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Original Article

Sleep restoration is associated with reduced plasma C-reactive protein and depression symptoms in military personnel with sleep disturbance after deployment

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ABSTRACT

Background: Deployed military personnel are vulnerable to chronic sleep disturbance, which is highly comorbid with post-traumatic stress disorder (PTSD) and depression, as well as declines in health-related quality of life (HRQOL). Inflammation is associated with HRQOL declines and sleep-related comorbidities; however, the impact of sleep changes on comorbid symptoms and inflammation in this population is unknown.
Methods: In this observational study, we examined the relationship between reported sleep changes and concentrations of inflammatory biomarkers, interleukin 6 (IL-6), and C-reactive protein (CRP) in peripheral blood. The sample was dichotomized into two groups: (1) decrease in Pittsburgh Sleep Quality Index (PSQI; restorative sleep) and (2) no change or increase in PSQI (no change). Mixed between–within subjects analysis of variance tests were used to determine group differences on changes of inflammation and comorbid symptoms.
Results: In our sample of 66 recently deployed military personnel with insomnia, 34 participants reported restorative sleep whereas 32 reported no sleep changes. The two groups did not differ in demographic or clinical characteristics, with the exception of PTSD diagnosis at baseline. The restorative sleep group had significant reductions in CRP concentrations and depression symptoms, as well as reduced fatigue and improvements in emotional well-being, social functioning, and physical functioning at follow-up.
Conclusions: Military personnel who report sleep restoration after deployment have reduced CRP concentrations, decreased severity of depression, and improved HRQOL. These findings suggest that treatment for sleep disturbances may be associated with improvements in mental and physical health, thereby supporting continued study in this line of research.

1. Introduction

Approximately one-third of military personnel who were deployed in Operations Enduring Freedom or Iraqi Freedom (OEF/OIF) report disturbed sleep that does not resolve within 1 year following their return [1]. Sleep disturbance can be attributed to alterations in sleep–wake schedules, as well as the intensive psychological and physical conditions associated with deployment [2–6]. There is often an inability to restore sleep quality upon return from deployment, resulting in the diagnosis of insomnia [7]. Sleep disturbance in military personnel is associated with high rates ofpost-traumatic stress disorder (PTSD) and depression [8,9], and these diagnoses are likely to perpetuate sleep disturbance symptoms. We and others have reported higher levels of inflammation, as assessed by the concentrations of interleukin 6 (IL-6), in participants with PTSD, depression, and insomnia, with the highest levels in those with the greatest severity of these comorbidites [10]. We also reported that recovery from PTSD and depression is associated with resolution of inflammation [11]. This led us to question

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if sleep restoration might have a positive impact on the comorbid symptoms of PTSD and depression, and if inflammation is related to sleep and comorbid symptom change.

Sleep is shaped by a complex system of regulatory neuronal mechanisms and neuropeptides that can be influenced by inflammatory biomarkers in a bidirectional manner. Reductions in sleep quality and duration result from administration of inflammatory cytokines in preclinical models and administration of interferon gamma (INF-γ) in clinical patients [12]. In preclinical models, stressors that mimic deployment increase inflammation that is linked to neurological alterations (e.g., reductions in the volume and function of stress-regulating centers including the hippocampus and amygdala) and the onset of anxiety and depression [13–15]. In healthy individuals, an increase in inflammatory cytokine concentrations has been linked to sleep restriction [16,17]. Therefore, inflammation and sleep have complex interactions that affect the health and well-being of military personnel, and the mechanisms underlying these risks have not been fully elucidated.

Historically, research into biological mechanisms of psychiatric disorders and sleep disturbance were segregated according to diagnostic classification. The high symptom overlap within these disorders in military personnel after returning from deployment led us and others to question this approach. Previously, we and others have shown that inflammation is associated with PTSD and depression [10,18–20]. Therefore, independent of the interactive mechanism of inflammation, sleep, and mental health, it is likely that chronic inflammation is common following deployment and may be a contributing factor to increases in medical morbidity for the 2.4 million U.S. military personnel who have been deployed [21]. This line of research is essential, because many military personnel might not have yet developed the morbidity and mortality risks linked to inflammation [22–26], thus providing a window of opportunity to intervene to reduce the risk.

To address this critical issue, we examined military personnel who were seeking care for sleep disturbance, by assessing changes in sleep, comorbid symptoms, and inflammation following standard-of-care interventions that include at least one of the following: cognitive behavioral therapy (CBT), pharmacological agents, and automatically adjusting positive airway pressure (APAP) over a 3-month period. We included all participants with a diagnosis of insomnia, which may also include obstructive sleep apnea (OSA), who completed the study. In this pilot study, we examined associations among self-reported sleep restoration and changes in comorbid symptoms and inflammation in a recently deployed military population.

2. Methods

2.1. Study design

This study is part of a larger ongoing study of U.S. military personnel who presented for evaluation of sleep disturbance at the Madigan Army Medical Center and were evaluated for PTSD, depression, and health-related quality of life (HRQOL) using validated clinical instruments. For this sub-study, all participants with insomnia who completed the study were included, resulting in 66 participants. The following groups of participants were excluded: 1) participants with OSA and no insomnia ($n = 22$), 2) participants who reported sleep disturbance but did not qualify for a diagnosis of insomnia or OSA ($n = 10$), and 3) participants who did not complete the follow-up data collection point for the study ($n = 18$). This resulted in 66 participants with insomnia who completed the study at baseline and 3-month follow-up. All participants were determined to have insomnia in accordance with the International Classification of Sleep Disorders second edition. Active duty military personnel who were deployed to OIF/OEF within the previous 18 months were eligible for participation, and participants were excluded from the study if they were undergoing active treatment or military administrative actions related to drug or alcohol abuse or unstable psychiatric conditions (i.e., schizophrenia or bipolar disorder). All participants underwent a clinical evaluation and polysomnogram as part of a sleep medicine evaluation; these findings were previously reported [27].

2.2. Assessment of depression, PTSD, and HRQOL

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 cutoff for the diagnosis [28]. The PTSD Checklist-Military Version (PCL-M) was used to assess for PTSD [29]. We used a score of ≥50 to determine a PTSD diagnosis because this score provides the maximum specificity (0.98) and is consistent with the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised (DSM-III-R) [30].

The RAND 36-Item Health Survey (RAND-36), comprising 36 items that assess eight health concepts, was used to determine HRQOL. The subcomponents of the instrument include the following: physical functioning, role limitations caused by physical health, role limitations caused by emotional problems, social functioning, emotional well-being, energy/fatigue, pain, and general health perceptions. A high score defines a more favorable health state. The RAND-36 is the most widely used measure of HRQOL and is both valid and reliable (test–retest correlation coefficient = 0.86) in traumatized participants [31].

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, processed, and frozen at –80 °C. Each sample was batch-assayed at the same time by a technician who was blinded to the participant group. Plasma IL-6 and C-reactive protein (CRP) levels (pg/mL) were measured using an antibody-coated tube radioimmunoassay (R&D Systems, Minneapolis, MN, USA); the inter-assay and intra-assay coefficients of variation were 7.8% and 8.9%, respectively, with a lower limit detection of 0.80 pg/mL for IL-6 and 0.78 pg/mL for CRP.

2.4. Statistical analysis

Participants were first dichotomized based on change in Pittsburgh Sleep Quality Index (PSQI) scores between baseline and follow-up visits. Scores on the PSQI, a 19-item questionnaire about sleep quality (subsections: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medications, and daytime dysfunction), range from 0 to 21, with a difference of five points indicating a significant change in sleep quality [32]. Some participants demonstrated improved sleep quality (restorative sleep) and others demonstrated no change or decline in sleep quality (no change).

We used descriptive statistics to describe our sample in terms of demographic characteristics (age, body mass index (BMI), gender, race, and military rank) and clinical variables (sleep, traumatic brain injury (TBI), depression, and PTSD diagnoses) using SPSS Statistics (IBM SPSS Inc., Chicago, IL, USA). Comparisons were made between these two groups using independent *t*-tests and chi-squared tests for continuous and categorical variables, respectively. Mixed within group and between groups analysis of variance (ANOVA) tests were then used to determine group differences between the

restorative and no-change sleep groups in changes of IL-6 and CRP concentrations, symptoms of depression and PTSD, and subcomponent scores of HRQOL. A priori p values <0.05 were considered significant.

3. Results

3.1. Demographics and clinical features

The demographic and clinical characteristics of the 66 participants are described in Table 1. The restorative sleep group and the no-change group did not differ in demographic characteristics (age, BMI, gender, race, and military rank) and diagnoses of sleep disorders, TBI, or depression, but did differ in PTSD diagnosis, with the no-change group having a rate of 59.4% at baseline compared to 32.4% in the restorative sleep group ($\chi^2 = 3.83$, $p = 0.05$). The sample was primarily male and Caucasian, and demonstrated high rates of comorbid symptoms of sleep disorders, TBI, depression, and PTSD.

3.2. Inflammation change

The results from mixed between-within subjects ANOVA showed that there was a significant interaction effect between the sleep group and time on CRP concentrations, Wilks' $\lambda = 0.87$, $F(1, 64) = 9.35$, $p < 0.01$ (Fig. 1a). The main effect for time was also significant, Wilks' $\lambda = 0.92$, $F(1, 64) = 5.37$, $p = 0.02$, partial $\eta^2 = 0.08$ (moderate effect size), with the restorative sleep group, in particular, showing a decrease in CRP concentrations from baseline to 3-month follow-up. However, no significant main effect comparing the two sleep groups was found, $F(1, 64) = 0.67$, $p = 0.42$, partial $\eta^2 = 0.01$. There was no difference between the two sleep groups in IL-6 concentrations over time (Fig. 1b).

3.3. Symptom change: HRQOL, depression, and PTSD

There were significant interaction effects between the sleep group and time on two of the eight RAND-36 components: physical functioning, Wilks' $\lambda = 0.94$, $F(1, 64) = 4.26$, $p = 0.04$; and social functioning, Wilks' $\lambda = 0.93$, $F(1, 64) = 4.86$, $p = 0.03$ (Table 2). No main effect for group or time was significant for these components. For emotional well-being and energy/fatigue, there were significant group × time interaction effects (emotional well-being, Wilks' $\lambda = 0.92$, $F(1, 64) = 5.24$, $p = 0.03$; and energy/fatigue, Wilks' $\lambda = 0.82$, $F(1, 64) = 14.09$, $p < 0.001$), as well as significant main effects for time (emotional well-being, Wilks' $\lambda = 0.94$, $F(1, 64) = 4.10$, $p = 0.05$, partial $\eta^2 = 0.06$; and energy/fatigue, Wilks' $\lambda = 0.93$, $F(1, 64) = 4.97$, $p = 0.03$, partial $\eta^2 = 0.07$), indicating the restorative sleep group with a significant increase in both scores over time.

Depressive symptoms also significantly changed over time, especially in the restorative sleep group showing a decrease in QIDS scores over time with a significant group × time interaction effect (Wilks' $\lambda = 0.87$, $F(1, 64) = 9.63$, $p < 0.01$) and a time main effect (Wilks' $\lambda = 0.94$, $F(1, 64) = 4.06$, $p = 0.05$, partial $\eta^2 = 0.06$). For PTSD symptoms, there was no significant interaction or main time effects on PCL-M score changes in 3 months, yet we found a trend of the main effect comparing the two groups on PCL-M scores, $F(1, 64) = 2.99$, $p = 0.09$, partial $\eta^2 = 0.05$, which indicates lower levels of PCL-M in the restorative sleep group than the no-change group.

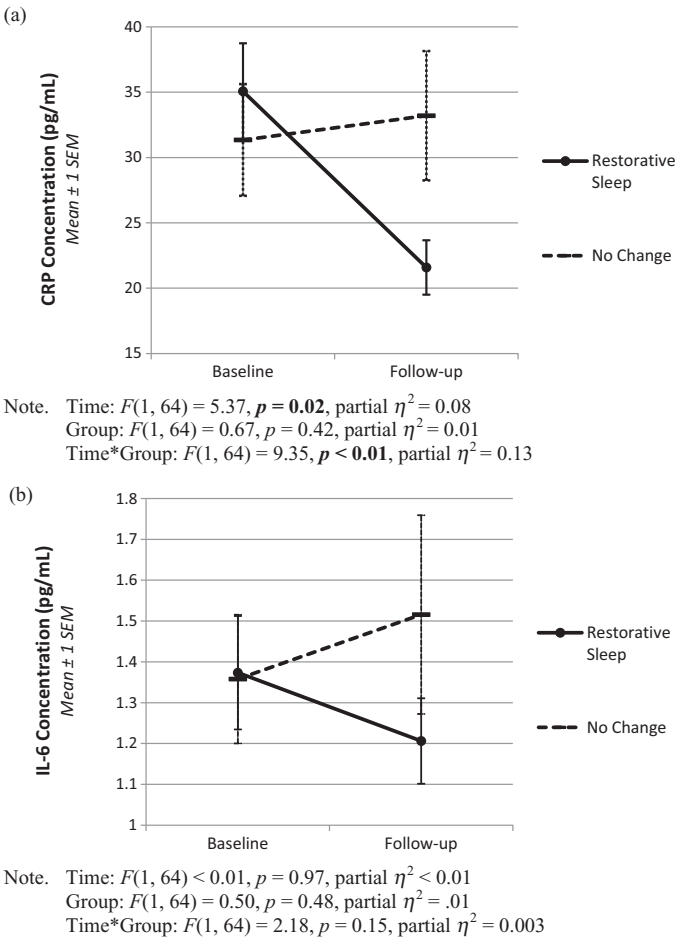

Fig. 1. Change in Inflammation Markers (CRP and IL-6 Concentrations) between Baseline and Follow-up for the Restorative Sleep ($N = 34$) and No-Change ($N = 32$) Groups. (a) Change in CRP Concentrations. (b) Change in IL-6 Concentrations.

Table 1
Demographic and Clinical Characteristics for Restorative Sleep ($N = 34$) and No-Change ($N = 32$) Groups.

	Restorative Sleep ($N = 34$)	No Change ($N = 32$)	t or χ^2	P
Mean age in years (sd)	33.24 (7.24)	36.53 (8.60)	–1.69	0.10
Mean BMI (sd)	30.50 (4.21)	31.02 (3.79)	–0.53	0.60
Gender, % (no.)			0.58	0.45
Male	100.0% (34)	93.8% (30)		
Race, % (no.)			1.67	0.64
Caucasian	64.7% (22)	53.1% (17)		
Mixed	17.6% (6)	15.6% (5)		
African American	8.8% (3)	15.6% (5)		
All Other	8.8% (3)	15.6% (5)		
Rank, % (no.)			0.76	0.68
Lower enlisted	58.8% (20)	68.8% (22)		
Senior enlisted	38.2% (13)	28.1% (9)		
Officer	2.9% (1)	3.1% (1)		
Mean baseline PSQI (sd)	13.62 (3.84)	12.59 (3.58)	1.12	0.27
Comorbid OSA, % (no.)	61.8% (21)	68.8% (22)	0.11	0.74
Apnea Hypopnea Index (sd)	9.9 (5.7)	10.2 (6.8)	0.89	0.67
TBI Diagnosis, % (no.)	44.1% (15)	50.0% (16)	0.05	0.82
Diastolic blood pressure	78.9 (14.7)	77.1 (11.2)	0.28	0.74
Systolic blood pressure	133.4 (18.5)	130.5 (17.6)	0.30	0.42
Depression Diagnosis, % (no.)	52.9% (18)	56.3% (18)	<0.01	0.98
PTSD Diagnosis, % (no.)	32.4% (11)	59.4% (19)	3.83	0.05

Abbreviations: BMI: body mass index, OSA: obstructive sleep apnea, PSQI: Pittsburgh Sleep Quality Index, PTSD: post-traumatic stress disorder, TBI: traumatic brain injury.

4. Discussion

To our knowledge, we are the first to report that sleep restoration in patients with insomnia is associated with inflammation and symptoms of depression. Examining this relationship is important, because large population-based studies show associations of

Table 2
Mixed Between–Within Subjects Comparisons of the Scores of Comorbid Symptoms between Restorative Sleep ($N = 34$) and No-Change ($N = 32$) Groups at Baseline and 3-Month Follow-up.

	Restorative Sleep ($N = 34$)		No Change ($N = 32$)		Time:		Group:		Time*Group:	
	Baseline (mean ± SD)	Follow-up (mean ± SD)	Baseline (mean ± SD)	Follow-up (mean ± SD)	F[a]	Effect size[a]	F[b]	Effect size[b]	F[c]	Effect size[c]
RAND-36										
Physical Functioning	72.35 ± 24.78	75.44 ± 25.65	69.84 ± 18.99	65.31 ± 24.72	0.15	<0.01	1.30	0.02	**4.26***	0.06
Role Limitations: Physical Health	50.00 ± 44.81	52.21 ± 44.96	36.88 ± 44.32	35.16 ± 35.84	<0.01	<0.01	2.39	0.04	0.25	<0.01
Role Limitations: Emotional Problems	53.91 ± 45.73	61.79 ± 44.31	52.06 ± 44.79	43.75 ± 44.38	<0.01	<0.01	1.03	0.02	2.59	0.04
Social Functioning	58.26 ± 28.96	63.72 ± 31.13	57.66 ± 25.31	54.02 ± 25.51	0.19	<0.01	0.92	0.01	**4.86***	0.07
Emotional Well-being	54.00 ± 25.48	62.12 ± 20.66	56.63 ± 19.86	56.13 ± 24.73	**4.10***	0.06	0.10	<0.01	**5.24***	0.08
Energy/fatigue	30.15 ± 23.60	44.85 ± 25.00	33.75 ± 18.58	30.00 ± 19.43	**4.97***	0.07	1.37	0.02	**14.09*****	0.18
Pain	58.31 ± 29.63	58.99 ± 27.58	48.31 ± 20.65	46.02 ± 24.97	0.18	<0.01	3.52	0.05	0.61	0.01
General Health Perceptions	53.82 ± 21.95	56.32 ± 22.57	51.56 ± 17.62	47.50 ± 19.01	0.16	<0.01	1.42	0.02	2.89	0.04
QIDS	11.65 ± 5.48	8.85 ± 5.09	11.44 ± 4.84	12.03 ± 6.13	**4.06***	0.06	1.50	0.02	**9.63****	0.13
PCL-M	40.41 ± 15.22	38.12 ± 17.23	44.69 ± 16.75	47.22 ± 18.39	0.01	<0.01	2.99	0.05	2.45	0.04

* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$.
[a] Values of F and partial eta-squared estimates for within-subject differences (Baseline vs. Follow-up).
[b] Values of F and partial eta-squared estimates for between-subject differences (Restorative Sleep vs. No Change).
[c] Values of F and partial eta-squared estimates for interaction between time (Baseline vs. Follow-up) and sleep group (Restorative Sleep vs. No Change).

high concentrations of CRP with insomnia [33,34]. CRP elevations in young adults place these individuals at a high risk of morbidity and mortality [35], which suggests that therapeutic interventions to mitigate this risk are essential. Therefore, our finding that there were significant associations between only 3 months of sleep restoration and dramatic improvements in inflammation and depression in military personnel provides an opportunity to consider another avenue to promote the health and well-being of patients with insomnia.

Reports suggest that CRP, a protein found in blood plasma that increases in concentration in response to inflammation, is a marker of morbidity and health mortality. Inflammation plays a pivotal role in the development of morbidity and mortality in aging veterans with PTSD, placing them at twice the risk of developing cardiovascular disease, diabetes, hypertension, arthritis, and chronic pain [36–38]. It is estimated that medical care and diminished productivity in our military personnel as they age will be >$4 trillion; therefore, efforts to reduce morbidity are crucial [21]. Recently deployed military personnel are still relatively young and do not yet display traditional morbidity or mortality risks. Moreover, early intervention and treatment in military personnel with high combat exposure have already led to fewer reported symptoms of PTSD, depression, and sleep disturbance, providing further evidence that treating these personnel while they are relatively young is critical [39].

Measures of inflammation have been found to increase in healthy adults experiencing brief periods of sleep deprivation [16,17]. Therefore, treating sleep disturbance may decrease CRP which would, in turn, decrease morbidity and mortality. Because of the stigma associated with PTSD, recent studies report that military personnel are more likely to seek treatment for sleep disturbance, one of the many symptoms of PTSD, rather than for PTSD [40]. With 2.5 million service members who have been deployed since 2001, there are major ramifications for our findings in the reduction of CRP concentrations and sleep deprivation. Our key finding that sleep restoration is associated with reduced inflammation and increased health and well-being suggests that there may be a window of opportunity to provide interventions to mitigate the risks of morbidity and mortality by treating sleep disturbance. Specifically, this is relevant in our younger sample, in which the classic cardiovascular risk factors of higher blood pressure and BMI are not yet present.

Second, we report that symptoms of depression decrease in the restorative sleep group, which may also relate to observed CRP reductions. Increased CRP has been reported to be associated with depression [41]. In a large population-based study, patients with the highest CRP concentrations were at the highest risk of being hospitalized for depression [42]. Previous studies that evaluated the impact of pharmacological agents used to treat depression report contradictory findings regarding CRP changes [43–45]. Therefore, our finding that the treatment of sleep disturbance, with standard-of-care treatments of CBT, medication, or APAP, is associated with reductions in depressive symptoms that may also relate to CRP reductions provides further evidence of the need to treat comorbidity within military personnel.

Additionally, we report a trend for less PTSD symptoms in the restorative sleep cohort, although the symptoms did not significantly change over time. This is important to explore further because studies in veterans link health declines with increases in symptoms of PTSD [11,25,26,46]. Previously, a behavioral sleep intervention was shown to both improve sleep and reduce PTSD symptoms in military personnel [47]. Thus, further studies are suggested to investigate potential impacts of sleep treatment on these co-occurring disorders following deployment in a larger sample of military personnel. In support of this, sleep disturbance following deployment has been shown to mediate one-third of the risk for PTSD or depression onset [48]. Because PTSD continues to have an associated stigma in military populations [49], the assessment and treatment for sleep disorders may provide an advantageous treatment arena for the often-comorbid conditions of PTSD and depression. Therefore, an accurate assessment of sleep-related disturbance and early treatment may decrease the risk of health declines in those with PTSD and depression. Lastly, the high comorbidity of PTSD, depression, and sleep disorders suggests that comprehensive, multidisciplinary interventions are required to address this critical issue.

The limitations of this study include a small sample of participants from one military treatment facility who were only followed up over a 3-month period and were diagnosed with insomnia. As we included participants with insomnia, the role of OSA was not clarified. In addition, to diagnose PTSD and depression, we utilized validated questionnaires, which do not necessarily represent clinical diagnoses. We could not distinguish the potentially different impacts of CBT, medication, or APAP on comorbid symptoms and inflammation in our sample. Furthermore, we only included two

markers of inflammation, which might not reflect the complete inflammatory milieu/spectrum in military personnel with mental health disorders. Nonetheless, our findings provide initial evidence that restorative sleep in military personnel may be associated with reductions in a biological predictor of morbidity and mortality, decreases in symptoms of depression, and improvements in health quality, warranting future studies in this line of work.

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Conflict of interest

No author has any conflicts of interest to disclose. The opinions and assertions in this manuscript are those of the authors and do not necessarily represent those of the Department of the Army, Department of Defense, U.S. Government, or the Center for Neuroscience and Regenerative Medicine.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2014.08.004.

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