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# Insomnia Severity, Subjective Sleep Quality, and Risk for Obstructive Sleep Apnea in Veterans With Gulf War Illness

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## Abstract

Despite the fact that sleep disturbances are common in veterans with Gulf War Illness (GWI), there has been a paucity of published sleep studies in this veteran population to date. Therefore, the present study examined subjective sleep quality (assessed with the Pittsburgh Sleep Quality Index), insomnia severity (assessed with the Insomnia Severity Index), and risk for obstructive sleep apnea (assessed with the STOP questionnaire) in 98 Gulf War veterans. Veterans with GWI, defined either by the Kansas or Centers for Disease Control and Prevention criteria, had greater risk for obstructive sleep apnea (i.e., higher STOP scores) than veterans without GWI. This difference persisted even after accounting for potentially confounding demographic (e.g., age, gender) and clinical variables. Veterans with GWI, defined by either the Kansas or Centers for Disease Control and Prevention criteria, also had significantly greater insomnia severity and poorer sleep quality than veterans without GWI ($p < 0.05$), even after accounting for potentially confounding variables. Furthermore, there were significant, positive correlations between insomnia severity, subjective sleep quality, and GWI symptom severity ($p \leq 0.01$). In stepwise linear regression models, insomnia severity significantly predicted GWI status over and above demographic and clinical variables. Together these findings provide good rationale for treating sleep disturbances in the management of GWI.

## INTRODUCTION

Gulf War illness (GWI) is a multisymptom condition resulting from service in the 1990–1991 Gulf War (GW). Characterized by multiple concurrent symptoms such as persistent headaches, cognitive difficulties, widespread pain, fatigue, gastrointestinal problems, and other chronic abnormalities, GWI is estimated to affect at least one-fourth of the 697,000

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U.S. GW veterans.[1] Although the symptoms of GWI have not been accounted for by medical or psychiatric conditions routinely diagnosed in clinical practice,[2] civilians with fibromyalgia and chronic fatigue syndrome experience the same variety of symptoms as veterans with GWI.[3] For example, sleep complaints (e.g., unrefreshing or nonrestorative sleep) are common among GW veterans, patients with chronic fatigue syndrome,[4] and more than 90% of fibromyalgia patients.[5]

The few published studies that have investigated sleep in GW veterans have yielded mixed results concerning the prevalence of obstructive sleep apnea (OSA) in this veteran population. Peacock et al[6] reported sleep apnea-hypopnea syndrome in 8% of the participants of a Comprehensive Clinical Evaluation Program for GW veterans at Brooke Army Medical Center in Texas. Although 8% is slightly higher than the estimated prevalence of OSA in the general adult male population (3–7%),[7] another study failed to find evidence of increased sleep apnea in 22 ill GW veterans compared to 19 matched control GW veterans.[8] A more recent study reported a higher incidence of sleep apneas, hypopneas, and mild inspiratory airflow limitation in 18 male veterans with GWI compared to 18 obesity-matched asymptomatic male GW veterans.[4] In light of the ambiguity concerning the prevalence of OSA among GW veterans, one aim of the current study was to examine the risk for OSA in GW veterans using the STOP questionnaire,[9] a validated screening tool that consists of 4 yes/no self-report questions about snoring, tiredness during daytime, observed apnea, and high blood pressure. Because no published sleep study of GW veterans to date has examined sleep quality, a second aim of the study was to investigate subjective sleep quality and insomnia severity in GW veterans. Finally, we examined the relationship between subjective sleep quality, insomnia severity, and GWI symptoms because there is clinical evidence that sleep quality influences pain, fatigue, mood state, cognitive performance, and daily functioning.[10,11]

## METHODS

### Participants

The study examined data from 98 consecutive GW veterans recruited from 2014 to 2015 at the San Francisco Veterans Affairs Medical Center as part an ongoing study on the longitudinal effects of predicted sarin exposure on brain structure and brain function. This study was approved by the University of California at San Francisco and the Veterans Administrations Committees on Human Research and all study participants signed informed consents.

### Clinical Assessments

All subjects were evaluated by a PhD-level psychologist using the Structured Clinical Interview for the *Diagnostic and Statistical Manual of Mental Disorders-IV* Diagnosis,[12] the Clinician Administered Post-Traumatic Stress Disorder (PTSD) Scale (CAPS),[13] and an interview version of the Life Stressor Checklist-Revised.[14] The Life Stressor Checklist-Revised assesses 21 stressful life events (e.g., experiencing or witnessing serious accidents, illnesses, sudden death, and physical and sexual assault) to determine exposure to traumatic events. The CAPS was used to diagnose current PTSD. The Structured Clinical Interview for

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the *Diagnostic and Statistical Manual of Mental Disorders-IV* Diagnosis was used to diagnose current major depressive disorder (MDD) and to rule out individuals with a lifetime history of psychotic or bipolar disorders and alcohol or drug abuse or dependence within the previous 12 months. Other exclusion criteria were neurological illness, head trauma with loss of consciousness greater than 10 minutes, medical disorders affecting brain function, and conditions contradictory for magnetic resonance imaging. Information about the veterans' predicted exposure to low-levels of nerve agents were obtained from the Directorate for Deployment Health Support of the Special Assistant to the Under Secretary of Defense (Personnel and Readiness) for Gulf War Illness Medical Readiness and Military Deployments.[15]

## Outcome Measures

The Pittsburgh Sleep Quality Index (PSQI)[16] was used to obtain a self-reported measure of sleep quality and disturbances during the previous month. Higher PSQI global scores (range = 0–21; 10 items: 6-item Likert scale, 4 open-ended items) indicate worse sleep quality. In the current sample, PSQI scores ranged from 0 to 20 and Cronbach's α was 0.80.

The Insomnia Severity Index (ISI)[17] was used to obtain a self-reported measure of insomnia severity. The ISI consists of 7 items with responses ranging from 0 to 4, producing total scores of 0 to 28. Total ISI scores can be categorized into the following: no clinically significant insomnia (0–7), subthreshold insomnia mild (8–14), moderate clinical insomnia (15–21), and severe clinical insomnia (22–28). In the current cohort, ISI ranged from 0 to 28, and Cronbach's α was 0.92.

The STOP questionnaire[9] was used to assess risk for OSA. Although normally a self-report, forced-choice (yes/no) questionnaire, we used the participants' responses to questions about snoring and observed apneas from the PSQI, daytime tiredness from the Kansas Gulf War Military History and Health Questionnaire,[18] and high blood pressure from a personal health questionnaire to determine their STOP scores. In the current study, STOP scores ranged from 0 to 4 and Cronbach's α was 0.58.

The Beck Depression Inventory (BDI)[19] was used to obtain a self-reported measure of current depressive symptomology (i.e., sadness, guilt, self-hate) during the past week. The BDI is a 21-item self-report questionnaire where participants are asked to respond to phrases that signal increasing symptom severity on a scale of 0 to 3. Scores can range from 0 to 63, with scores at or above 10 reflecting clinical significance.[20] In the current sample, BDI ranged from 0 to 36 and Cronbach's α was 0.90.

## Determination of GWI Status

The Committee on the Development of a Consensus Case Definition for Chronic Multisymptom Illness in 1990–1991 GW Veterans[21] identified the U.S. Centers for Disease Control and Prevention (CDC)[22] and the Kansas[18] criteria for GWI as the two case definitions that captured the array of symptoms most frequently reported by GW veterans as evidenced by the GWI literature. Furthermore, the committee recommended that researchers studying GW veterans use these two case definitions on the basis of their concordance with the evidence and their ability to identify specific symptoms commonly reported by GW

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veterans. Therefore, we used the Kansas Gulf War Military History and Health Questionnaire[18] to determine GWI cases according to the CDC[22] and the Kansas[18] criteria. The CDC-GWI case definition required the following: symptom for the past 6 months in at least two of the following three symptom groups: (1) fatigue, (2) mood/cognition, and (3) musculoskeletal pain. Veterans who reported fewer than 2 or no symptoms were considered *not* to have GWI according to CDC criteria. The Kansas-GWI case definition required the following: (1) symptoms for the past 6 months in at least 3 of 6 symptom groups (i.e., fatigue and sleep problems, pain, neurologic and mood, gastrointestinal, respiratory, and skin symptoms), and (2) at least one moderately severe symptom or two or more symptoms within a symptom group. Veterans were excluded as Kansas-GWI cases if they reported being diagnosed by a physician with chronic medical conditions that might account for their symptoms (e.g., diabetes, heart disease other than hypertension, stroke, lupus, multiple sclerosis, cancer other than non-melanoma skin cancers, liver disease) or had persistent health problems as a result of chronic infection or serious injury or if they reported being hospitalized since the GW for alcohol or drug dependence, depression, or PTSD. Diagnoses of schizophrenia or bipolar disorder were exclusionary for both the Kansas GWI case definition and inclusion for the present study.

## Quantification of GWI Symptom Severity

We used the symptom portion of the Kansas Gulf War Military History and Health Questionnaire,[23] which consists of 32 questions about various symptoms and abnormalities associated with GWI on the basis of the Kansas[18] and CDC[22] case definitions, to quantify GWI symptom severity. The Kansas Gulf War Military History and Health Questionnaire[23] asks subjects to indicate whether or not they have a particular symptom and if they do have a particular symptom, how severe the symptom is. Thus, the symptom portion of the Kansas Gulf War Military History and Health Questionnaire is like a 4-point Likert scale, (e.g., 0 = no symptom; 3 = symptom is severe). We derived a GWI Symptom Severity score by summing the answers to 27 symptom questions about fatigue, pain, gastrointestinal, respiratory, neurological, mood, and skin symptoms. Because we wanted to examine the relationship between GWI symptom severity and sleep quality, we excluded 2 questions from the Kansas Gulf War Military History and Health Questionnaire about sleep difficulties. This strategy yielded a GWI Symptom Severity score that ranged from 0 to 67 and a Cronbach's $\alpha$ of 0.73 in the present sample. Higher GWI Symptom Severity scores indicate more symptoms and/or symptoms of greater severity.

## Statistical Analyses

All statistical analyses were conducted using SPSS, version 23.0 (IBM Inc., Armonk, New York). Demographic and descriptive characteristics were compared across groups with and without GWI using Student *t* tests for continuous variables and Fisher's exact tests for categorical variables. Because the CDC case definition of GWI has no exclusionary conditions, all subjects were included in the analyses of CDC-GWI group effects. In contrast, subjects with conditions that were exclusionary for the Kansas GWI case definition were not included in the analyses of Kansas-GWI group effects.

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We also examined group differences on self-reported sleep and insomnia measures with analysis of covariance (ANCOVA) to account for age, sex, years of education, current PTSD and MDD status, and history of alcohol and/or substance abuse/dependence, predicted sarin exposure, body mass index (BMI), and STOP scores. Similarly, group differences on STOP scores were also examine with an ANCOVA that accounted for age, sex, years of education, current PTSD and MDD status, and history of alcohol and/or substance abuse/dependence, predicted sarin exposure, and BMI.

Spearman's correlations were used to examine the associations between ISI, PSQI, STOP scores GWI, PTSD, and depressive symptomology. Next, we constructed stepwise linear regression models for each case definition of GWI. Separate models were constructed for the CDC[22] and Kansas[18] case definition of GWI (dependent variable) with the following independent variables: age, sex, years of education, predicted sarin exposure status, diagnosis of current PTSD and/or MDD, BMI, STOP score, PSQI, and ISI. Default $p$ values for entry in the stepwise models were $p < 0.10$.

## RESULTS

### Demographic Data and Clinical Characteristics

Table I summarizes the demographics and clinical characteristics of the veterans with and without GWI according to the CDC[22] and Kansas[18] case definitions and the veterans who had conditions that were exclusionary for the Kansas-GWI case definition. As expected, veterans with GWI according to both case definitions had higher GWI symptom severity scores than veterans without GWI ($t \geq 6.49$, $p < 0.001$). Veterans with GWI also had higher BDI scores ($t \geq 3.60$, $p \leq 0.001$) than veterans without GWI. There was a higher incidence of current MDD among veterans with Kansas-GWI than veterans without GWI (Fisher's exact test, $p = 0.02$). Although significantly more veterans with GWI, defined according to both criteria, had trauma exposure compared to veterans without GWI (Fisher's exact test, $p < 0.001$), there was only one significant group difference in the incidence of current PTSD between veterans with and without Kansas-GWI (Fisher's exact test, $p = 0.01$). Other group differences included age (veterans with CDC-GWI were younger than veterans without GWI, $t = 2.41$, $p = 0.02$) and education (veterans with Kansas-GWI had fewer years of formal education than veterans without GWI, $t = 2.95$, $p = 0.004$).

### Group Differences in Risk for OSA

Student $t$ tests revealed that veterans with GWI according to both case definitions had higher STOP scores than veterans without GWI ($t = 3.75$, *degrees of freedom* [$df$] = 96, $p < 0.001$ for CDC-GWI; $t = 2.58$, $df = 71$; $p = 0.01$ for Kansas-GWI; see Table I). The difference in STOP scores between veterans with and without GWI defined according to the CDC criteria remained significant even after accounting for age, sex, education, predicted sarin exposure, current diagnoses of MDD and/or PTSD, and BMI ($F_{1,97} = 16.95$, $p < 0.001$). In the ANCOVA with the CDC-GWI case definition, predicted nerve agent exposure ($F_{1,97} = 4.73$, $p = 0.03$) and BMI ($F_{1,97} = 6.22$, $p = 0.01$) were significantly associated with STOP scores although the other covariates were not ($F_{1,97} \leq 0.86$, $p \geq 0.36$). Similarly, the difference in STOP scores between veterans with and without GWI defined according to the Kansas

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criteria remained significant ($F_{1,72} = 6.33$, $p = 0.01$) even after accounting for the potentially confounding covariates. In the ANCOVA with the Kansas-GWI case definition, predicted nerve agent exposure ($F_{1,72} = 3.97$, $p = 0.051$) was marginally associated with STOP scores although the other covariates were not ($F_{1,72} \leq 3.07$, $p \geq 0.09$).

### Group Differences in Subjective Sleep Measures

Student *t* tests revealed that veterans with GWI according to both case definitions had significantly greater insomnia severity (i.e., ISI: $t = 5.78$, $df = 96$ for CDC-GWI; $t = 6.27$, $df = 71$ for Kansas-GWI $p < 0.001$ for both, see Table I) and poorer subjective sleep quality (i.e., PSQI, $t = 4.96$, $df = 96$ for CDC-GWI; $t = 5.38$, $df = 71$, $p < 0.001$ for both, see Table I) compared to veterans without GWI. As with the STOP scores, the group differences in ISI ($F_{1,97} = 25.24$ for CDC-GWI; $F_{1,72} = 18.28$ for Kansas-GWI, $p < 0.001$ for both) and PSQI ($F_{1,97} = 18.96$, $p < 0.001$ for CDC-GWI; $F_{1,72} = 13.16$, $p = 0.001$ for Kansas-GWI) remained significant even after accounting age, sex, education, predicted sarin exposure, BMI, STOP scores, and current diagnoses of MDD and/or PTSD. Of the covariates entered into the model, only diagnoses of current MDD ($F_{1,97} = 4.28$, $p = 0.04$) and PTSD ($F_{1,97} = 16.38$, $p < 0.001$) were significantly associated with ISI scores when GWI was defined by CDC criteria. Current PTSD was significantly associated with ISI score ($F_{1,72} = 11.24$, $p = 0.001$) when GWI was defined by the Kansas criteria. Current PTSD was also significantly associated with PSQI score when GWI was defined by the CDC ($F_{1,97} = 18.31$, $p < 0.001$) and Kansas ($F_{1,72} = 11.32$, $p = 0.001$) GWI criteria. None of the other potentially confounding covariates were significantly associated with ISI ($F_{1,97} \leq 3.11$, $p \geq 0.08$ for CDC-GWI; $F_{1,72} \leq 3.36$, $p \geq 0.07$ for Kansas-GWI) or PSQI ($F_{1,97} \leq 2.86$, $p \geq 0.09$ for CDC-GWI; $F_{1,72} \leq 1.46$, $p \geq 0.23$ for Kansas-GWI).

### Relationship Between Subjective Sleep Measures, OSA risk, and GWI

Table II summarizes results of the correlational analyses. GWI symptom severity was positively and significantly correlated with PSQI (Spearman's $\rho = 0.65$, $p < 0.001$), ISI (Spearman's $\rho = 0.73$, $p < 0.001$), STOP (Spearman's $\rho = 0.26$, $p = 0.01$), CAPS (Spearman's $\rho = 0.64$, $p < 0.001$), and BDI scores (Spearman's $\rho = 0.61$, $p < 0.001$). The subjective sleep measures were also significantly correlated with CAPS (PSQI: Spearman's $\rho = 0.45$, ISI: Spearman's $\rho = 0.46$, $p < 0.001$ for both), BDI (PSQI: Spearman's $\rho = 0.61$, ISI: Spearman's $\rho = 0.65$, $p < 0.001$ for both) and STOP scores (PSQI: Spearman's $\rho = 0.29$, $p = 0.004$, ISI: Spearman's $\rho = 0.38$, $p < 0.001$).

Next, we used stepwise linear regression models to further examine the relationship between subjective sleep measures and GWI status. Separate models were created for each case definition of GWI (dependent variable) with age, sex, education, predicted sarin exposure status, current PTSD and/or MDD diagnoses, BMI, STOP score, PSQI, and ISI entered as independent variables. Results indicated that ISI (model $R^2 = 0.26$, $F_{1,96} = 33.36$, $p < 0.001$; standardized coefficient $\beta = 0.51$, $t = 5.78$, $p < 0.001$) and STOP scores (model $R^2 = 0.29$, $F_{1,95} = 4.38$, $p = 0.04$; standardized coefficient $\beta = 0.20$, $t = 2.09$, $p = 0.04$) significantly predicted CDC-GWI status although ISI significantly predicted Kansas-GWI status (model $R^2 = 0.36$, $F_{1,71} = 39.27$, $p < 0.001$; standardized coefficient $\beta = 0.60$, $t = 6.27$, $p < 0.001$).

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## DISCUSSION

The present study quantitatively examined the risk for OSA, subjective sleep quality and insomnia severity in GW veterans, and the relationship between these measures and GWI status. We found the following: (1) Veterans with GWI defined by both the CDC[22] and Kansas[18] criteria have significantly greater risk for OSA (i.e., higher STOP scores) than veterans without GWI even after accounting for potentially confounding demographic and clinical variables. (2) Veterans with GWI defined by both the CDC[22] and Kansas[18] criteria also have significantly poorer subjective sleep quality and greater insomnia severity than veterans without GWI, even after accounting for potentially confounding demographic and clinical variables. (3) Insomnia severity and subjective sleep quality were positively correlated with GWI symptom severity. (4) Insomnia severity significantly predicted GWI status, defined according to both the CDC and Kansas criteria, over and above demographic and clinical variables. We discuss the significance of these findings below.

Only a few studies have examined the prevalence of OSA among GW veterans to date and these have yielded mixed results.[4,6,8] Thus, one aim of the present study was to investigate the risk for OSA in GW veterans using the STOP questionnaire.[9] We found that veterans with GWI defined by either the CDC[22] or Kansas[18] criteria had significantly higher STOP scores than veterans without GWI. It is note-worthy that there were significant STOP score differences even when we used the Kansas-GWI case definition, which excludes conditions that have previously been associated with greater risk for OSA (e.g., diabetes, heart disease, and stroke).[24–28] Moreover, the group differences in STOP scores remained significant even after we accounted for potentially confounding demographic and clinical variables. This suggests that the relationship between GWI and increased risk for OSA independent of demographic and clinical variables. Interestingly, age and sex were not significantly associated with STOP scores, despite the well documented effects of these variables on risk for OSA.[29,30] This finding may be attributable, at least in part, to the small percentage of women and the restricted age range of current the study sample.

Understanding the cause(s) of GWI has proved to be a complex challenge in the years since the end of the GW, partly because military personnel encountered so many different kinds of potentially hazardous chemicals during deployment and there was poor record keeping about which personnel was exposed to which potentially hazardous substance(s) and at what levels. Nevertheless, investigators have focused on GW veterans' exposures to organophosphates (OPs) and carbamate compounds because population studies of environmental and occupational exposure to pesticides containing these chemicals have reported health problems similar to GWI.[31,32]

In a study that compared veteran-reported wartime experiences using logistic modeling to account for possible confounds among deployment variables and stratified analyses to accommodate differences among veteran subgroups, Steele et al[23] reported that only a limited number of exposures, which differed in importance with the deployment milieu in which the veterans served, were significantly associated with GWI. For forward-deployed personnel (i.e., Iraq and/or Kuwait, where all battles took place), GWI was most strongly associated with use of pyridostigmine bromide (PB), a carbamate and reversible

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acetylcholinesterase inhibitor taken in pill form as a protective measure against nerve agent exposure[33,34] and proximity to exploded SCUD missiles. For personnel who remained in support areas, GWI was most strongly associated with wearing pesticide-treated uniforms and using skin pesticides. These findings are consistent with previous GW studies that assessed individual risk factors for symptomatic illness using statistical methods that controlled for confounding effects of concurrent exposures.[33,35] In general, the only consistently identified risk factors associated with GWI have been exposure to toxicants, prominently OP and carbamate chemicals (e.g., use of PB pills, exposure to pesticides and nerve agents) that can adversely affect the nervous system.[35,36] The Department of Defense estimates that 250,000 GW personnel took PB pills, 41,000 service members were overexposed to carbamate- and OP-containing pesticides in the military's effort to control insect-borne diseases,[34,37] and approximately 100,000 GW personnel may have been exposed to low levels of OP nerve agents (e.g., sarin and cyclosarin) after demolitions of the Khamisiyah munitions depot in March 1991.[15]

It is well documented that acute exposure to high doses of OP[38] and chronic exposure to low doses of OP[39,40] can result in adverse health effects. There have also been reports that OP exposure is associated with increased risk for chronic obstructive respiratory diseases,[41] which has been linked with risk for OSA.[24] Sleep disturbances have also been reported in individuals suffering from OP poisoning.[42] Consistent with these reports, we found that predicted nerve agent exposure was significantly associated with increased risk for OSA in the ANCOVAs of group differences in STOP scores.

Although the toxicity of OPs and carbamates, which have been hypothesized to be involved in the etiology of GWI,[35,36] has traditionally been viewed in terms of their acetylcholinesterase inhibition, there is evidence that the toxicity and lethality of these chemicals is also attributable to oxidative stress and mitochondrial dysfunction.[43] Recent findings from Beatrice Golcomb's group[44] provide empirical support for a role of mitochondrial dysfunction and oxidative stress, which promotes and is caused by mitochondrial dysfunction,[45] in GWI. With respect to this finding, it is noteworthy that sleep pathology is a known complication of mitochondrial dysfunction, possibly because cellular energy failure causes both central neurological and peripheral neuromuscular degenerative changes that commonly present as central sleep apnea and poor ventilatory response to hyperapnea.[46]

Despite the fact that GW veterans commonly complain of sleep disturbances, no published study to date has examined sleep quality in this veteran population. Therefore, another aim of this study was to investigate subjective sleep quality and insomnia severity in GW veterans. We found that veterans with GWI, defined according to the CDC[22] or the Kansas[18] criteria, had significantly greater insomnia severity and poorer subjective sleep quality than veterans without GWI, even after accounting for potentially confounding demographic and clinical variables. We also found significant, positive correlations between GWI symptom severity, insomnia severity, and subjective sleep quality. This is consistent with clinical findings that sleep quality influences pain, fatigue, mood state, cognitive performance, and daily functioning.[10,11,47]

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There is evidence that sleep disruption can adversely affects systems (e.g., cognition,[48] neuroendocrine,[49] and autonomic[50]) that likely play important roles in GWI. However, it is also plausible that the systems disrupted in GWI (e.g., immune and neuroendocrine system) can adversely impact sleep. For example, research suggests that there is a strong symbiotic relationship between sleep and the immune system.[51] Not only have there been reports of immune dysregulation in veterans with GWI,[52] but animal models have also shown that PB, hypothesized to be involved in the etiology of GWI,[36] adversely affects immune function.[53] Similarly, insomnia has been linked to dysregulation of the hypothalamo-pituitary-adrenal axis[54] and alterations in neuroendocrine activity, which, in turn, have been associated with adverse health outcomes in GW veterans and with specific GW-related environmental exposures.[55]

It is conceivable that some of the causes of GWI may have produced sleep disturbances in GW veterans, which interact with and exacerbate other GWI symptoms, which then worsen the veterans' sleep disturbances. This vicious cycle may account for the significant correlations that we found between insomnia severity and GWI symptom severity. There were also significant correlations between insomnia severity, GWI symptom severity, PTSD, and depressive severity. Previous studies have shown that successfully treating insomnia can alleviate non–sleep-related PTSD[56] and depressive[57] symptoms. Because there is evidence for reciprocal links between sleep quality, sleep-wake regulation, and fatigue[58] among individuals with insomnia,[59] it is reasonable to hypothesize that treating GW veterans' insomnia and sleep disturbances may also improve non–sleep-related GWI symptoms. Evidence in support of this comes from a clinical trial that showed treatment with continuous positive airway pressure improved non-sleep GWI symptoms in veterans with GWI and sleep disordered breathing.[60]

To our knowledge, this is the first study to examine insomnia and sleep quality in GW veterans. The finding that insomnia severity significantly predicted GWI status over and above demographic and clinical variables, together with evidence that successful insomnia treatment can alleviate non–sleep-related PTSD and depression symptoms,[56] provide good rationale for treating sleep disturbance in the management of GWI. The fact that untreated insomnia is associated with significant medical and psychiatric morbidity,[61] together with recent evidence linking deficits in deep non-REM sleep with higher risk for build-up of beta-amyloid proteins believed to play a role in triggering Alzheimer's disease[62] present further impetus for treating sleep disturbances in this veteran population, particularly as they approach old age.

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**TABLE I**

Demographic and Descriptive Characteristics of Study Sample

| | CDC Case Definition | | | | Kansas Case Definition | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **GWI−** | **GWI+** | ***t* Value** | ***p* Value** | **GWI−** | **GWI+** | ***t* Value** | ***p* Value** | **Excluded From Kansas Definition** |
| N | 21 | 77 | | | 26 | 47 | | | 25 |
| Age (Years) | 56.2 (8.9) | 51.4 (7.9) | 2.41 | 0.02 | 53.6 (8.2) | 50.9 (7.7) | 1.41 | 0.16 | 54.0 (9.2) |
| Education (Years) | 16.3 (2.2) | 15.3 (2.2) | 1.84 | 0.07 | 16.5 (1.9) | 15.0 (2.3) | 2.95 | 0.004 | 15.4 (2.2) |
| Number of Females | 3 (14%) | 14 (18%) | | 1.00[b] | 3 (12%) | 9 (19%) | | 0.52[b] | 5 (20%) |
| Number of Whites | 18 (86%) | 55 (71%) | | 0.26[b] | 23 (89%) | 34 (72%) | | 0.15[b] | 16 (64%) |
| Number of Persons in Army | 16 (76%) | 60 (78%) | | 1.00[b] | 20 (77%) | 36 (77%) | | 1.00[b] | 20 (80%) |
| Rank | | | | 0.003[b] | | | | 0.001[b] | |
| Enlisted | 10 (48%) | 63 (82%) | | | 12 (46%) | 40 (85%) | | | 21 (84%) |
| Officer | 11 (52%) | 14 (18%) | | | 14 (54%) | 7 (15%) | | | 4 (16%) |
| Number of Persons With Predicted Nerve Agent Exposure | 14 (67%) | 43 (56%) | | 0.46[b] | 14 (54%) | 25 (53%) | | 1.00[b] | 18 (72%) |
| Number of Persons With Trauma Exposure | 9 (43%) | 64 (83%) | | <0.001[b] | 11 (42%) | 43 (92%) | | <0.001[b] | 6 (24%) |
| Number of Persons With Current PTSD | 0 (0%) | 10 (13%) | | 0.11[b] | 0 (0%) | 10 (21%) | | 0.01[b] | 0 (0%) |
| CAPS | 5.0 (7.7) | 23.1 (20.4) | 2.62 | 0.01 | 7.5 (11.5) | 25.7 (22.5) | 2.59 | 0.01 | 17.7 (14.0) |
| Number of Persons With Current MDD | 0 (0%) | 10 (13%) | | 0.11[b] | 0 (0%) | 9 (19%) | | 0.02[b] | 1 (4%) |
| BDI | 3.3 (2.6) | 10.7 (7.8) | 4.26 | <0.001 | 4.8 (6.1) | 11.4 (8.1) | 3.60 | 0.001 | 9.2 (6.3) |
| Number of Persons With ETOH History[a] | 6 (29%) | 22 (29%) | | 1.00[b] | 6 (23%) | 14 (30%) | | 0.60[b] | 8 (32%) |
| Number of Persons With Substance History[a] | 2 (10%) | 6 (8%) | | 0.68[b] | 2 (8%) | 5 (11%) | | 1.00[b] | 1 (4%) |
| GWI Symptom | 3.0 (3.0) | 25.3 (15.6) | 6.49 | <0.001 | 4.9 (5.0) | 27.8 (15.7) | 7.20 | <0.001 | 23.3 (15.5) |

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| | CDC Case Definition | | | | Kansas Case Definition | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | GWI− | GWI+ | *t* Value | *p* Value | GWI− | GWI+ | *t* Value | *p* Value | Excluded From Kansas Definition |
| Severity Score | | | | | | | | | |
| BMI | 28.9 (3.8) | 29.0 (4.6) | 0.13 | 0.90 | 28.3 (4.1) | 28.6 (4.5) | 0.4328 | 0.78 | 30.4 (4.4) |
| STOP | 1.4 (1.0) | 2.4 (1.0) | 3.78 | <0.001 | 1.6 (1.1) | 2.3 (0.9) | 2.58 | 0.01 | 2.5 (1.2) |
| PSQI | 4.2 (2.8) | 9.0 (4.1) | 4.96 | <0.001 | 4.6 (2.9) | 9.8 (4.4) | 5.38 | <0.001 | 8.1 (3.5) |
| ISI | 4.5 (3.9) | 12.8 (6.3) | 5.78 | <0.001 | 5.1 (3.6) | 14.1 (6.8) | 6.27 | <0.001 | 11.5 (5.2) |

[a]History of abuse or dependence.

[b]From Fisher's exact test. ETOH, alcohol.

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**TABLE II**

Correlations Between GWI, PTSD, and Depressive Symptoms, OSA Risk, and Subjective Sleep Measures

| | GWI Symptom Severity | PTSD Symptom Severity (CAPS) | Depressive Symptomology (BDI) |
|---|---|---|---|
| STOP | 0.26* | 0.18 | 0.27* |
| PSQI | 0.65** | 0.45** | 0.61** |
| ISI | 0.73** | 0.46** | 0.65** |
| CAPS | 0.64** | – | 0.53** |
| BDI | 0.61** | 0.53** | — |

Spearman's rank order correlation.

* $p \leq 0.01$,

** $p < 0.001$.