Journal of the American Heart Association

ORIGINAL RESEARCH

Association of Atherosclerotic Cardiovascular Disease, Hypertension, Diabetes, and Hyperlipidemia With Gulf War Illness Among Gulf War Veterans

Sarah T. Ahmed, MBBS, MPH, PhD; Ruosha Li, PhD; Peter Richardson, PhD; Saurendro Ghosh, BS; Lea Steele, PhD; Donna L. White, PhD; Alice Nono Djotsa, PhD; Kellie Sims, PhD; Elizabeth Gifford, PhD; Elizabeth R. Hauser, PhD; Salim S. Virani, MD, PhD; Robert Morgan, PhD; George Delclos, MD, PhD; Drew A. Helmer, MD, MS

BACKGROUND: Approximately 30% of the 700 000 Gulf War veterans report a chronic symptom-based illness of varying severity referred to as Gulf War illness (GWI). Toxic deployment-related exposures have been implicated in the cause of GWI, some of which contribute to metabolic dysregulation and lipid abnormalities. As this cohort ages, the relationship between GWI and atherosclerotic cardiovascular disease (ASCVD) is a growing concern.

We evaluated associations between GWI and ASCVD, diabetes, hyperlipidemia, and hypertension in veterans of the Gulf War (1990–1991).

METHODS AND RESULTS: Analysis of survey data collected in 2014 to 2016 from a national sample of deployed Gulf War veterans (n=942) and Veterans Health Administration electronic health record data (n=669). Multivariable logistic regression models tested for associations of GWI with self-reported ASCVD, diabetes, hyperlipidemia, and hypertension, controlling for confounding factors. Separate models tested for GWI associations with ASCVD and risk factors documented in the electronic health record.

GWI was associated with self-reported hypertension (adjusted odds ratio [aOR], 1.67 [95% CI, 1.18–2.36]), hyperlipidemia (aOR, 1.46 [95% CI, 1.03–2.05]), and ASCVD (aOR, 2.65 [95% CI, 1.56–4.51]). In the subset of veterans with electronic health record data, GWI was associated with documented diabetes (aOR, 2.34 [95% CI, 1.43–3.82]) and hypertension (aOR, 2.84 [95% CI, 1.92–4.20]). Hyperlipidemia and hypertension served as partial mediators of the association between GWI and self-reported ASCVD.

CONCLUSIONS: Gulf War veterans with GWI had higher odds of hyperlipidemia, hypertension, diabetes, and ASCVD compared with Gulf War veterans without GWI. Further examination of the mechanisms underlying this association, including a possible shared exposure-related mechanism, is necessary.

Key Words: atherosclerotic cardiovascular disease ■ diabetes ■ Gulf War illness ■ Gulf War veterans ■ hyperlipidemia ■ hypertension ■ veteran

Correspondence to: Drew A. Helmer, MD, MS, Health Services Research and Development (152), Michael E. DeBakey Veterans Affairs Medical Center, 2002 Holcombe Blvd, Houston, TX 77030. Email: drew.helmer@bcm.edu

This article was sent to Tazeen H. Jafar, MD, MPH, Associate Editor, for review by expert referees, editorial decision, and final disposition.

Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.123.029575

For Sources of Funding and Disclosures, see page 8.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- Gulf War veterans diagnosed with Gulf War Illness may be at elevated risk for developing atherosclerotic cardiovascular disease and clinical risk factors of hypertension, diabetes, and hyperlipidemia.

What Are the Clinical Implications?

- In Gulf War veterans, awareness of elevated risk of atherosclerotic cardiovascular disease should inform clinical risk stratification and evaluation.
- Clinicians and Gulf War veterans should collaborate to optimize established modifiable risk factors for atherosclerotic cardiovascular disease given the increased risk in this cohort.

Nonstandard Abbreviations and Acronyms

CDC	Centers for Disease Control and Prevention
GWECB	Gulf War Era Cohort and Biorepository
GWI	Gulf War illness
GWV	Gulf War veteran
VHA	Veterans Health Administration

More than 3 decades after the end of the 1990 to 1991 Gulf War, the complex medical challenges faced by Gulf War veterans (GWVs) persist.[1,2] Population studies indicate that about one-third of the nearly 700 000 US military personal who served during the Gulf War may be affected by the chronic multisymptom illness commonly referred to as Gulf War illness (GWI).[2] There is no clinical case definition to diagnose GWI in health care settings, but research case criteria for GWI recommended by a 2014 report of the Institute of Medicine are based on veterans' symptoms, including persistent fatigue, neurocognition/mood difficulties, pain, and gastrointestinal, skin, and respiratory symptoms.[3] GWVs encountered diverse hazards and chemical exposures while in theater, and several neurotoxicants have been identified as prominent risk factors for GWI.[1,4,5]

With the increasing burden of aging-related chronic diseases in this cohort, most of whom are now in their 50s and older, the diagnosis of GWI has become more difficult.[1] Many chronic symptoms that were previously unexplained could now be attributed to chronic diseases of aging. This is especially true for diseases such as atherosclerotic cardiovascular disease (ASCVD), including stroke, myocardial infarction, and peripheral arterial disease, as well as other clinical risk factors of ASCVD (ie, hypertension, hyperlipidemia, and diabetes), which become more common with age and may produce symptoms that can be confused with GWI.[6,7]

Some of the deployment-related toxicants encountered by GWVs have also been associated with ASCVD and the clinical risk factors in other populations and in limited studies among GWVs.[8–10] Many of the military exposures experienced in the Gulf War, such as pyridostigmine bromide pills and pesticides, are organophosphates and carbamates known to inhibit acetylcholinesterase and have been associated with cardiac arrythmias and high blood pressure.[4,5] Many GWVs were also exposed to smoke from oil well fires, inhaling pollutants, including lead, arsenic, cadmium, volatile organic compounds, and particulate matter. These compounds can affect lipid regulation, affect blood pressure control, and promote atherogenesis.[11,12] Therefore, it is possible that GWVs with GWI may have higher rates of ASCVD and associated clinical risk factors of diabetes, hyperlipidemia, and hypertension because of the pathophysiological effects of military exposures above and beyond their baseline risk based on age and sex. Indeed, limited studies have shown higher prevalence of these conditions among GWVs.[13,14]

The purpose of our study was to investigate associations between GWI and ASCVD, diabetes, hypertension, and hyperlipidemia using both self-reported and electronic health record (EHR) data.

METHODS

The Veterans Affairs Cooperative Studies Program 585, Gulf War Era Cohort and Biorepository (GWECB) (n=1343), is a national sample of Gulf War era veterans; 942 GWVs were deployed to the Persian Gulf War from August 1990 to July 1991, 380 were in the military during that period but were not deployed to the Gulf War, and 21 had missing information on their deployment status. Details about the cohort are provided elsewhere.[15,16] The study data cannot be made available to other researchers because of the nature of the data and Veterans Affairs privacy rules.

We used the deployed subcohort of 942 GWVs for the purpose of our analysis. Study participants completed a mailed survey between 2014 and 2016 that provided detailed information on self-reported symptoms and health conditions diagnosed by a health care provider of relevance to this analysis.

We further identified a subset of 669 GWVs from the GWECB cohort who also had EHR data in the Veterans Health Administration (VHA) system to conduct parallel analyses using clinician-documented cardiovascular and clinical risk factor outcomes from VHA records.

GWI Status

For our analysis, we used the Centers for Disease Control and Prevention (CDC) case definition for severe chronic multisymptom illness, also known as GWI. The Institute of Medicine recommends the use of 2 case definitions: (1) CDC and (2) Kansas case definition.[17,18] The Kansas GWI case criteria exclude veterans with other diagnoses, including heart disease, that potentially explain their symptoms. Therefore, we did not use the Kansas definition in our analysis. In contrast, the CDC GWI definition does not have exclusion criteria and further classifies cases as mild, moderate, or severe. According to the CDC GWI criteria, GWI cases are required to have ≥1 symptom (present for ≥6 months) from 2 or more of 3 symptom domains, including the following: (1) fatigue; (2) symptoms related to mood/cognition (feeling depressed, difficulty concentrating or remembering things, trouble finding words, difficulty sleeping, feeling moody, and feeling anxious); and (3) musculoskeletal (joint pain, joint stiffness, and muscle pain) symptoms. Symptoms are characterized on the basis of their severity, with a case defined as severe GWI if at least 1 symptom in each case-defining domain is rated as severe. Applying the CDC severe definition results in a smaller proportion of GWVs meeting the criteria for GWI. These individuals demonstrate greater health care–seeking behavior, and the CDC severe criteria are more strongly associated with Gulf War service than CDC mild-moderate GWI.[15] For the purpose of our analysis, GWVs who do not report the CDC symptoms at the higher severity are classified as not having GWI. Further, we could not ascertain the case status of 24 GWVs due to missing symptom item responses, and they were excluded from analysis.

The GWECB survey included symptom items and responses that map directly on to the CDC criteria. Details about the application of the CDC severe case definition using self-reported symptoms from this survey are explained elsewhere.[19]

Self-Reported ASCVD and Risk Factor Variables

The GWECB questionnaire asked respondents to report medical conditions as follows: "Please tell us if a doctor or other health care provider has ever told you that you have any of the following conditions. Mark No or Yes for each. If yes, write the year you were told, and whether you currently take any medication(s) ("Currently Taking Meds") for that condition." For the current study, ASCVD was defined as a composite outcome, indicating the self-reported presence of ≥1 of the following: heart attack, coronary artery/coronary heart disease (includes angina), stroke, transient ischemic attack, or peripheral vascular disease. Because the GWECB survey questionnaire did not independently capture a question on peripheral arterial disease, we included peripheral vascular disease as a proxy in the composite self-report ASCVD variable. Analysis of clinical risk factors for ASCVD used responses to GWECB survey questions on hypertension, diabetes, and high cholesterol.

Identification of ASCVD and Clinical Risk Factors From EHRs

We were able to link 669 (71%) GWV respondents with VHA EHR data indicating Veterans Affairs health care use anytime between 1999 and the end of survey completion in 2016. We used the *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*), and *International Classification of Diseases, Tenth Revision, Clinical Modification* (*ICD-10-CM*), diagnostic codes and Current Procedural Terminology codes, defined in the Veteran Affairs Phenomics Library–Centralized Interactive Phenomics Resource phenotype database, to operationalize identification of diabetes, hypertension, and hyperlipidemia in the EHR.[20] A physician (D.A.H.) reviewed the *ICD-9-CM* and *ICD-10-CM* codes to ensure appropriate capture of all these conditions[20–23] (Table S1). Unlike the self-reported ASCVD, we were able to identify veterans with peripheral arterial disease based on diagnostic and procedural codes from the EHR. Using an algorithm of at least 2 outpatient codes on separate days or 1 inpatient code in the EHR, we identified the patients with clinician-documented diabetes, hypertension, hyperlipidemia, and ASCVD.[24]

Other Variables of Interest

We also used the survey responses to assess other established ASCVD risk factors and additional demographic and military variables in relation to GWI and cardiovascular outcomes. These included the following: age at time of survey (years), sex (male or female), race and ethnicity (White, not Hispanic; Black, not Hispanic; Hispanic [any race]; Other [American Indian or Alaska Native, Chinese, Japanese, Asian Indian, Other Asian, Filipino, Pacific Islander, Other who were not Hispanic]; and unknown), military branch of service (Army, Navy, Air Force, Marine Corps, or other), lifetime history of smoking at least 100 cigarettes, cigars, or pipes (yes/no), and self-reported history of diagnosed posttraumatic stress disorder (PTSD). PTSD has previously been associated with development of ASCVD, hypertension, hyperlipidemia, and diabetes in veteran populations.[25–27]

Statistical Analysis

We described the demographic, military, ASCVD, and risk factor characteristics (self-reported and from the EHR) of the cohort and used χ^2 tests to assess differences between veterans with and without GWI. We also assessed bivariate associations of demographic, military, and health characteristics with both self-reported and EHR-based ASCVD (Table S2).

We used change in estimate criterion for selecting adjustment variables and found, besides age and sex, race and ethnicity, and PTSD met the threshold of >10% change. We then conducted multivariable logistic regression to evaluate the independent association of GWI with both self-reported and EHR-based ASCVD, hyperlipidemia, hypertension, and diabetes in separate models, controlling for age, sex, race and ethnicity, and PTSD.

Because hypertension, hyperlipidemia, and diabetes could serve as mediators in the relationship between GWI and ASCVD, we conducted mediation analysis to better understand these associations. In a series of models adjusting for confounders, we first conducted preliminary assessments by regressing the following: (1) the main outcome (ASCVD) on the primary predictor variable (severe GWI), (2) the potential mediators (each of the 3 clinical risk factors) on the exposure, and (3) the main outcome on the exposure and the mediators. We then conducted causal mediation analysis for only the clinical risk factors indicating significant associations in the first 2 of the above steps to estimate the percentage of total effect mediated by a clinical risk factor.[28] $P<0.05$ was considered statistically significant for all comparisons.

All analyses were performed using SAS, version 9.4 (SAS Institute, Inc, Cary, NC) and Stata, version 17 (StataCorp, College Station, TX). This research project was approved by the Institutional Review Board and Research and Development Committee of Michael E. DeBakey VA Medical Center (Houston, TX), with a waiver of informed consent.

RESULTS

We found the following characteristics among the 942 GWVs who completed the GWECB survey and the 669 GWVs with EHR data.

Gulf War Illness

In the GWV cohort (n=942), 245 (26%) veterans met the CDC criteria for severe GWI (Table 1). Veterans with GWI differed in multiple ways from veterans without GWI. They were significantly younger and included higher proportions of female and Black (not Hispanic), Hispanic (any race), other and unknown race veterans as well as Army veterans versus other branches. They also self-reported PTSD more frequently (56%) than veterans without GWI (18%; $P<0.01$).

Among GWVs with GWI, 137 (56%) self-reported hypertension, 142 (58%) self-reported hyperlipidemia, 50 (20%) self-reported diabetes, and 37 (15%) self-reported ASCVD. The demographic details, military characteristics, and prevalence of self-reported and EHR-based medical conditions are reported in Table 1.

Most GWVs in the cohort had EHR data available in the VHA system. This included nearly all (n=214 [87%]) GWVs with GWI and about two-thirds (n=436 [65%]) of veterans who did not have GWI. Of those with GWI, 116 (54%) had documented hypertension, 106 (49%) had documented hyperlipidemia, 53 (25%) had documented diabetes, and 17 (8%) had documented ASCVD.

Self-Reported ASCVD and Clinical Risk Factor Analysis

In multivariable models of self-reported outcomes (Table 2), severe GWI was statistically significantly associated with hypertension (odds ratio [OR], 1.67 [95% CI, 1.18–2.36]), hyperlipidemia (OR, 1.46 [95% CI, 1.03–2.05]), and ASCVD (OR, 2.65 [95% CI, 1.56–4.51]).

Established risk factors demonstrated expected associations with ASCVD in our sample. For example, older age (OR, 1.11 [95% CI, 1.08–1.14]) was associated with ASCVD. In addition, women had lower odds of developing ASCVD compared with men, although the association was not statistically significant.

EHR-Based ASCVD and Clinical Risk Factor Analysis

In models using the EHR-based outcome variables (Table 3), GWVs with GWI had higher odds of documented hypertension (OR, 2.84 [95% CI, 1.92–4.20]) and diabetes (OR, 2.34 [95% CI, 1.43–3.82]). Although elevated, the associations of GWI with hyperlipidemia (OR, 1.28 [95% CI, 0.87–1.87]) and documented ASCVD were not statistically significant (OR, 1.86 [95% CI, 0.89–3.92]) in this subset.

Mediation Analysis

We conducted mediation analysis for self-reported variables only because self-reported ASCVD was statistically significantly associated with GWI, but a similar association was not found with EHR-derived ASCVD and GWI. We found hyperlipidemia (OR, 1.46 [95% CI, 1.03–2.05]) and hypertension (OR, 1.67 [95% CI, 1.18–2.36]) to be statistically significantly associated with GWI (main exposure). Both hyperlipidemia (OR, 4.70 [95% CI, 2.63–8.41]) and hypertension (OR, 2.63 [95% CI, 1.61–4.30]) were statistically significantly associated with the outcome of ASCVD. We further checked if the clinical risk factors were mediators by adjusting for them in the model with ASCVD and GWI and found the association was statistically significant, but the estimates were of slightly smaller magnitude (OR, 2.33 [95% CI, 1.35–4.02]) than in the model without the mediator (OR, 2.65 [95% CI, 1.56–4.51]). Causal mediation analysis demonstrated a 12% (95% CI, 7%–26%) total effect of GWI on ASCVD was mediated by hyperlipidemia and a 10% (95% CI, 6%–23%) effect was

Table 1. Descriptive Analysis of Demographics, Military Characteristics, and Medical Conditions by GWI Case Status

Deployed GWVs	Overall (n=942)	GWI– (n=673)	GWI+ (n=245)	*P* value
Age, y				
40–49	381 (40.45)	256 (38.04)	115 (46.94)	<0.05
50–59	340 (36.09)	249 (37.0)	83 (33.88)	
≥60	221 (23.46)	168 (24.96)	47 (19.18)	
Sex				
Men	727 (78.26)	532 (80.12)	179 (73.97)	<0.05
Women	202 (21.74)	132 (19.88)	63 (26.03)	
Race and ethnicity				
White, not Hispanic	600 (63.69)	472 (70.13)	113 (46.12)	<0.01
Black, not Hispanic	166 (17.62)	108 (16.05)	53 (21.63)	
Hispanic (any race)	85 (9.02)	45 (6.69)	39 (15.92)	
Other	55 (5.84)	27 (4.01)	26 (10.61)	
Unknown	36 (3.82)	21 (3.12)	14 (5.71)	
Education				
High school GED or less	95 (10.08)	68 (10.10)	23 (9.39)	<0.01
Bachelor's degree	622 (66.03)	429 (63.74)	180 (73.47)	
Advanced degree	193 (20.49)	157 (23.33)	30 (12.24)	
Unknown	32 (3.40)	19 (2.82)	12 (4.90)	
Branch of service				
Army only	425 (45.12)	281 (41.75)	131 (53.47)	<0.05
Navy only	155 (16.45)	119 (17.68)	33 (13.47)	
Air Force only	95 (10.08)	75 (11.14)	16 (6.53)	
Marine Corps only	126 (13.38)	94 (13.97)	29 (11.84)	
Other or multiple	141 (14.97)	104 (15.45)	36 (14.69)	
Military component				
Active duty only	547 (58.50)	373 (55.92)	157 (64.34)	<0.01
Both active/reserve	238 (25.45)	167 (25.04)	67 (27.46)	
Reserve only	150 (16.04)	127 (19.04)	20 (8.20)	
Lifetime smoking history				
Smoke >100 cigarettes, cigars, or pipes	478 (52.07)	331 (50.30)	134 (56.07)	0.13
Self-reported conditions				
PTSD	259 (28.18)	121 (18.31)	132 (55.70)	<0.01
Hypertension	450 (47.92)	301 (44.79)	137 (55.92)	<0.01
Diabetes	158 (16.97)	103 (15.51)	50 (20.49)	0.08
Hyperlipidemia	489 (52.36)	339 (50.60)	142 (58.44)	<0.05
ASCVD	103 (10.97)	61 (9.06)	37 (15.16)	<0.01
EHR outcomes	Overall (n=669)	GWI– (n=436)	GWI+ (n=214)	
Hypertension	253 (37.82)	129 (29.59)	116 (54.21)	<0.01
Diabetes	110 (16.44)	53 (12.16)	53 (24.77)	<0.01
Hyperlipidemia	280 (41.85)	164 (37.61)	106 (49.53)	<0.01
ASCVD	45 (6.73)	24 (5.50)	17 (7.94)	0.23

Data are given as number (percentage) of each group excluding missing responses. All medical conditions were physician diagnosed and self-reported. Advanced degree indicates master's degree/professional or doctorate; and bachelor's degree includes associate's degree/some college. ASCVD indicates atherosclerotic cardiovascular disease; EHR, electronic health record; GED, general equivalency diploma; GWI, Gulf War illness; GWV, Gulf War veteran; and PTSD, posttraumatic stress disorder.

mediated by hypertension. Thus, we cannot discount the partial mediation of hyperlipidemia and hypertension in the association between GWI and self-reported ASCVD.

DISCUSSION

Among the GWECB cohort of deployed GWVs who completed surveys between 2014 and 2016, we found

Table 2. Multivariable Logistic Regression Models of GWI and Veteran-Reported Clinical Risk Factors and ASCVD

Variable	Hypertension	Diabetes	Hyperlipidemia	ASCVD
GWI	1.67 (1.18–2.36)	1.39 (0.89–2.17)	1.46 (1.03–2.05)	2.65 (1.56–4.51)
Age	1.05 (1.04–1.07)	1.07 (1.05–1.09)	1.06 (1.04–1.08)	1.11 (1.08–1.14)
Sex				
Men	Reference	Reference	Reference	Reference
Women	0.50 (0.35–0.71)	0.41 (0.24–0.71)	0.64 (0.46–0.89)	0.70 (0.35–1.17)
Race and ethnicity				
White, not Hispanic	Reference	Reference	Reference	Reference
Black, not Hispanic	1.82 (1.25–2.67)	1.83 (1.14–2.95)	0.88 (0.61–1.29)	1.01 (0.55–1.86)
Hispanic	1.56 (0.96–2.55)	1.39 (0.75–2.59)	1.31 (0.81–2.14)	0.65 (0.28–1.54)
Other	1.04 (0.56–1.91)	1.11 (0.51–2.43)	1.22 (0.66–2.27)	0.52 (0.18–1.47)
Unknown	3.03 (1.07–8.55)	1.65 (0.64–4.26)	1.29 (0.50–3.28)	1.23 (0.43–3.49)
PTSD	1.14 (0.81–1.59)	1.68 (1.10–2.56)	1.33 (0.95–1.85)	1.39 (0.83–2.34)

Data are given as adjusted odds ratio (95% CI). The adjusted odds ratio is the prevalence odds ratio, adjusted for age at survey, sex, race and ethnicity, and PTSD. For ASCVD, the logistic regression model includes covariates described above. ASCVD indicates atherosclerotic cardiovascular disease; GWI, Gulf War illness; and PTSD, posttraumatic stress disorder.

GWI defined using CDC severe GWI criteria was significantly associated with moderately increased risk of self-reported hypertension, hyperlipidemia, and ASCVD. Among the subset with EHR data, we found statistically significant associations between GWI and documented hypertension and diabetes, but the associations with hyperlipidemia and ASCVD were not statistically significant. The strength of these associations adds to the growing evidence that veterans with GWI may be at increased risk for adverse cardiovascular outcomes and reinforces the importance of further clarifying the treatment needs of GWVs (Figure).

Our findings were largely consistent with the limited literature on ASCVD and its risk factors in GWVs. Previous studies have investigated the prevalence of coronary heart disease, hypertension, and hyperlipidemia, along with multiple other chronic medical conditions, in deployed GWVs compared with nondeployed Gulf War era veterans and the general population. The results vary, with some analyses indicating an increase in cardiovascular risk factors alone and others showing an increase in ASCVD, as well.[8,13,14] In the GWECB cohort, we found the prevalence of self-reported ASCVD (11%) among deployed GWVs in 2014 to 2016 was similar to the frequency of heart attack among the men in the Fort Devens Cohort (9.2%) but higher than the frequency of coronary heart disease (5.6%) in the 2012 Follow-up Study of a National Cohort of Gulf War and Gulf Era Veterans of deployed GWVs.[8,13] Possible explanations for differences in the observed rates include differences in the samples and respondents, methodological design of the study, survey questions, and year of survey completion.

Table 3. Multivariable Logistic Regression Models of GWI and EHR-Based Outcomes

Variable	Hypertension	Diabetes	Hyperlipidemia	ASCVD
GWI	2.84 (1.92–4.20)	2.34 (1.43–3.82)	1.28 (0.87–1.87)	1.86 (0.89–3.92)
Age	1.04 (1.01–1.06)	1.06 (1.03–1.09)	1.02 (1.00–1.05)	1.06 (1.02–1.10)
Sex				
Men	Reference	Reference	Reference	Reference
Women	0.73 (0.48–1.12)	0.71 (0.40–1.26)	0.56 (0.37–0.84)	0.47 (0.18–1.25)
Race and ethnicity				
White, not Hispanic	Reference	Reference	Reference	Reference
Black, not Hispanic	2.57 (1.67–3.96)	1.52 (0.86–2.70)	1.27 (0.83–1.94)	1.01 (0.43–2.37)
Hispanic	1.57 (0.89–2.78)	2.68 (1.40–5.14)	2.25 (1.28–3.95)	0.79 (0.25–2.48)
Other	1.02 (0.49–2.10)	2.18 (0.97–4.88)	1.07 (0.54–2.14)	0.29 (0.04–2.31)
Unknown	3.73 (1.35–10.31)	1.46 (0.48–4.40)	2.86 (1.04–7.86)	3.19 (1.00–10.21)
PTSD	1.39 (0.95–2.04)	1.41 (0.87–2.29)	2.06 (1.42–2.99)	1.38 (0.67–2.85)

Data are given as adjusted odds ratio (95% CI). Data were adjusted for age at survey, sex, race and ethnicity, and PTSD. ASCVD indicates atherosclerotic cardiovascular disease; EHR, electronic health record; GWI, Gulf War illness; and PTSD, posttraumatic stress disorder.

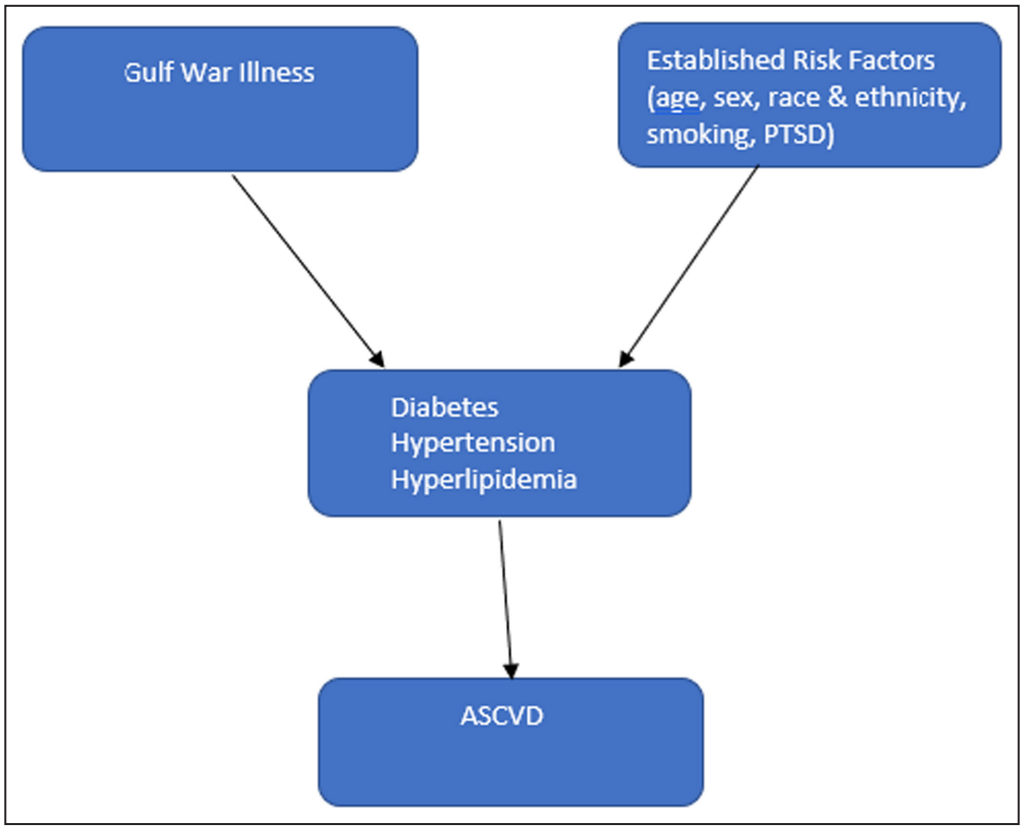

Figure. Role of Gulf War illness in atherosclerotic cardiovascular disease (ASCVD) among US service members deployed to Persian Gulf War. PTSD indicates posttraumatic stress disorder.

Our findings were also consistent with growing evidence of metabolic dysfunction and autonomic alterations possibly related to toxic exposures encountered during the Persian Gulf War in 1990 to 1991. Indeed, animal studies have demonstrated long-term adverse effects of repeated low-level exposure to Gulf War toxicants, including dysregulation of lipid metabolism, resulting in metabolic disturbance, oxidative stress, and inflammation.[29,30] There has also been evidence showing an association between Gulf War exposures with cardiovascular structural changes and autonomic dysfunction in animal models.[31,32] Deployed GWVs with chronic multisymptom illness have had a higher prevalence of metabolic syndrome and abnormal heart rate variability.[33] Studies indicate that both these effects may be attributable to the distinctive exposures incurred during the Gulf War and suggest that these exposures can be precursors for development of ASCVD and its associated clinical risk factors.[8,33,34] Interestingly, our mediation analysis indicated a small contribution of hyperlipidemia and hypertension as potential partial mediators in the pathway between GWI and self-reported ASCVD. The high prevalence of both conditions in this cohort supports the possibility that toxic exposures associated with GWI may also increase the risk for hyperlipidemia and hypertension through similar pathophysiological mechanisms.

Although largely consistent in the direction of the associations, we note differences in magnitude and statistical significance of the associations within the overall cohort using self-reported information and the subset with EHR data. We found both EHR-documented diabetes and hypertension to be significantly associated with GWI, whereas EHR-documented ASCVD was not. The EHR-based outcomes were evaluated in only the subset of veterans who were VHA users; and although 87% of the sample who met the GWI criteria had VHA records, only two-thirds of those without GWI had VHA records. In particular, the number of veterans with GWI and identified ASCVD was reduced by half in the EHR-based sample compared with the self-report–based sample. A larger sample of GWVs with complete ascertainment of clinician-documented diagnoses is required to more definitively determine the magnitude and significance of the association between GWI and ASCVD.

Our findings are important in alerting clinicians to the prevalence of ASCVD and clinical risk factors among GWVs. Some of the symptoms may overlap between these conditions; therefore, it is important to accurately

elucidate and diagnose the pathophysiological conditions underlying the patient concerns. Clinicians may also want to consider exploring exposure histories of GWVs and others. Although some exposures of concern to GWVs are relatively unique to this cohort (eg, low-dose sarin/cyclosarin), other exposures may be experienced by nonmilitary personnel, especially within certain occupational or geographically determined groups (eg, particulate matter and smoke from burning petrochemicals). Broader exploration of the links between toxic exposures and ASCVD is warranted.

Our study had several important strengths. We used a recommended definition of GWI derived from self-reported symptoms, the current best practice. We also used both self-reported and *ICD-9-CM*– and *ICD-10-CM*–based outcomes and demonstrated generally consistent results. We further conducted mediation analysis to test if any clinical risk factors were mediators in the pathway between GWI and ASCVD.

However, our study had limitations. There was a low response rate (12.5%) for the GWECB survey. Therefore, there may be a potential for response bias and selection bias as veterans who completed the survey may be more engaged and sicker compared with other GWVs. As a result, this sample may not be representative of the larger population of deployed GWVs. Also, although most veterans who completed the GWECB survey were VHA users (71%), veterans still may have sought care outside the VHA. Because we lacked access to non-VHA medical records, our results likely underdetect ASCVD and clinical risk factors in the analysis of EHR data. Although clinicians may provide a more expert assessment of disease presence, many veterans receive care outside the VHA, and VHA clinicians may not always record diagnoses codes for conditions evaluated by other providers. This would produce lower rates of diagnosis in our sample and result in misclassification of those with ASCVD and clinical risk factors into the nondiseased categories, biasing our results toward the null. Also, although EHR-based results show moderately elevated point estimates of magnitude, the lack of statistical significance for hyperlipidemia and ASCVD may well be attributable to the relatively small sample size.

CONCLUSIONS

GWVs with GWI experienced high rates of hyperlipidemia, hypertension, and diabetes and were twice as likely to self-report ASCVD compared with GWVs without GWI. Hyperlipidemia and hypertension appeared to partially mediate the association between self-reported ASCVD and GWI. Further research with a larger sample size is necessary to better understand the association between GWI and ASCVD and its clinical risk factors.

Perspectives

Competency in patient care and procedural skills: in GWVs, awareness of elevated risk of ASCVD should inform clinical risk stratification and evaluation. Translational outlook: clinicians and GWVs should collaborate to optimize established modifiable risk factors for ASCVD given the increased risk in this cohort.

ARTICLE INFORMATION

Received January 20, 2023; accepted July 20, 2023.

Affiliations

Center for Innovations in Quality, Effectiveness and Safety, Michael E. DeBakey VA Medical Center, Houston, TX (S.T.A., P.R., S.G., D.L.W., A.N.D., S.S.V., D.A.H.); Section of Health Services Research, Department of Medicine, Baylor College of Medicine, Houston, TX (S.T.A., P.R., S.G., D.L.W., A.N.D., D.A.H.); Department of Biostatistics and Data Sciences, School of Public Health, The University of Texas Health Science Center at Houston, Houston, TX (R.L.); Yudofsky Division of Neuropsychiatry, Department of Psychiatry and Behavioral Sciences, Baylor College of Medicine, Houston, TX (L.S.); Cooperative Studies Program Epidemiology Center–Durham, Durham VA Medical Center, Durham VA Health Care System, Durham, NC (K.S., E.G., E.R.H.); Duke Molecular Physiology Institute and Department of Biostatistics and Bioinformatics, Duke University Medical Center, Durham, NC (E.R.H.); Section of Cardiology and Cardiovascular Research, Department of Medicine, Baylor College of Medicine, Houston, TX (S.S.V.); Section of Cardiology, Department of Medicine, Michael E. DeBakey VA Medical Center, Houston, TX (S.S.V.); Department of Management, Policy and Community Health (R.M.), and Southwest Center for Occupational and Environmental Health, Department of Epidemiology, Human Genetics and Environmental Sciences (G.D.), School of Public Health, The University of Texas Health Science Center at Houston, Houston, TX.

Acknowledgments

The authors wish to thank the Gulf War veterans who participated in the Cooperative Studies Program (CSP) 585 Gulf War Era Cohort and Biorepository study.

Sources of Funding

This work was supported by Veterans Health Administration Health Outcomes Military Exposures service (formerly Post-Deployment Health Services) and the Center for Innovations in Quality, Effectiveness and Safety (VA Health Services Research & Development CIN 13-413) at the Michael E. DeBakey VA Medical Center (Houston, TX).

The opinions expressed reflect those of the authors and not necessarily those of the Department of Veterans Affairs or the US government.

Disclosures

Dr Virani reports the following disclosures: grant support from Department of Veteran Affairs, National Institutes of Health (NIH), and Tahir and Jooma Family. Honorarium: American College of Cardiology (Associate Editor, *Innovations*, acc.org); relationship ended June 30, 2021. Dr Morgan reports funding support from NIH (National Institute on Aging), US Department of Veteran Affairs, and the Episcopal Health Foundation. Dr White reports salary support from US Department of Veteran Affairs, Cooperative Studies Program 2006, NIH (National Cancer Institute and National Institute of Diabetes and Digestive and Kidney Diseases), and Cancer Prevention and Research Institute of Texas. The remaining authors have nothing to disclose.

Supplemental Material

Tables S1–S2

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