and body mass index. Natural killer cell (NK) cytotoxicity, cytokines (tissue necrosis factor α , interleukin (IL)-10, IL-6, IL-5, IL- α , interferon Y), and expression levels of 20,000 genes were measured immediately before, immediately after, and 4 hours following a standard bicycle ergometer exercise challenge. Significant differences were observed in three NK cell subsets and NK cytotoxicity. Veterans with GWI had impaired immune function as shown by decreased NK cytotoxicity and altered gene expression associated with NK cell function. In addition, pro-inflammatory cytokines and dysregulated mediators of the stress response, with low baseline salivary cortisol, were altered in GWI cases compared to controls. The exercise challenge augmented these differences. A further finding was that genes distinguishing cases from controls were associated with the glucocorticoid signaling pathway. The findings of Whistler et al. (2009) suggest a role for immune cell dysfunction in sustaining GWI over time.

In a pilot study involving 9 GWI cases and 11 control subjects (numbers of male and female subjects not reported), Broderick et al. (2011) examined whether GWI presents with a distinct pattern of immune signaling. Rather than examining cytokines in isolation, these investigators examined the patterns of interaction of cytokines and other immune markers in an attempt to identify a characteristic GWI signature. Blood was collected prior to a graded exercise test, at peak effort and 4 hours post-exercise. Salivary cortisol and plasma, serum or culture supernatants were analyzed for concentration of neuropeptide Y, tissue necrosis factor α , interleukin (IL)-10, IL-6, IL-5, IL-1 α , interferon Y, and soluble CD26. Mutual information networks linking these immune markers were generated in each group at each time point. Graph theory was then used to describe each network's structure. GWI networks had more connections but were less organized. Under effort, significant restructuring was observed around nodes for CD19+ β cell population, IL-5, IL-6, and soluble CD26 concentrations. In addition, IL-1 α and CD2+CD26+ nodes strongly influenced B and T cell network patterns. These results indicating altered cytokine signaling are consistent with an autoimmune component in the etiology of GWI. Immune processes involving cytotoxic T cells and NK cells may be temporarily disrupted by normal responses to exercise such as the release of cortisol. IL-5 promotes B cell growth and immunoglobulin secretion. CD26 plays a key role in T cell-dependent antibody production and the switching of immunoglobulin isotype in B cells and also contributes to the regulation of CD4+ T cells and NK cells (Broderick et al. 2011).

Broderick et al. (2011) extended their research on patterns of immune signaling in GWI in a study of 20 male GWI cases, 22 healthy veterans, and 7 patients with chronic fatigue syndrome (CFS). Like in the earlier study (Broderick et al. 2009), blood was drawn during a graded exercise test, prior to exercise, at peak effort, and 4-hours post exercise. Circulating lymphocytes collected at each time point were analyzed for gene expression using a conventional single-gene approach and also with a novel approach whereby transcript levels were projected onto the regulatory circuitry of known pathways. Significant increases in immune-neuroendocrine signaling and inflammatory activity and down-regulation of apoptotic signaling were observed in GWI cases.

In addition to clarifying the pathophysiology of GWI and factors that contribute to the continuation or progression of the illness over time, studies of biomarkers of immune function may also help to identify biomarkers of GWI. Broderick et al. (2012) examined the coexpression of 12 biomarkers of immune and endocrine function in a study of 26 GWI patients, 13 health controls, and 9 unhealthy controls with CFS. All of the subjects were male. Blood was collected at 3 time points during a graded exercise challenge. The 3 groups were separated almost completely on the basis of two coexpression patterns (sensitivity 70%, specificity 90%).

Smylie et al. (2013) compared sex-specific immune signatures in GWI and CFS. Blood was drawn during a graded exercise test, prior to exercise, at peak effort, and 4-hours post exercise. The concentrations of tissue necrosis factor β , tissue necrosis factor α , IL-23, 17, 15, 13, 12, 10, 6, 5, 4, 2, 1 α , and interferon Y were measured at each time point. Using between 2 and 5 cytokine markers, classification accuracies in excess of 80% were observed. In male subjects, IL-10 and IL-23 expression contributed in an illness and time-dependent manner in the context of IL-15, 12, 2, and interferon Y. In contrast, IL-10 was identified as a delineator in the context of IL-17, 5, and 4 in female subjects with GWI or CFS. These findings are consistent with the involvement of the IL-23/IL-17 axis in a sex-specific manner. Overlap between IL-23 as a marker of GWI and its contribution as a marker of sex-specific response to exercise suggests the involvement of the sex hormone axis in modulating the IL-23/IL-17 immune response (Smylie et al. 2013).

Brain Imaging Studies

Alterations in brain structure and functioning have been associated with specific exposures in theater, including pyridostigmine bromide and nerve gas agents. Neuroimaging studies employing magnetic resonance imaging (MRI), functional MRI (fMRI) and other sophisticated noninvasive imaging techniques have demonstrated abnormalities in brain tissues in veterans with GWI (Haley et al. 2009; Calley et al. 2010; Li et al. 2011; Chao et al. 2011; Rayhan et al. 2013; for a recent review, see White et al. 2016). As an example, in the fMRI study by Rayhan et al. (2013), GW veterans with GWI or CFS were found to have white matter integrity loss in cortico-cortical and corticospinal areas. In the MRI study by Chao et al. (2011), GW veterans exposed to sarin and cyclosarin had significantly reduced total gray and white matter volumes compared to unexposed controls.

Neurocognitive Abnormalities

Neurocognitive research involving GW veterans has consistently shown exposure-related dysfunction among GW veterans who were deployed to the Persian Gulf. The abnormalities identified in these studies (for example, poorer visuospatial and motor skills) among GW veterans who were exposed to neurotoxins such as sarin and pyridostigmine bromide during deployment) are consistent with structural and functional pathology of the central nervous system (Axelrod et al. 1997; Anger et al. 1999; Binder et al. 1999; Storzach et al. 2001; Sullivan et al. 2003; Proctor et al. 2006). GWI symptoms commonly include complaints about memory and concentration as well as dysregulated mood (White et al. 2016).

Proposed Neuroimmune Model of Gulf War Illness

The proposed neuroimmune model of GWI is shown in Figure 1. This model is based upon a large body of research involving GW veterans suffering from GWI and is also supported by animal studies (for a recent review of animal studies of GWI see White et al. 2016). Likely exposures to neurotoxicants in theatre are shown on the left-hand side of the figure. The model allows for the possibility that veterans suffering from GWI may have been exposed to multiple known or unknown neurotoxicants including organophosphate pesticides, sarin or cyclosarin nerve agents, and pyridostigmine bromide. Genetic susceptibility is shown on the upper left-hand side. This includes genetic factors that may modulate the effects of environmental exposures such as number of copies of specific HLA alleles (O'Bryan et al. 2003; Georgopoulos et al. 2016). As another example, Steele et al. (2015) observed a gene-exposure interaction involving butyryl cholinesterase genotype and enzyme activity in a case-control study of Gulf War veterans. The proposed model is therefore relevant to studies that test the hypothesis that exposures of GW veterans at the time of the 1991 conflict served as environmental triggers that contributed to the development of GWI in genet-

ically susceptible veterans who had lower frequencies of HLA alleles that conferred protection.

Changes in humoral immunity such as autoantibodies to neuronal and glial proteins are highlighted in the model as they may serve as useful biomarkers of GWI (Abou-Donia et al. 2017). Currently, there are no universally accepted and validated biomarkers for GWI. This is an area of active research which could contribute importantly to the diagnosis of GWI and to the selection of therapeutic interventions.

Additional aspects of immune dysfunction are shown in the middle of the figure, towards the bottom (Figure 1). This includes decreased NK cytotoxicity, altered gene expression, alterations in pro-inflammatory cytokines, altered cytokine signaling, and immune cell dysfunction (Whistler et al. 2009; Broderick et al. 2011 Broderick et al. 2012; Smylie et al. 2012). The arrow indicating the linkages between immune dysfunction and persistent GWI is bidirectional and immune cell dysfunction may have an important role in sustaining GWI over time (Whistler et al. 2009). The model takes into account the fact that sex hormones may modulate the proinflammatory cytokine immune response (Smylie et al. (2013).

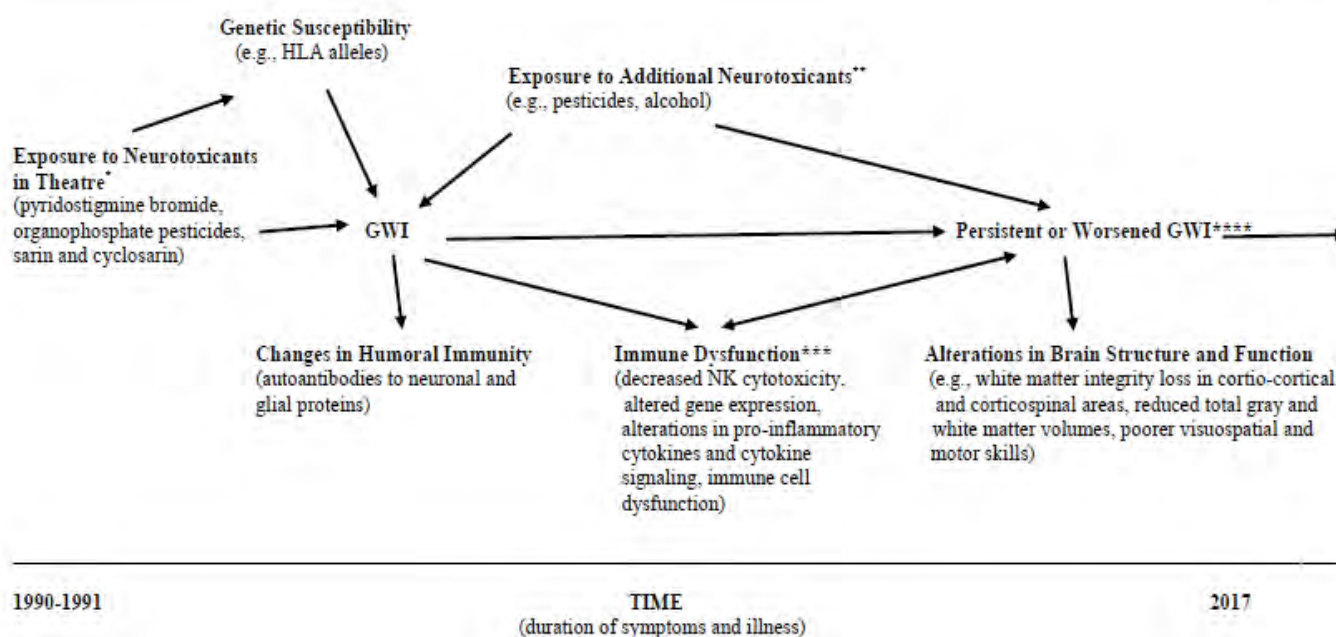


Figure 1: Proposed Neuroimmune Model of Gulf War Illness.

*Initial exposures at the time of the 1991 conflict that may have precipitated GWI.

**More recent exposures that may worsen symptoms and illness.

***Sex hormones may modulate the proinflammatory cytokine immune response. Immune dysfunction may contribute to persistent GWI.

****Persistent GWI can co-occur with neurological conditions such as neuritis/neuralgia and epilepsy that may occur along a continuum with GWI, and with comorbid conditions such as diabetes and cardiovascular disease that can cause fatigue and other symptoms and which become more prevalent with age. comorbid factors including neurological conditions such as neuritis/neuralgia and epilepsy that may occur along a continuum with GWI, and chronic, comorbid conditions such as diabetes and cardiovascular disease that can cause fatigue and other symptoms and which become more prevalent as people advance in age.

Exposures to neurotoxicants that may have occurred long after the 1991 conflict are shown in the middle of the figure, at the top. Men and women are potentially exposed to a number of neurotoxicants in daily life including pesticides used in gardening, consumption of alcohol, and solvents used in some occupations. Little is known about the potential adverse effects of such environmental exposures among GW veterans who suffer from GWI. It is conceivable that exposure to such neurotoxicants could worsen GWI or contribute to its persistence over long periods of time. Thus, the model highlights the need for additional research in this area, which could contribute to the development of evidence-based guidelines for veterans suffering from GWI and their health care providers who counsel them.

Finally, the model highlights alterations in brain structure and function such as white matter integrity loss in cortico-cortical and corticospinal areas, reduced total gray and white matter volumes (in GW veterans exposed to sarin and cyclosarin), and poorer visuospatial and motor skills (Figure 1). Such abnormalities have been observed in neuroimaging studies employing MRI, functional MRI, fMRI, and other sophisticated noninvasive imaging techniques (Haley et al. 2009; Calley et al. 2010; Li et al. 2011; Chao et al. 2011; Rayhan et al. 2013). Neurocognitive studies have shown exposure-related abnormalities such as poorer visuospatial and motor skills which are consistent with structural and functional pathology of the central nervous system (Axelrod et al. 1997; Anger et al. 1999; Binder et al. 1999; Storzbach et al. 2001; Sullivan et al. 2003; Proctor et al. 2006).

Conclusions

The proposed neuroimmune model of GWI is likely to be useful for designing and planning new research studies of GWI, clarifying factors involved in the continuation or worsening of GWI, and identifying biomarker screening algorithms for the illness. The proposed model goes beyond previously proposed frameworks for GWI by taking into account potential differences in risk based upon female vs. male sex, time elapsed since exposure to neurotoxicants, duration and severity of illness, genotype, and comorbid conditions including neurological conditions such as neuritis/neuralgia and epilepsy that may be on a continuum with GWI. As GW veterans advance in age, they are increasingly at risk of chronic conditions such as diabetes and cardiovascular disease that can cause fatigue and other symptoms and which can co-occur with GWI (Coughlin et al. 2013). There is a pressing need for research to identify validated biomarkers of GWI in order to identify veterans suffering from both GWI and comorbid conditions and to facilitate the identification of effective therapeutic interventions. The proposed model highlights these important issues.

Results from longitudinal studies suggest that rates of GWI and symptoms reported by GW veterans are fairly constant with little or no improvement over time (Wolfe et al. 2002; Hotopf et al. 2003; Ozakinci et al. 2006). The proposed model takes into account time elapsed since exposure to neurotoxicants, the potential for additional exposures to neurotoxicants long after the 1991 conflict, and the duration and severity of GWI. It is possible that alterations in brain structure may be more likely to occur among veterans who have suffered from GWI over long periods of time or who have more severe illness.

Finally, the proposed model highlights the fact that sex-differences in GWI may occur and that sex hormones may modulate the proinflammatory cytokine immune response (Smylie et al. 2013). Unfortunately, many of the clinical research studies reviewed in this article were limited to male veterans or had too few women veterans for separate analysis. The study by Smylie et al. (2013) is an important exception. Additional studies are needed that explore potential sex-differences in risk of GWI (Coughlin 2016; Coughlin et al. 2017).

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

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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 (GWECEB) 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 GWECEB, 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, GWECEB 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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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 non-white 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 (GWEBCB) 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 GWEBCB 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 GWEBCB have previously been detailed.²⁶ Briefly, veterans were eligible to participate in the GWEBCB 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 GWEBCB 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 research¹⁶ 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 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).

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). 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

Female DMDC data	Pilot mailing		Completed survey	
	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.

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		Not deployed to Gulf		p-value chi-squared or Fisher's exact test
	n	%	n	%	
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	

^aChi-square test.

^bFisher's exact test.

GED, general equivalency degree.

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

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 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 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

<i>Symptoms</i>	<i>Deployed to Gulf (N = 202)</i>		<i>Not deployed to Gulf (N = 98)</i>		<i>Excess prevalence (%)</i>	<i>OR</i>	<i>95% CI</i>	<i>c-stat</i>
	<i>n</i>	<i>%</i>	<i>n</i>	<i>%</i>				
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 GWEGB 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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Author Disclosure Statement

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Article

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

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

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

1. Introduction

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

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

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

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

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

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

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

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

2. Materials and Methods

2.1. Participants

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

2.2. Self-Report of Medical Conditions

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

2.3. Self-Report of Exposures

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

2.4. Statistical Analysis

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

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

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

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

3. Results

3.1. Demographics

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

Table 1. Demographics.

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

Table 1. Cont.

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

* $p < 0.05$.

3.2. Chronic Conditions in the FDC and NHANES Cohort

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

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

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

Table 2. Cont.

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

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

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

3.3. Age and Gender Comparisons in FDC and NHANES Cohorts

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

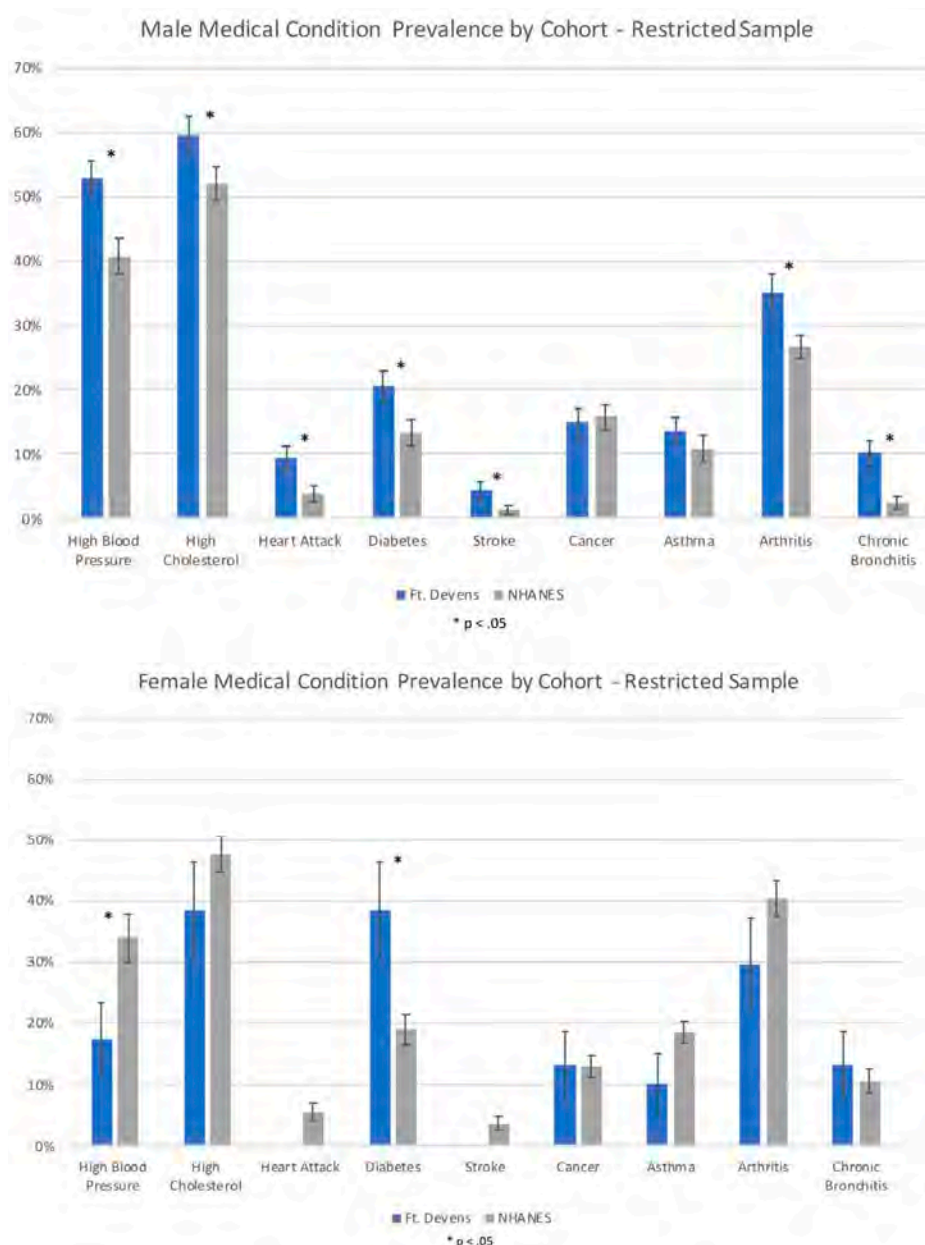


Figure 1. Prevalence of medical conditions in male and female participants from FDC and NHANES cohorts in the restricted sample. (Error bars represent Standard Error).

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

Condition	Ft. Devens	NHANES	Excess Prevalence [CI]	p-Value	OR [CI]
40s	% (n = 142)	% (n = 387)			
Self-reported doctor diagnosed medical conditions					
High Blood Pressure	43.6%	26.4%	17.2% [7.9–26.5]	0.000	2.16 [1.423–3.272]
High Cholesterol	50.8%	37.6%	13.2% [3.3–23.1]	0.009	1.71 [1.144–2.561]
Heart Attack	4.5%	1.8%	2.7% [–1.4–6.7]	0.199	2.54 [0.612–10.509]
Diabetes	14.2%	9.3%	4.9% [–2.2–12.0]	0.174	1.62 [0.808–3.232]
Stroke	0%	0.8%	–0.8% [–1.6–0.01]	N/A	N/A
Cancer	5.4%	2.8%	2.6% [–2.0–7.1]	0.267	1.95 [0.599–6.373]
Asthma	12.8%	10.9%	2.0% [–5.0–9.0]	0.578	1.21 [0.618–2.373]
Arthritis	17.0%	12.2%	4.8% [–3.1–12.7]	0.231	1.48 [0.780–2.789]
Chronic Bronchitis	4.7%	1.8%	2.9% [–1.4–7.1]	0.183	2.66 [0.629–11.256]

Table 3. Cont.

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

* Actual N may vary due to missing data.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

4. Discussion

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

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

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

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

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

Strengths and Limitations

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

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

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

5. Conclusions

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

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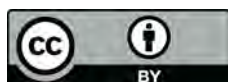
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Neurotoxicant exposures and rates of Chronic Multisymptom Illness and Kansas Gulf War Illness criteria in Gulf War deployed women veterans

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ABSTRACT

Aims: This study analyzed deployment-related exposures and risk of Persian Gulf War Illness (GWI) in women veterans from the Veterans Affairs (VA) Cooperative Studies Program 585 Gulf War Era Cohort and Biorepository (GWECB CSP#585).

Main methods: We examined the associations between GW deployment-related exposures and case definitions for GWI in deployed GW women. Multivariate regression analyses controlling for demographic outcomes were performed.

Key findings: Surveys were obtained from 202 GW deployed women veterans. Self-reported exposure to smoke from oil well fires as well as chemical and biological warfare were the only exposures significantly associated with the Center for Disease Control and Prevention (CDC) GWI criteria. Seventy-nine women were excluded from the rest of the analyses as they met Kansas GW illness exclusion criteria. Eligible women who self-reported deployment-related exposure to smoke from oil wells, pyridostigmine bromide (PB) pills, pesticide cream, pesticide treated uniforms, and insect baits were significantly more likely to meet the Kansas GWI criteria ($n = 123$) than those unexposed and exposures were related to Kansas symptom subdomain endorsements.

Significance: These results suggest that women GW veterans reporting deployment related exposures of pesticide, oil well fire and PB pills are significantly more likely to meet the Kansas GWI criteria in this national cohort of GW women suggesting its utility in future studies. In addition, based on these results it appears that women exposed to particular toxicants during the war may benefit from more targeted treatment strategies dependent upon the mechanism of exposure of their toxicant induced outcomes.

1. Introduction

Enhanced military roles for women in the 1990–1991 Persian Gulf War (GW) increased their exposure to levels of combat and neurotoxicants during their deployment [1]. Women comprised nearly 7% of those deployed and results from some studies, but not all, suggest that GW illness (GWI) is more common in women GW veterans than their

male counterparts [2–6]. It is possible that the differences in rates of GWI vary dependent upon what criteria is used. While it is well known that men and women GW veterans were exposed to numerous neurotoxicants during deployment, in the 30 years since the war, few studies have been designed to evaluate environmental exposures specifically in relation to case criteria in GW women veterans [7,8]. This is important because prior studies have shown different health trajectories with

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respect to environmental exposures in men and women GW veterans [6]. The exposures of interest have included smoke from oil well fires, pesticides, pyridostigmine bromide (PB) pills, tent heaters, chemical/biological warfare agents (CBW), delousing sprays, insect baits and mixtures of the above [7,9,10]. Most of these exposures have been shown to impact central nervous system (CNS) function overall and as such have resulted in chronic health symptoms in men and women who have been exposed [6,8–12]. What remains largely unknown is whether exposures affect rates of GWI and chronic health symptoms differently for women GW veterans dependent upon criteria used and if certain exposures during the war tend to result in varying symptom clusters within case definitions.

There are two well-known criteria that were recommended by the National Academy of Science for use in research studies and in documenting clinical presence of GWI. These criteria are the Center for Disease Control (CDC) GW illness criteria known as Chronic Multi-symptom Illness (CMI) and the Kansas GWI Criteria [3,13]. Rates of GWI tend to differ in study samples depending upon which criteria are used [1,7,14–16]. In addition, associations between exposures and GWI case status vary by case criteria such that the Kansas criteria may be more specific because it encompasses more bodily symptom domains relevant to the disorder. Specifically, the CDC criteria requires symptoms in two out of three symptom domains (mood/cognition, fatigue and pain) while the Kansas GWI criteria requires symptoms in three out of six symptom domains (fatigue, pain, neurological/cognitive/mood, skin, gastrointestinal, and respiratory). The Kansas criteria also excludes those with comorbid conditions that could be alternative causes for their chronic health symptoms.

Although these two criteria are the most widely used within GW illness research studies, rarely have they been studied in the same cohort to document risk ratios of each case criteria within exposed groups [2,8]. In two of our recent studies, we evaluated rates of both CDC and Kansas GWI criteria in the same veteran cohorts. The first study found that GW deployed men and women veterans had higher rates of both CDC and modified Kansas GWI rates with rates of Kansas criteria lower than the rates of CDC criteria [2]. These results again suggested that the CDC criteria may be more sensitive, but the Kansas criteria was more specific in these groups. However, in that study, the case criteria were not examined in relationship to neurotoxicant exposures. The second study reported rates of GWI in women veterans from the large VA Gulf War Era Cohort and Biorepository (GWECB) study [8,17]. The results of that study indicated that GW deployed women veterans reported higher rates of symptoms from two of the Kansas domains, neurological/mood/cognition and respiratory, compared with non-deployed women suggesting that the individual symptoms should be further studied in this cohort of women GW veterans, especially with exposure related symptom outcomes. This report is in response to our prior work and to our knowledge is one of the few studies in the literature that focuses on exposures during the war and rates of both the Kansas and CDC GWI case criteria in women GW veterans.

The current study, also using the women veterans from the 1274 participants from the Veterans Affairs (VA) Cooperative Studies Program 585 Gulf War Era Cohort and Biorepository (GWECB CSP#585), evaluated deployment-related exposures and risk of GWI in women veterans deployed to the 1991 GW. We examined the associations between GW exposures and CMI and Kansas criteria and compared the risk of GWI for each deployment-related toxicant exposure. We specifically compared the difference in rates of Kansas and CMI case criteria relative to these exposure groupings to better understand the risk of these exposures on chronic GWI rates in women veterans. We also compared the exposures with each of the six Kansas health symptom domains (fatigue, pain, neurological/cognitive/mood, skin, gastrointestinal, and respiratory) in this cohort. The importance of this work is that very few other studies have focused on and had the power to perform exposure-outcome analyses in GW women veterans specifically. Further documenting these toxicant induced outcomes in GW women will aid in

establishing the need for service-connected disability and improved healthcare coverage in particular clinical specialties.

2. Methods

2.1. Data

The methods used for the GWECB have previously been detailed [8,18]. Briefly, the cohort included active-duty service members who were in the military between August 1990 to July 1991, regardless of deployment or combat status. Recruitment consisted of a Department of Defense Manpower Data Center (DMDC) population-based sample ($n = 10,042$) and self-referrals as detailed in Khalil et al. [18]. As part of the Gulf War Women Cohort Study (W81X-WH-16-1-0774), a subset of 202 women GWECB GW deployed veterans were included for the current exposure-outcome analysis. The Augusta University and Boston University Institutional Review Boards (IRB) determined that this secondary data analysis was exempt from IRB review.

2.2. Ethical statement

Approval for the secondary use of the GWECB data for this study was obtained from the Augusta University Institutional Review Board on 6/19/2019 and from the Boston University Medical Campus Institutional Review Board on 11/18/2016. The specific protocol components for Augusta University were: Protocol ID: 1409335-3, Principal Investigator: Steven Coughlin, Protocol Title: 'Gulf War Women's Health Cohort'. The specific protocol components for Boston University were Protocol ID: H-35625, Principal Investigator: Kimberly Sullivan, Protocol Title: 'Gulf War Women's Health Cohort.'

2.3. Data collection

In 2014–2016, 25 years after the conflict had ended, veterans in the 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. [18].

2.4. Survey instrument

As described by Khalil et al. [18], the GW-era veterans' survey assessed deployment history and exposures at the time of the GW as well as demographics and physical/mental health outcomes. Validated instruments for use with GW veterans were used for health symptom reporting. Exposure outcomes were assessed by self-reported categorically (yes/no/not sure) responses to the known deployment related neurotoxicants. These included oil well fires, tent heaters, sarin, pyridostigmine bromide (PB) pills, chemical or biological agents (CBW), pesticides including working with prisoners of war, use of pesticide cream, wearing a uniform sprayed with pesticides, and using insect baits during the war.

2.5. CDC GWI criteria

The CDC criteria for GWI was defined by Fukuda et al. [13]. 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 difficulty remembering recent information, difficulty concentrating, feeling moody, feeling anxious, feeling down or depressed, trouble finding words when speaking, difficulty getting to sleep/staying asleep, and not feeling rested after you sleep), and (3) musculoskeletal (symptoms of joint pain, joint stiffness, or muscle pain).

2.6. Kansas GWI criteria

The Kansas GWI case definition was developed by Steele [3]. 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. The fatigue domain was defined as symptoms of fatigue, feeling unwell after physical exercise or exertion, problems getting to sleep or staying asleep, and not feeling rested after you sleep. The pain domain was defined as symptoms of pain in your joints, pain in your muscles, and body pain where you hurt all over. The neurological/cognitive/mood domain was defined as symptoms of headaches, feeling dizzy, lightheaded or faint, eyes very sensitive to light, blurred or double visions, numbness or tingling in your extremities, tremors or shaking, low tolerance for heat or cold, night sweats, having physical or mental symptoms in response to certain smells or chemicals, difficulty concentrating, difficulty remembering recent information, trouble finding words when speaking, feeling down or depressed, feeling irritable of having angry outbursts, feeling anxious. The skin domain was defined as skin rashes or other skin problems. The gastrointestinal domain was defined as diarrhea, nausea or upset stomach, and abdominal pain or cramping. The respiratory domain was defined as difficulty breathing or shortness of breath, frequent coughing when you don't have a cold, and wheezing in your chest. Therefore, total Kansas criteria and symptom domain criteria for each of the six symptom domains can be determined by these methods. This definition also excludes veterans who had one or more medical conditions that could account for their symptoms. For the purposes of this study we excluded veterans from the Kansas analyses if they endorsed any of the following medical conditions: Diabetes, heart disease, stroke, lupus, multiple sclerosis, rheumatoid arthritis, Parkinson's disease, amyotrophic lateral sclerosis, seizure disorders, Alzheimer's disease, cancer other than skin cancer, liver disease, kidney disease, schizophrenia, or bi-polar disorder. A total sample of 123 veterans remained after these exclusions.

2.7. Statistical methods

This study examined the frequency of GWI, and associations between GWI and deployment-related exposures, among woman veterans who served during the GW. Multivariate logistic regression analyses, including age, race, smoking status, and service branch as covariates, were performed to examine the associations between GW-specific neurotoxicant exposures and rates of GWI (CDC and Kansas Criteria), and between these exposures and the symptom domains of the Kansas criteria. We report the odds ratio (OR) and corresponding 95% confidence intervals for each exposure. Exposures were classified as yes, no or unknown if there were missing values or no answer for an exposure. All analyses were conducted using STATA 14 [19], and p -values <0.05 were considered significant.

3. Results

A total of 202 GW women veterans participated in the survey and were included in the CMI and total demographic analyses. Seventy-nine women were excluded from the Kansas GWI analyses as they met exclusionary criteria thus leaving 123 women veterans in the Kansas analyses. Mean ages of the total sample at the time of the survey in 2016 were 53 years and about three-quarters of the participants were White (Table 1). About 8% of the participants were Hispanic or Latino (Table 1). All branches of the military were represented in this national cohort of GW women (Table 1).

Using the CDC criteria, a statistically significant association ($p < 0.05$) was observed between self-reported exposure to smoke from oil well fires and rates of GWI with those reporting this exposure being more than 10 times as likely to meet the criteria for GWI (OR = 10.09, CI

Table 1

Summary statistics of the demographic and GWI measures (N = 202).

Variable	Mean + SD N (%)
Age	53.0 + 7.3
Race	
White	145 (71.8)
Black	42 (20.8)
Other	15 (7.4)
Ethnicity	
Not Hispanic	184 (91.5)
Hispanic	15 (7.5)
Service branch	
Army	101 (5.0)
Navy	45 (22.3)
Air force	34 (16.8)
Marine corps	16 (7.9)
Other/missing	6 (3.0)
Education	
HS/GED or less	9 (4.5)
BS or some college	136 (67.3)
Masters, professional degree, doctorate	53 (26.2)
Unknown	4 (2.0)
Smoking status	
Current smoker	25 (12.4)
Former smoker	53 (28.2)
Never smoker	106 (52.5)
Rates of GWI	
CDC criteria	169 (83.7)
Kansas criteria ^a	87 (70.7)

^a Total sample for the Kansas case definition is 123 due to exclusions as described in the Methods section.

= [2.92–34.86]), as compared to those reporting no exposure. An association was also observed between self-reported chemical or biological weapons (CBW) exposure and rates of GWI with those reporting this exposure being more than 11 times as likely to meet with criteria for GWI (OR = 11.71, CI = [1.22–112.66]), as compared to those reporting no exposure. These results are displayed in Table 2.

Using the Kansas criteria for GWI, significant associations were observed for five of the GW-specific neurotoxicant exposures. Those who reported smoke from oil well fires exposures were more than 7.5 times as likely to meet criteria for GWI (OR = 7.51, CI = [1.95–28.88]). Those who reported taking PB pills were more than 4 times as likely to meet criteria for GWI (OR = 4.86, CI = [1.55–15.25]). Those who reported using pesticide cream were also more than 4 times as likely to meet criteria for GWI (OR = 4.55, CI = [1.34–15.42]). Those who reported wearing a uniform treated with pesticides were more than 5 times as likely to meet criteria for GWI (OR = 5.78, CI [1.13–29.69]). Those who reported using insect baits were more than 3 times as likely to meet criteria for GWI (OR = 3.91, CI = [1.14–13.42]). No association was observed between CBW or prisoners of war exposure and rates of GWI (p 's > 0.05). These results are displayed in Table 3.

Oil well fire exposure was significantly associated with Kansas symptom domain scores of fatigue (OR = 4.47, CI = [1.21–16.48]), pain (OR = 5.43, CI = [1.48–19.92]), neurological (OR = 5.86, CI = [1.03–33.30]), and skin (OR = 18.41, CI = 1.65–205.34), as compared to those reporting no exposure. PB pill usage was significantly associated with domain scores of pain (OR = 3.95, CI = [1.31–11.91]), and gastrointestinal (OR = 3.89, CI = 1.30–11.64). CBW exposure was significantly associated with the gastrointestinal domain score (OR = 18.14, CI = [2.50–131.50]). Use of pesticide cream was associated with domain scores of pain (OR = 3.63, CI = [1.20–11.00]), skin (OR = 4.11, CI = [1.07–15.86]) and gastrointestinal symptoms (OR = 9.72, CI = [3.11–30.41]). In addition, pesticide treated uniforms was associated with domain scores of gastrointestinal (OR = 4.79, CI = [1.40–16.34]) symptoms. Lastly, use of insect baits was significantly associated with domain score of pain (OR = 3.71, CI = [1.17–11.78]). These results are presented in Table 4.

Table 2

Associations between GW-specific neurotoxicants and rates of GWI using the CDC criteria.

Exposure	CDC criteria		Adjusted OR [CI]
	No GWI	GWI	
	N (%)	N (%)	
Smoke from oil well fires			
No	11 (37)	23 (15)	Ref.
Yes	7 (23)	98 (62)	10.09 [2.92–34.86]
Not sure	12 (40)	37 (23)	2.74 [0.90–8.34]
Took pyridostigmine bromide			
No	13 (42)	53 (34)	Ref.
Yes	14 (45)	78 (49)	1.04 [0.36–3.05]
Not sure	4 (13)	27 (17)	2.05 [0.48–8.76]
Chemical or biological agents			
No	12 (40)	41 (25)	Ref.
Yes	2 (7)	27 (17)	11.71 [1.22–112.66]
Not sure	16 (53)	94 (58)	2.46 [0.92–6.60]
Worked with prisoners of war			
No	22 (72)	122 (76)	Ref.
Yes	8 (26)	32 (20)	0.57 [0.19–1.67]
Not sure	1 (3)	6 (4)	0.49 [0.05–5.05]
Used pesticide cream			
No	20 (65)	79 (51)	Ref.
Yes	10 (32)	55 (34)	1.37 [0.48–3.83]
Not sure	1 (3)	27 (15)	5.28 [0.064–43.60]
Wore uniform treated with pesticides			
No	19 (61)	72 (47)	Ref.
Yes	3 (10)	29 (17)	2.31 [0.47–11.42]
Not sure	9 (29)	60 (36)	2.79 [0.99–7.89]
Used insect baits			
No	14 (48)	66 (41)	Ref.
Yes	6 (21)	54 (34)	2.18 [0.62–7.64]
Not sure	9 (31)	41 (25)	0.99 [0.35–2.84]

Adjusted ORs control for age, race, smoking status, and service branch.

Bold OR values indicate statistical significance at $p < 0.05$; $N = 202$.

4. Discussion

In this study we analyzed rates of GWI in women veterans from the large GWECB cohort and associations with exposures to toxicants during the war. We then examined, separately, the associations between specific neurotoxicants and the six health symptom domains that make up the case criteria for Kansas GWI. The results from this study revealed that specific neurotoxicant exposures were associated with increased odds of meeting the CDC and Kansas criteria in GW women. Specifically, those reporting exposure to oil well fires and exposure to CBW agents were more than 10 times as likely to meet the CDC GWI criteria compared to those reporting no exposure. Interestingly, significant associations were observed for all but two exposures (chemical or biological agents and worked with prisoners of war) for the Kansas criteria for GWI suggesting that this criteria may be more sensitive to toxicant induced outcomes from the GW.

The specific exposures were also related differently to the health symptom domains of the Kansas GWI criteria. Exposure to CBW was associated with the gastrointestinal domain, with those reporting this exposure being more than 18 times more likely to report these symptoms. Exposure to PB was associated with the Kansas symptom domains of gastrointestinal and pain, with those exposed being more than 3 times as likely to report these symptoms. The 3 pesticide exposures showed differing associations with the domain scores, depending on the exposure. Specifically, pesticide cream was used as a proxy for the insect repellent DEET exposure and those reporting this exposure were more than 3 times more likely to report pain, skin and gastrointestinal symptoms as compared to those reporting no exposure. Pesticide treated uniforms was used as a proxy for permethrin exposure and those

Table 3

Associations between GW-specific neurotoxicants and rates of GWI using the Kansas criteria.

Exposure	Kansas criteria		Adjusted OR [CI]
	No GWI	GWI	
	N (%)	N (%)	
Smoke from oil well fires			
No	11 (32)	10 (13)	Ref.
Yes	13 (38)	53 (66)	7.51 [1.95–28.88]
Not sure	10 (29)	17 (21)	4.47 [1.05–18.98]
Took pyridostigmine bromide			
No	21 (60)	22 (28)	Ref.
Yes	10 (29)	43 (54)	4.86 [1.55–15.25]
Not sure	4 (11)	14 (18)	4.63 [1.00–21.39]
Chemical or biological agents			
No	19 (53)	12 (15)	Ref.
Yes	2 (6)	10 (12)	5.13 [0.72–36.43]
Not sure	15 (42)	59 (73)	7.41 [2.42–22.71]
Worked with prisoners of war			
No	28 (82)	58 (71)	Ref.
Yes	5 (15)	19 (23)	1.38 [0.40–4.71]
Not sure	1 (3)	5 (6)	2.07 [0.18–23.39]
Used pesticide cream			
No	24 (71)	32 (40)	Ref.
Yes	6 (18)	37 (46)	4.55 [1.34–15.42]
Not sure	4 (12)	12 (15)	1.70 [0.41–7.08]
Wore uniform treated with pesticides			
No	23 (66)	31 (38)	Ref.
Yes	2 (6)	21 (26)	5.78 [1.13–29.69]
Not sure	10 (29)	29 (36)	4.46 [1.41–14.13]
Used insect baits			
No	18 (51)	27 (34)	Ref.
Yes	6 (17)	32 (40)	3.91 [1.14–13.42]
Not sure	11 (31)	21 (26)	1.11 [0.35–3.55]

Adjusted ORs control for age, race, smoking status, and service branch.

Bold OR values indicate statistical significance at $p < 0.05$, $N = 123$.

reporting this exposure were 4 times more likely to report gastrointestinal symptoms compared with those reporting no exposure. Use of insect baits was used as a proxy for the insecticide methomyl and those reporting this exposure were 3 times more likely to report pain symptoms than those not reporting exposure. Lastly, those reporting oil well fire smoke were 3 times more likely to report fatigue, pain, neurological, and skin symptoms compared to those reporting no exposure. This is one of the few studies in the literature that compares these exposure-case criteria outcomes in a cohort of GW women representing each branch of the military in a national cohort.

In general, it has been found that rates of CDC criteria GWI are higher than rates of Kansas GWI because the former is generally more sensitive and does not have exclusionary criteria [2,7,14]. Our prior results with women in this GWECB cohort found that GW deployed women veterans reported higher rates of symptoms from the Kansas neurological/mood/cognition and respiratory health symptom domains [8].

In this study, we analyzed GWI rates dependent on exposure criteria and found that the Kansas criteria was associated with more environmental exposures than the CDC criteria. This is likely due to the additional three symptom domains (gastrointestinal, respiratory, skin) that were shown to be associated with exposure to GW-relevant toxicants in the GWECB cohort of women veterans. Specifically, the gastrointestinal domain was associated with exposure to PB, CBW, and pesticides and the skin domain was associated with exposure to smoke from oil well fires and pesticide cream (DEET) suggesting that these specific exposures are related to these specific health symptoms (toxicant induced outcomes).

Our findings are highly complementary with those of prior studies showing CBW and pesticide exposures being related to chronic health symptoms in GW veterans. Specifically, Proctor et al. [11] found that in members of the Ft. Devens Cohort, musculoskeletal symptom reporting was associated with pesticide and CBW exposure, while neurological and psychological symptoms were linked to self-reported exposure to

Table 4

Adjusted analyses of associations between neurotoxicant exposures and Kansas GWI criteria symptom domain scores.

Exposure status	Kansas domain								
	Fatigue			Pain			Neurological		
	Score 0–1	Score 2+	Adjusted OR [CI]*	Score 0–1	Score 2+	Adjusted OR [CI]	Score 0–1	Score 2+	Adjusted OR [CI]
	N (%)	N (%)		N (%)	N (%)		N (%)	N (%)	
Smoke from oil well fires									
No	8 (31)	13 (15)	Ref.	13 (30)	8 (11)	Ref.	5 (45)	16 (16)	Ref.
Yes	11 (42)	55 (63)	4.47 [1.21–16.48]	18 (42)	48 (68)	5.43 [1.48–19.92]	5 (45)	61 (59)	5.86 [1.03–33.30]
Not sure	7 (27)	20 (23)	3.12 [0.74–13.14]	12 (28)	15 (21)	3.92 [0.94–16.33]	1 (9)	26 (25)	12.20 [1.01–147.37]
Took pyridostigmine bromide pills									
No	16 (62)	27 (31)	Ref.	24 (55)	19 (27)	Ref.	5 (45)	38 (37)	Ref.
Yes	7 (27)	46 (52)	3.30 [1.00–10.93]	14 (32)	39 (56)	3.95 [1.31–11.91]	4 (36)	49 (48)	1.29 [0.25–6.78]
Not sure	3 (12)	15 (17)	3.77 [0.68–20.88]	6 (14)	12 (17)	2.78 [0.70–11.09]	2 (18)	16 (16)	0.72 [1.00–5.27]
Chemical or biological agents									
No	13 (48)	18 (20)	Ref.	19 (43)	12 (16)	Ref.	6 (50)	25 (24)	Ref.
Yes	2 (7)	10 (11)	2.23 [0.32–15.39]	3 (7)	9 (12)	3.63 [0.51–25.65]	2 (17)	10 (10)	0.67 [0.06–7.83]
Not sure	12 (44)	62 (69)	4.14 [1.37–12.51]	22 (50)	52 (71)	3.83 [1.34–10.96]	4 (33)	70 (67)	3.87 [0.83–18.02]
Used pesticide cream									
No	19 (73)	37 (42)	Ref.	28 (65)	28 (39)	Ref.	7 (64)	49 (47)	Ref.
Yes	6 (23)	37 (42)	3.12 [0.88–11.03]	10 (23)	33 (46)	3.63 [1.20–11.00]	3 (27)	40 (38)	2.02 [0.33–12.17]
Not sure	1 (4)	15 (17)	6.87 [0.77–61.39]	5 (12)	11 (15)	3.16 [0.69–14.54]	1 (9)	15 (14)	2.02 [0.19–21.01]
Wore uniform treated with pesticides									
No	17 (65)	37 (41)	Ref.	27 (61)	27 (38)	Ref.	7 (64)	47 (45)	Ref.
Yes	3 (12)	20 (22)	2.00 [0.47–8.55]	4 (9)	19 (26)	3.74 [0.95–14.69]	1 (9)	22 (21)	1.98 [0.19–20.15]
Not sure	6 (23)	33 (37)	4.55 [1.22–17.03]	13 (30)	26 (36)	4.85 [1.58–14.90]	3 (27)	36 (34)	2.71 [0.52–14.21]
Used insect baits									
No	12 (46)	33 (37)	Ref.	23 (52)	22 (31)	Ref.	6 (55)	39 (38)	Ref.
Yes	5 (19)	33 (37)	2.19 [0.58–8.34]	10 (23)	28 (39)	3.71 [1.17–11.78]	1 (9)	37 (36)	5.09 [0.52–49.48]
Not sure	9 (35)	23 (26)	0.63 [0.18–2.16]	11 (25)	21 (30)	1.61 [0.51–5.07]	4 (36)	28 (27)	1.29 [0.26–6.40]
Exposure status	Kansas domain								
	Skin			Gastrointestinal			Respiratory		
	Score 0–1	Score 2+	Adjusted OR [CI]	Score 0–1	Score 2+	Adjusted OR [CI]	Score 0–1	Score 2+	Adjusted OR [CI]
	N (%)	N (%)		N (%)	N (%)		N (%)	N (%)	
Smoke from oil well fires									
No	20 (25)	1 (3)	Ref.	16 (24)	5 (11)	Ref.	17 (21)	4 (12)	Ref.
Yes	40 (50)	26 (76)	18.41 [1.65–205.34]	38 (57)	28 (60)	4.05 [0.98–16.72]	42 (53)	24 (71)	1.94 [0.40–9.39]
Not sure	20 (25)	7 (21)	12.55 [1.04–150.92]	13 (19)	14 (30)	8.84 [1.85–42.26]	21 (26)	6 (18)	1.16 [0.19–7.16]
Took pyridostigmine bromide pills									
No	35 (42)	8 (26)	Ref.	31 (46)	12 (26)	Ref.	35 (43)	8 (24)	Ref.
Yes	37 (45)	16 (52)	1.68 [0.42–6.73]	26 (38)	27 (59)	3.89 [1.30–11.64]	33 (41)	20 (61)	3.96 [0.92–17.04]
Not sure	11 (13)	7 (23)	3.02 [0.58–15.78]	11 (16)	7 (15)	1.34 [0.33–5.39]	13 (16)	5 (15)	1.61 [0.25–10.26]
Chemical or biological agents									
No	29 (35)	2 (6)	Ref.	25 (36)	6 (13)	Ref.	27 (33)	4 (12)	Ref.
Yes	7 (8)	5 (15)	4.78 [0.49–46.29]	5 (7)	7 (15)	18.14 [2.50–131.50]	5 (6)	7 (21)	7.48 [0.92–61.05]
Not sure	47 (57)	27 (79)	7.53 [1.30–43.71]	40 (57)	34 (72)	8.59 [2.44–30.29]	51 (61)	23 (68)	2.32 [0.56–9.61]
Used pesticide cream									
No	44 (54)	12 (36)	Ref.	45 (66)	11 (23)	Ref.	44 (54)	12 (35)	Ref.
Yes	28 (34)	15 (45)	4.11 [1.07–15.86]	15 (22)	28 (60)	9.72 [3.11–30.41]	26 (32)	17 (50)	1.20 [0.32–4.40]
Not sure	10 (12)	6 (18)	5.17 [0.84–31.87]	8 (12)	8 (17)	4.39 [1.07–18.03]	11 (14)	5 (15)	2.62 [0.48–14.25]
Wore uniform treated with pesticides									
No	39 (48)	15 (44)	Ref.	40 (58)	14 (30)	Ref.	41 (50)	13 (38)	Ref.
Yes	13 (16)	10 (29)	2.72 [0.73–10.16]	8 (12)	15 (32)	4.79 [1.40–16.34]	12 (15)	11 (32)	2.22 [0.56–8.85]
Not sure	30 (37)	(26)	0.74 [0.20–2.67]	21 (30)	18 (38)	2.57 [0.93–7.10]	29 (35)	10 (29)	1.98 [0.54–7.22]

(continued on next page)

Table 4 (continued)

Exposure status	Kansas domain								
	Skin			Gastrointestinal			Respiratory		
	Score	Score	Adjusted OR [CI]	Score	Score	Adjusted OR [CI]	Score	Score	Adjusted OR [CI]
	0–1	2+		0–1	2+		0–1	2+	
	N (%)	N (%)		N (%)	N (%)		N (%)	N (%)	
Used insect baits									
No	34 (41)	11 (33)	Ref.	31 (45)	14 (30)	Ref.	35 (43)	10 (30)	Ref.
Yes	27 (33)	11 (33)	1.39 [0.40–4.86]	21 (30)	17 (37)	1.94 [0.69–5.51]	25 (30)	13 (39)	1.65 [0.45–6.02]
Not sure	21 (26)	11 (33)	0.82 [0.20–3.34]	17 (25)	15 (33)	2.23 [0.71–6.97]	22 (27)	10 (30)	1.04 [0.24–4.54]

Adjusted ORs control for age, race, smoking status, and service branch.

Bold OR values indicate statistical significance at $p < 0.05$, $N = 123$.

debris from SCUD missiles and CBW agents. Similarly, McCauley et al. [20] found that self-reported exposure to CBW was associated with fatigue and gastrointestinal symptoms, and Cherry [21] found that exposure to pesticides was related to neurological, dermatological and musculoskeletal symptoms. Our prior findings also showed that GW veterans with high pesticide and PB exposure had increased rates of gastrointestinal symptoms, cognitive symptoms, and mood complaints [12,22]. However, these cohorts had very few women veterans that were able to be compared separately. The present study now adds a national representative sample of women veterans to the study of toxicant induced outcomes in GW deployed women veterans.

Many pesticides and nerve agents (CBW) that GW veterans were exposed to belong to the class of chemicals called acetylcholinesterase (AChE) inhibitors suggesting a common mechanism for these chronic health symptoms [7,9,12]. More recent research has shown that these specific exposures are related to chronic neuroinflammation [22–29]. Additional animal and veteran research have shown that permethrin and PB exposure were associated with changes in the gut-brain-axis and increased neuroinflammation that were associated with higher rates of gastrointestinal symptoms and irritable bowel syndrome, therefore suggesting pathobiological causes for these toxicant induced outcomes that should be further validated [24,27,29,30].

4.1. Limitations

As with any research study, this study has limitations. The first issue is that each exposure category was documented by self-report many years after the war and higher rates of “don't know” were seen in several categories. Some of these veterans were exposed to environmental toxicants and may not have been aware of these exposures. Therefore, we felt it important to not combine the “don't knows” into the non-exposed category which may have reduced our power to detect differences. Additionally, while women veterans were asked to report on exposures during the war, each exposure category was not mutually exclusive because it would be difficult to recall all the exposures that occurred during the war and we would have no way to control for all possible combinations. In some cases due to Kansas exclusionary criteria, there were small sample sizes for exposures, and this may have also reduced our power to detect differences.

5. Conclusion

These results suggest that women GW veterans from all branches of the military reporting pesticide, oil well fire, and PB pill exposures during the war are significantly more likely to meet the Kansas GWI criteria in this national cohort of GW women, suggesting its utility in future studies. In addition, we found exposure-specific health symptom outcomes that should be further followed-up clinically. The results also suggest that treatments focused on reducing neuroinflammation and improving gut health could specifically benefit women GW veterans and further pathobiological studies should be conducted to confirm these toxicant induced outcome relationships.

Declaration of competing interest

There are no conflicts of interest.

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