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# Lower health related quality of life in U.S. military personnel is associated with service-related disorders and inflammation

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ABSTRACT

Military personnel who have combat exposures are at increased risk for the service-related disorders of post-traumatic stress disorder (PTSD), depression, sleep disturbances and decreased health related quality of life (HRQOL). Those with a traumatic brain injury (TBI) are at even greater risk. Inflammation is associated with these disorders and may underlie the risk for health declines. We evaluated 110 recently deployed, military personnel presenting with sleep disturbances for service-related disorders (TBI, PTSD, and depression) as well as HRQOL. ANOVA models were used to examine differences among military personnel with two or more service-related disorders (high comorbid group), or one or no disorders (low comorbid group). Logistic regression models were used to determine associations among interleukin-6 (IL-6) to HRQOL and service-related disorders. Approximately one-third of the sample had two or more service-related disorders. HRQOL was lower and IL-6 concentrations were higher in military personnel with PTSD or depression, with the most profound differences in those with more service-related disorders, regardless of sleep disorder. Having symptoms of depression and PTSD resulted in a 3.5-fold risk to be in the lower quartile of HRQOL and the highest quartile of IL-6. In a linear regression model, 41% of the relationship between HRQOL and IL-6 concentrations was mediated by PTSD and depression. Military personnel with PTSD and depression are at high risk for lower HRQOL, and higher IL-6 concentrations. Comprehensive treatment is required to address co-occurring service-related disorders in military personnel to promote health and well-being.



## 1. Introduction

The estimated cost of medical care for the 2.4 million U.S. military personnel who deployed in operations enduring freedom (OEF) and Iraqi freedom (OIF) is between 4 and 6 trillion dollars (Edwards, 2010). The majority of the medical care is for the service-related disorders of depression, post-traumatic stress disorder (PTSD), and physical injuries including traumatic brain injury (TBI), as well as associated morbidity. Deployment and combat operations make up a highly stressful period that requires constant vigilance. This prolonged stress in combination with TBI, which occurs in 17–26% of military personnel, results in substantial morbidity (Fisher, 2010; Mac Donald et al., 2011). In addition, military personnel are required to adjust to differing sleep–wake schedules because of mission requirements (Centers for Disease Control and Prevention, 2012; Ferrer et al., 1995; Joint Mental Health Advisory Team 7 (J-MHAT 7) Operation Enduring Freedom, 2010; Miller et al., 2010; Peterson et al., 2008). Their disturbed sleep is linked to PTSD and depression (Luxton et al., 2011). Together, the stress and physical trauma that often occur during deployment place military personnel at high risk for PTSD and depression (Wilk et al., 2012), with greater risks in military personnel who sustain a TBI (Hoge et al., 2008). This leads us to question the mechanisms underlying high rates of comorbid conditions following deployment, and the effects of these comorbid conditions on health.

Deployment is consistently linked to health related quality of life (HRQOL) declines (Polusny et al., 2011), with greater declines in

*Abbreviations:* PTSD, post-traumatic stress disorder; HRQOL, health related quality of life; TBI, traumatic brain injury; ANOVA, analysis of variance; IL-6, interleukin-6; OEF, operation enduring freedom; OIF, operation Iraqi freedom; OSA, obstructive sleep apnea; QIDS, quick inventory of depressive symptomatology; PCL-M, PTSD checklist-military version; WARCAT, warrior administered retrospective casualty assessment tool; SF-36, RAND 36-item short form health survey; EDTA, ethylenediaminetetraacetic acid; CRP, C-reactive protein; BMI, body mass index; HTN, hypertension

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military personnel who sustain a TBI (Heltemes et al., 2012; Polusny et al., 2011), or develop PTSD (Polusny et al., 2011) or depression (Polusny et al., 2011). However, because the symptoms of these disorders overlap, the unique contribution of each disorder is not well established. A recent study undertaken by Polusny et al. (2011) reported that PTSD, but not TBI symptoms, were related to poor health recovery one year following deployment (Polusny et al., 2011); however, these disorders have overlapping pathways that may have contributed to HRQOL declines. Notably, a symptom common to PTSD, depression, and TBI is sleep disturbance. Although sleep disturbances are consistently linked to HRQOL declines in studies of civilians (Leger et al., 2012; Wagner et al., 2012; Xu et al., 2012), studies in military personnel have not established this link. A better understanding of the relationship between sleep disturbance and HRQOL following deployment is needed to better define the disease-specific aspects of depression, PTSD, and TBI.

We postulated that inflammation may underlie HRQOL declines in military personnel following deployment based on our recent finding that high concentrations of interleukin-6 (IL-6) were related to HRQOL reductions in a clinical sample of PTSD patients in which more than half had comorbid depression (Gill et al., 2013). There is an established link between high IL-6 concentrations and symptoms of depression, fatigue, disturbed sleep, cognitive impairment, and fatigue (Maes et al., 2012a). Administration of interferon-alpha, an inflammatory cytokine, as a treatment for hepatitis C is consistently linked to the onset of depression (Krueger et al., 2011). Our research as well as that by others show that PTSD and depression are both associated with inflammation (Maes et al., 2012b), with the highest concentrations of IL-6 found when these disorders are co-occurring (Gill et al., 2010). There is also evidence that pre-deployment differences in immune cell functioning (van Zuiden et al., 2012a) and high mean numbers of glucocorticoid receptors are linked to high levels of depression and PTSD, respectively, following deployment (van Zuiden et al., 2012b). This suggests that insufficient regulation of inflammation prior to deployment may place military personnel at risk for psychiatric disorders including PTSD and depression.

The purposes of this study were to determine the role of co-occurring symptoms of PTSD and depression in HRQOL levels following deployment in military personnel and if inflammation might underlie this relationship. These findings are necessary to develop optimal interventions for military personnel who often have high levels of comorbidity following deployment as well as medical conditions.

## 2. Methods

### 2.1. Study design

In this study 110 U.S. military personnel with sleep disturbances were evaluated with clinical instruments for PTSD, depression, and HRQOL. TBIs were determined by review of medical records, and a clinical interview. Active duty military personnel who returned from deployment to OIF/OEF within 18 months were eligible for participation. Exclusionary criteria included active treatment or military administrative actions related to drug or alcohol abuse or unstable psychiatric diagnoses (i.e., schizophrenia). All participants underwent a clinical evaluation and polysomnogram as part of a sleep medicine evaluation with findings previously reported (Mysliwiec et al., 2013), resulting in the following diagnoses: obstructive sleep apnea (OSA), insomnia, and both OSA and insomnia. Control participants also underwent a polysomnogram study and clinical evaluation and were not diagnosed with a sleep disorder. The presence of a diagnosis of hypertension (HTN) in their electronic medical record was also obtained.

### 2.2. Clinical diagnosis of depression, post-traumatic stress disorder and history of traumatic brain injury

The diagnosis of depression was determined using the Quick Inventory of Depressive Symptomatology (QIDS) questionnaire. A score of 11, which indicates a moderate severity of depression, was used as the cut-off for the diagnosis (Trivedi et al., 2004). The PTSD Checklist Military Version (PCL-M) was used to assess for post-traumatic stress disorder (Weathers et al., 2001). We used a score of 50 or higher to determine a PTSD diagnosis because this score provides the maximum specificity (0.98) and is consistent with the Structured Clinical Interview for DSM-III-R (Wilkins et al., 2011).

The assessment of TBI was determined using a review of medical records as well as a warrior administered retrospective casualty assessment tool (WARCAT), which was administered by a research clinician. This tool obtains data on possible TBI-related war injuries as well as post-deployment injuries, assessing alteration of consciousness and presence of postconcussive symptoms at the time of injury (Terrio et al., 2009). The diagnosis of mild TBI was made in accordance with the American Congress of Rehabilitation Medicine mild TBI criteria, which required an injury event followed by a loss of consciousness or alteration of mental state (American Congress of Rehabilitation Medicine, 2013).

The SF-36 was used to determine HRQOL, including the subcomponents of: vitality, physical functioning, bodily pain, general health perception, physical role functioning, emotional role functioning, social role functioning, mental health. The SF-36 is the most widely used measure of HRQOL and is both valid (0.82) and reliable (test–retest = 0.86) in traumatized participants (MacKenzie et al., 2002).

### 2.3. Blood collection and analysis

Blood was collected in a non-fasting state into ethylenediaminetetraacetic acid (EDTA) tubes that were immediately placed on ice and then processed and frozen at −80 °C degrees until batch assayed by a technician who was blinded to the participant group. All samples were stored in a biorepository at −80 °C to prevent sample degradation. Each sample type was batch assayed at the same time. Plasma IL-6 and C-reactive protein (CRP) levels (pg/ml) were measured using an antibody coated tube radioimmunoassay (R&D Systems); the inter-assay and intra-assay coefficients of variation were 7.8% and 8.9%, respectively, with a lower limit detection of 0.8 pg/ml for IL-6 and 0.78 pg/mL for CRP.

### 2.4. Statistical analyses

Diagnoses of PTSD, depression, and TBI, as well as sleep diagnoses and demographic variables were compared in the high and low comorbidity groups using either a chi-square test or a one-way analysis of variance (ANOVA). For the purposes of analysis, participants were classified in one of the two groups: (a) low comorbidity in which individuals had 0−1 of the diagnoses of PTSD, depression, TBI or (b) high comorbidity in which participants had 2 or more of these diagnoses. In analyses that were significant, these groups were further broken down to examine which comorbid conditions were most associated with the outcome of interest. ANOVA models were also used to determine group differences between the high and low comorbidity groups on concentrations of IL-6 and CRP, as well as HRQOL and its subcategories, with post hoc analyses using the Bonferroni correction for multiple tests. Covariates in these analyses included BMI, age, and the use of psychotropic medications (yes/no). Logistic regression models were undertaken to examine the relationship of the co-occurring conditions of PTSD, depression, and TBI with IL-6 and HRQOL, respectively. All regression models were adjusted for age, body mass index (BMI), and the use of psychotropic medication. The mean and proportional differences among participant groups for the demographic characteristics and the health-related variables are reported. Lastly, we utilized multiple logistic regressions to examine the unique and shared contributions of depression and PTSD to elevated concentrations of CRP (highest 25%), IL-6 (highest 25%), overall HRQOL, and the six sub-components of this measure (lowest 25% of this measure).

Linear regression models were used to examine the relationship of HRQOL and IL-6 concentrations while adjusting for age, BMI, and the use of psychotropic medication. In these models, a forced entry method was used for all variables. Next, to examine the effects of comorbidities including depression and PTSD, both of these variables were entered into the model individually, and then together using the forced entry method. In the regression models we also controlled for sleep disorders (OSA and insomnia). Lastly, we used the Sobel test to evaluate the portion of the relationship between HRQOL and IL-6 that is mediated by PTSD and depression.

## 3. Results

### 3.1. Demographics and clinical features

There were 70 participants in the low comorbid group, and 40 in the high comorbid group. These groups did not differ in age, gender, race, or BMI, or HTN. There was a significant difference in the rates of TBI, with the high comorbid group having a rate of 67.6% compared to 29.6% in the low comorbid group ($p < 0.01$) (see Table 1). Within both groups, most TBIs were mild, 95.4%, and