ORIGINAL ARTICLE

Inspiratory airflow dynamics during sleep in veterans with Gulf War illness: a controlled study

Mohammad M. Amin · Zuzana Belisova · Sayeed Hossain · Morris S. Gold · Joan E. Broderick · Avram R. Gold

Abstract

Purpose To determine whether veterans with Gulf War Illness (GWI) are distinguished by sleep-disordered breathing, we compared inspiratory airflow dynamics during sleep between veterans with GWI and asymptomatic veterans of the first Gulf War.

Methods We recruited 18 male veterans with GWI and 11 asymptomatic male veterans of the first Gulf War by advertisement. The two samples were matched for age and body mass index. Each participant underwent a first full-night polysomnogram (PSG) while sleeping supine using standard clinical monitoring of sleep and breathing. A second PSG was performed measuring airflow with a pneumotachograph in series with a nasal mask and respiratory effort with a supraglottic pressure (Psg) catheter to assess the presence of inspiratory airflow limitation during supine N2 sleep. We determined the prevalence of flow-limited breaths by sampling continuous N2 sleep and plotting inspiratory flow against Psg for each breath in the sample. We expressed the prevalence of flow-limited breaths as their percentage in the sample.

Results Compared to controls, veterans with GWI had an increased frequency of arousals related to apneas, hypopneas, and mild inspiratory airflow limitation. During supine N2 sleep, veterans with GWI had 96±5% (mean ± SD) of their breaths flow-limited while controls had 36±25% of their breaths flow limited ($p < 0.0001$).

Conclusions Veterans with GWI experience sleep-disordered breathing that may distinguish them from asymptomatic veterans of the first Gulf War.

Keywords Gulf War illness · Functional somatic syndromes · Sleep disordered breathing · Inspiratory airflow limitation

M. M. Amin (✉) · Z. Belisova · S. Hossain · A. R. Gold
Division of Pulmonary/Critical Care/Sleep Medicine,
DVA Medical Center,
Northport, NY 11768, USA
e-mail: mohammad.amin2@va.gov

J. E. Broderick
Applied Behavioral Medicine Research Institute,
New York, USA

M. M. Amin · Z. Belisova · S. Hossain · J. E. Broderick ·
A. R. Gold
Stony Brook University School of Medicine,
Stony Brook, NY 11794, USA

M. S. Gold
Biostatistician, Novartis Consumer Health,
Parsippany, NJ, USA

Introduction

Up to half the veterans of the first Persian Gulf War experience a group of symptoms including fatigue, insomnia, body pain, mood and cognitive disturbances known as Gulf War Illness (GWI) [1–3]. The symptoms of GWI are not unique to veterans of the first Gulf War. Non-veterans with chronic fatigue syndrome, fibromyalgia, and irritable bowel syndrome experience the same variety of symptoms as veterans with GWI [4, 5]. Because of their similarity with respect to symptoms and their unknown etiology, many investigators have grouped the above syndromes into the functional somatic syndromes [4, 5]. Such a grouping encourages researchers to broaden their thinking and to consider generalizing lessons learned.

Although the etiology of the functional somatic syndromes is unknown, these syndromes have been associated with stress. Adult chronic fatigue syndrome

patients are distinguished from healthy controls by a history of childhood sexual abuse, emotional abuse, and emotional neglect [6]. Among fibromyalgia patients, there is a more frequent history of infection as well as emotional and physical trauma [7, 8]. Among women reporting a situation of domestic violence to the police, 47% reported current irritable bowel syndrome [9]. Thus, the symptoms of the functional somatic syndromes are associated with individuals who have undergone an episode of physical/emotional stress in their lives.

In addition to the well-established relationship between the functional somatic syndromes and stress, a possible relationship has been hypothesized between the functional somatic syndromes and mild sleep-disordered breathing. Symptoms of the functional somatic syndromes are more common among patients with UARS and mild to moderate sleep apnea [10–12]. Inspiratory airflow limitation during sleep is more common among young females with IBS than among healthy controls [13]. Sleep-disordered breathing is also common among females with fibromyalgia [14, 15] and treatment of fibromyalgia patients with nasal continuous positive airway pressure (CPAP) relieves fibromyalgia symptoms [15]. The literature suggests, therefore, that individuals experiencing both stress and sleep-disordered breathing may be predisposed to the functional somatic syndromes.

As one of the functional somatic syndromes, GWI also occurs in veterans who have been exposed to a variety of stressors, among them heat, sleep deprivation, air pollution from burning oil, and combat. Even so, not all the veterans who served during the first Gulf War returned with GWI. We hypothesized that veterans who returned with GWI are distinguished by the presence of sleep-disordered breathing. To test this hypothesis, we studied the sleep and breathing of veterans with GWI and compared it to that of healthy veterans of the first Gulf War.

Methods

Subject recruitment

We recruited two samples of male veterans of the first Gulf War by advertisement. The first sample consisted of 18 veterans with GWI and the second sample consisted of healthy controls; 11Gulf War veterans without symptoms of functional somatic symptoms (FSS). The two samples were matched for age and body mass index (BMI). All of the participants were registered in the Gulf War Veterans Registry.

Criteria for GWI participants were adapted from the VA Cooperative study #470, comparing cognitive behavioral therapy to aerobic exercise for symptoms of GWI [16]. Eligible veterans were deployed to the Persian Gulf between August 1990 and August 1991 and reported onset after August 1990 of each of the following symptoms: fatigue, pain involving at least two body regions and cognitive dysfunction (memory or concentration problems). All three symptoms must have lasted for more than 6 months, were present at the time of screening, and were unexplained by any clearly defined organic illness. Exclusion criteria included alcohol abuse, active clinical depression, active post-traumatic stress disorder, current use of opiates, and a prior diagnosis of sleep apnea. These exclusion criteria were needed to eliminate the confounding effects of respiratory depressant drugs and changes in therapy that would complicate a subsequent nasal CPAP trial that included our GWI participants.

Potential participants were screened for the relevant symptoms using three self-report instruments measuring cognitive difficulties, pain, and fatigue. The Cognitive Failures Questionnaire, a 25-item instrument that assesses frequency of difficulty with memory, attention, action, and perception in everyday life (increasing difficulty rated 0–100 with our clinical threshold at 20) [16, 17]. This instrument has been previously used to assess veterans with GWI. A pain visual analog scale (increasing pain rated 0–10) with a pain rating of 2 serving as the clinical threshold The Fatigue Severity Scale, an 11-item instrument measuring the level of disability related to fatigue [18] (increasing disability rated 1-7 with our clinical threshold at 2). To be included, GWI participants had to score above the designated clinical threshold on each of the questionnaires. Conversely, Gulf War veteran controls had to score below the clinical threshold to be included.

Our method for selecting Gulf War veteran controls resulted in an exclusive control group that did not return from the Gulf with symptoms and never developed symptoms. Our questionnaires, administered over a decade following the veterans' return excluded veterans of the first Gulf War who returned with cognitive dysfunction, pain, and fatigue and also veterans who returned without these symptoms, but developed them in subsequent years. We chose this method because sleep-disordered breathing is associated with a variety of functional somatic syndromes. Therefore, to maximize our ability to demonstrate a difference between groups in breathing during sleep, we excluded any veteran with current symptoms of FSS from our control group. It should be understood, however, that there may be many veterans who returned from the Gulf War without GWI who subsequently developed a functional somatic syndrome. These veterans without GWI are not represented in our control group.

First polysomnogram

Every subject underwent a full night polysomnogram (PSG) to evaluate sleep architecture and clinical respiratory parameters. After preparing for the PSG, participants got into bed between 10:00 and 11:00 pm and they awakened at 6:00 am (each subject spent between 7 and 8 h in bed). Sleep stages were monitored using surface electroencephalographic activity of the central and occipital regions, submental surface electromyographic activity, and left and right electrooculographic activity. Leg movement was detected using surface electromyographic activity of the right and left tibialis anterior muscle. Airflow at the nose and mouth were monitored with a nasal/oral pressure catheter. Thoraco-abdominal movement was monitored with piezoelectric belts. Oxyhemoglobin saturation was monitored at the finger using a pulse oximeter. A continuous electrocardiogram monitored heart rate and rhythm. All of the data was converted from analog to digital and stored on a computer for analysis by an individual masked to the identity of the subject.

Second polysomnogram

During the second night in the sleep laboratory, each participant underwent a PSG with quantitative measurement of airflow dynamics while sleeping supine. Sleep was monitored using the same methods used for the first PSG. To quantify airflow, each participant wore a nasal mask in series with a heated pneumotachograph (Model 3700A, Hans Rudolph, Kansas City, MO, USA). To ascertain that the participant's breathing was entirely nasal, a thermocouple was placed in front of the mouth to document episodes of oral breathing. Respiratory effort was measured as supraglottic pressure (Psg) using a pressure catheter (MPC–500, Millar Instruments, Houston, TX, USA). The pressure catheter was inserted trans-nasally a distance of 16 cm. Its supraglottic position was confirmed by indirect laryngoscopy with a dental mirror. All of the data was converted from analog to digital (with a sampling frequency of 128 Hz for Psg and airflow) and stored on a computer for analysis.

For this PSG, GWI participants and controls followed different protocols. Once asleep, each GWI participant was monitored supine for approximately 2 h to confirm the presence of inspiratory airflow limitation (IFL; a plateau of inspiratory airflow despite the continued decrease of Psg). Subjects who demonstrated IFL during supine NREM sleep at atmospheric pressure then underwent a CPAP titration to determine the therapeutic level of CPAP for the subsequent treatment trial. After the CPAP titration, the mask pressure was lowered to 4 cm H_2O and left for the duration of the study. Controls were monitored at atmospheric pressure

throughout the night. The study ended at approximately 6:00 am.

Sleep data analysis

The first PSG was staged using strict Rechtschaffen and Kales criteria [19] to determine wakefulness and the various sleep stages. Sleep architecture was summarized using standard definitions with the combination of NREM stages 3 and 4 into slow wave sleep. Arousals were scored using the 3-s frequency shift criterion [20]. These criteria were chosen (rather than the most recent AASM guidelines for sleep staging) to maintain consistency with our previous work [13, 15] in this field and to allow for comparisons to the previous work of others.

Sleep disordered breathing events were defined as: *apnea*, a decrease of inspiratory airflow to below 20% of waking levels lasting at least 10 s and *hypopnea*, a decrease of inspiratory airflow to below 50% of waking levels associated with an arousal from sleep. Arousals preceded by three or more breaths with an inspiratory airflow plateau that was above 50% of waking airflow were quantified as respiratory event related arousals (RERAs) [21].

Sleep fragmentation was characterized using an arousal index (spontaneous arousals+arousals related to apneas, hypopneas and RERAs), an apnea hypopnea index, a RERA index, and the total of sleep stage shifts from deeper to lighter sleep. The total of sleep stage shifts was defined as the sum of the shifts (a) from deeper NREM sleep to lighter non-REM sleep or wakefulness and (b) from REM sleep to any other sleep stage or wakefulness

For the second PSG, from the first 2 h, we sampled the airflow and Psg of the first three 2-min periods of continuous stage N2 sleep (approximately 90 breaths) to determine the prevalence of flow-limited breaths For participants with sleep apnea/hypopnea, sleep fragmentation often did not permit the sampling of two continuous minutes of NREM stage 2 sleep, For these individuals, shorter samples of continuous NREM stage 1 and NREM stage 2 sleep were summed with apneic breaths considered to be flow limited. The analysis of breaths for the presence of flow limitation was accomplished using a method similar to that of our study of inspiratory airflow dynamics during sleep in females with irritable bowel syndrome [13].

Following identification of the three 2-min samples, the airflow and Psg signals were exported from the sleep software into a plotting program (Microsoft Excel). For each inspiration, the inspiratory airflow was plotted against Psg (Fig. 1) providing approximately 16 inspiratory plots per minute. To characterize IFL, each breath was classified as flow limited or not flow limited by an
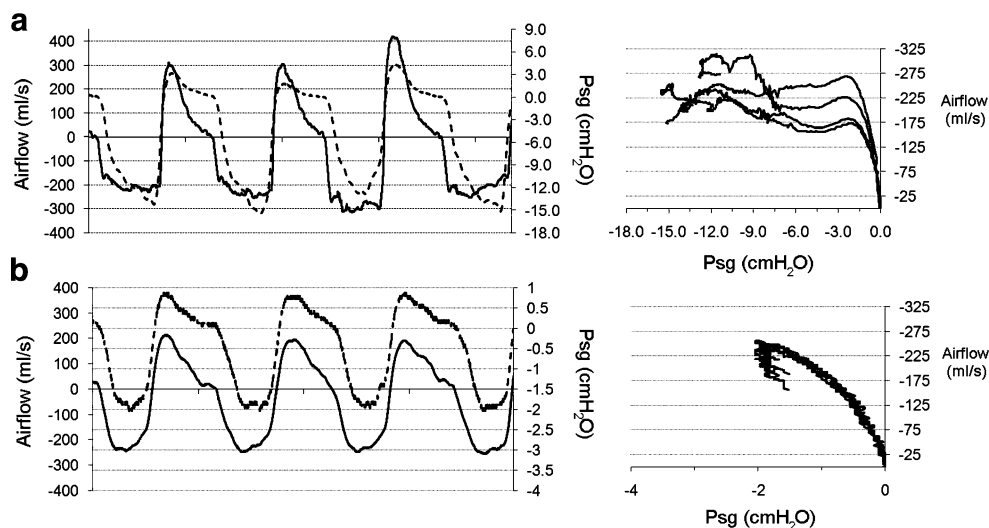
Fig. 1 **a** Demonstrates the airflow (*solid line*) and supraglottic pressure (Psg; *hatched line*) tracings for four flow-limited breaths (from a veteran with GWI) along with the plots of airflow against supraglottic pressure for the breaths (*right panel*). The plots demonstrate the plateau of airflow with decreasing supraglottic pressure and the increased inspiratory effort that characterizes flow-limited inspiration. **b** Demonstrates the same tracings for four non-flow-limited breaths (from a healthy control) along with the plots of airflow against supraglottic pressure for the breaths (*right panel*). The plots demonstrate the absence of a plateau of airflow with decreasing supraglottic pressure and the minimal inspiratory effort characterizing non-flow-limited inspiration

evaluator using a modification of the criteria of Rowley and associates [22]. We defined IFL as a 1-cmH$_2$O or greater decrease in Psg without a corresponding increase in airflow of at least 5 ml/s(Fig. 1). For each participant, the percentage of flow-limited breaths was calculated as the total number of flow-limited breaths divided by total breaths in all the samples.

Masking

Because we analyzed our treatment trial data [23] before we completed recruitment of the control group for this study, we performed a second complete analysis (including staging, arousals, and breathing parameters) of the GWI participants' first PSG's combined with those of our healthy controls by individuals who did not participate in the analysis of the treatment trial (this will explain small discrepancies between studies in the same parameters). Masking of the individual analyzing the PSGs was accomplished by assigning a random number to each PSG, unknown to the individual performing the analysis. During analysis of the pressure-flow plots to determine the presence of flow limitation, the Excel files for both GWI participants and controls were coded and mixed so that the interpreter did not know the status of the file being analyzed,

Statistical analysis

All *p* values were based on unpaired *t* tests. After the initial analysis of our data, the issue of the normality of our respiratory data was raised. To ascertain that statistical significance was robust to departures from normality, we ran a Wilcoxon test to confirm robust statistical significance. Ties were handled by using the average rank and exact *p* values were computed in SAS Version 8.1.

Results

To recruit our cohort of 18 veterans with GWI, we screened 25 potential participants. Two were excluded for having a prior diagnosis of obstructive sleep apnea and five were excluded because of chronic opiate use that could affect breathing during sleep.

The anthropometric and symptoms data characterizing our GWI participants and our healthy controls are represented in Table 1. Our male GWI participants and controls were well-matched for age and BMI. Our GWI participants

Table 1 Anthropometric and symptom data of the GWI participants and healthy controls

	GWI participants mean (SD)	Healthy controls	*p* value
Number of participants	18	11	
Age (years)	42 (4)	41 (6.6)	0.57
Body mass index (kg/m^2)	31 (3)	31 (4.2)	0.72
Cognitive Failure Questionnaire	57.9 (18.1)	14.9 (2.8)	< 0.0001
Pain visual analog scale	4.1 (2.2)	0.7 (0.6)	<0.0001
Fatigue Severity Scale	5.2 (1.4)	1.6 (0.3)	<0.0001

Table 2 Sleep parameters of the GWI participants and healthy controls

Parameter	GWI participants	Healthy controls	p value
Total sleep time (minutes)	333 (95)	329 (75)	0.90
Sleep efficiency (%)	73 (24)	76 (16)	0.66
Sleep latency (minutes)	13 (15)	28 (30)	0.08
REM latency (minutes)	137 (69)	136 (65)	0.97
NREM 1 (%)	29 (17)	22 (14)	0.26
NREM 2 (%)	48 (13)	46 (11)	0.74
Slow wave sleep (%)	12 (9)	17 (11)	0.17
REM (%)	12 (7)	11 (7)	0.73
Arousals/hour	34 (26)	10 (6)	0.006
Total stage shifts	39 (12)	40 (14)	0.89

Table 2 summarizes parameters of sleep architecture and fragmentation based upon the first PSG. GWI participants did not differ from controls in sleep efficiency or duration, latency to sleep onset or REM onset, sleep stage distribution, or total of sleep stage shifts. The GWI participants demonstrated an increased frequency of arousals.

Table 3 details the sleep-related respiratory parameters for the GWI participants and controls. During the first PSG, GWI participants had a significantly increased RERA index and apnea hypopnea index. During the second PSG, one control participant could not tolerate insertion of the supraglottic catheter and the second PSG was not performed (data from the remaining ten controls is presented). During the second PSG, GWI participants had a much higher prevalence of flow-limited breaths in continuous NREM stage 2 sleep.

were above the clinical threshold with moderate levels of cognitive dysfunction, pain, and fatigue while our healthy controls were below the clinical threshold for the same symptoms. Among our 18 GWI participants, eight had co-morbid PTSD, three had depression, and two had irritable bowel syndrome. In addition, five had gastroesophageal reflux disease and five had hypertension. Among our 11 controls, seven had no significant medical history. Two controls had both hyperlipidemia and asthma. One control had hyperlipidemia alone, and one had cholecystitis.

Discussion

Previous research suggests that patients with functional somatic syndromes have a history of exposure to stress and mild sleep-disordered breathing. Veterans who served during the first Persian Gulf War were exposed to a variety of stressors including heat, sleep deprivation, combat stress, and smoke inhalation. In this study, we compared inspiratory airflow dynamics during sleep between veterans of the

Table 3 Sleep-related respiratory parameters in GWI participants and controls

GWI participant	RERA index	AHI	% flow-limited	Control participant	RERA index	AHI	% flow-limited
1	7	7	100	1	1	0	65
2	28	9	100	2	3	0	0
3	38	9	83	3	4	0	13
4	11	61	89	4	6	0	0
5	1	46	100	5	11	0	44
6	11	0	97	6	9	11	32
7	8	7	92	7	5	1	47
8	11	5	100	8	13	3	65
9	15	8	98	9	9	1	62
10	16	10	89	10	2	16	[a]
11	34	38	97	11	7	4	32
12	12	92	100	Mean	6	3	36
13	33	8	94	SD	4	5	25
14	15	7	100				
15	26	3	100				
16	3	9	100				
17	2	9	100				
18	8	2	94				
Mean	16	18	96				
SD	12	25	5				
p value	0.018	0.006	<0.0001				

p values are relative to controls

[a] This control did not tolerate a supraglottic catheter

RERA Index is the number of respiratory event related arousals per hour of sleep AHI is the apnea/hypopnea index; the number of apneas and hypopneas per hour of sleep

% flow limited the percentage of breaths during continuous, supine stage 2 sleep that were flow limited

first Gulf War with GWI and veterans of the same war with no symptoms of GWI. We found that veterans with GWI have an increased frequency of arousals from sleep related to sleep-disordered breathing and that they have a greater prevalence of flow-limited breaths during stage NREM stage 2 sleep, reflecting a more collapsible upper airway. Therefore, similar to patients with other functional somatic syndromes, veterans of the first Gulf War with GWI have both a history of exposure to stress and mild sleep-disordered breathing.

One feature of our study design is worth noting. Consistent with our previous publications, our definition of hypopnea for this study did not include an oxygen desaturation in the absence of an arousal. Recent evidence suggests, however, that a 4% desaturation, even in the absence of an arousal from sleep, may predispose to cardiovascular disease in sleep apnea patients [24]. Although we do not know the effect of our definition of hypopnea on the apnea hypopnea index of our two cohorts, we do know that our definition was applied consistently in the two groups and we trust that the difference we observed in apnea hypopnea index between veterans with GWI and matched controls is a true difference

How to sample a population of veterans with GWI when the definition of GWI has not been established by consensus presents a challenge. Because of the absence of a consensus definition of GWI, we based our definition upon that of the largest multicenter treatment trial for GWI conducted by the VA [16]. To this choice, we added the stringency of documenting the severity of the three defining complaints using validated measures. Finally, all of our participants with GWI were enrolled in the Gulf War Registry with GWI and received care at the Northport DVA Medical Center. Thus, our sample of participants with GWI compares favorably with samples studied previously.

Although our findings demonstrate increased sleep-disordered breathing in veterans with GWI, we cannot be certain of their upper airway function at the time they developed GWI. In the 15 years that have elapsed between the first Gulf War and the start of our study, all of the veterans have aged and many have gained weight. Both age and increasing weight predispose to sleep-disordered breathing. However, our age- and obesity-matched veterans with no symptoms of GWI had a much lower prevalence of sleep-disordered breathing. While we cannot be certain, extrapolating back 18 years to a time when our participants were younger and leaner, we may have found only snoring among our veterans with GWI and no sleep-disordered breathing among our healthy veterans. While we can no longer study inspiratory airflow dynamics during sleep in newly diagnosed veterans with GWI, the veterans now returning from Operation Enduring Freedom and Operation Iraqi Freedom with war-related illness similar to GWI [25–27] provide us with the opportunity to study inspiratory airflow dynamics during sleep in a similar population at the onset of symptoms.

How might war-related stress and sleep-disordered breathing be related to the symptoms of GWI? First, the symptoms of GWI and the functional somatic syndromes, in general, are those that have been attributed to chronic activation of the HPA axis [28–30]. Recent studies in animal models have demonstrated that activation of the HPA axis by stress can sensitize the limbic system of the brain altering its response to internal and external stimuli [31–35] (neural sensitization) [36]. Our findings in this study can be explained with the hypothesis that war-related stress sensitizes the limbic system of soldiers to perceive pharyngeal collapse during sleep as an internal stress. In this way, after their service, veterans with pre-existing pharyngeal collapse during sleep experience nightly exposure to an internal stress while those without pharyngeal collapse do not experience this same nightly stress. One may imagine the relationship of war-related stress and sleep-disordered breathing to GWI through a model of stress-related neural sensitization of the limbic system to pharyngeal collapse.

This cross-sectional study comparing inspiratory airflow dynamics during sleep between veterans with GWI and healthy veterans of the same war suggests that sleep-disordered breathing may contribute to the symptoms of GWI. However, a difference in sleep-disordered breathing between groups does not establish that sleep-disordered breathing contributes to the symptoms of GWI. Moreover, even if sleep-disordered breathing does contribute to the symptoms of GWI, our comparing a group with three symptoms to a control with no symptoms does not allow us to determine which of the symptoms of GWI are related to sleep-disordered breathing. To establish such a relationship requires an appropriately controlled trial of pharyngeal splinting during sleep with monitoring of symptoms.

References

1. Barrett DH, Gray GC, Doebbeling BN, Clauw DJ, Reeves WC (2002) Prevalence of symptoms and symptom-based conditions among Gulf War veterans: current status of research findings. Epidemiol Rev 24(2):218–227

2. Kang HK, Mahan CM, Lee KY, Magee CA, Murphy FM (2000) Illnesses among United States veterans of the Gulf War: a population-based survey of 30, 000 veterans. J Occup Environ Med 42(5):491–501

3. Steele L (2000) Prevalence and patterns of Gulf War illness in Kansas veterans: association of symptoms with characteristics of person, place, and time of military service. Am J Epidemiol 152 (10):992–1002

4. Aaron LA, Buchwald D (2001) A review of the evidence for overlap among unexplained clinical conditions. Ann Intern Med 134(9 Pt 2):868–881

5. Barsky AJ, Borus JF (1999) Functional somatic syndromes. Ann Intern Med 130(11):910–921

6. Heim C, Nater UM, Maloney E, Boneva R, Jones JF, Reeves WC (2009) Childhood trauma and risk for chronic fatigue syndrome: association with neuroendocrine dysfunction. Arch Gen Psychiatry 66(1):72–80

7. Buskila D, Atzeni F, Sarzi-Puttini P (2008) Etiology of fibromyalgia: the possible role of infection and vaccination. Autoimmun Rev 8(1):41–43

8. Paras ML, Murad MH, Chen LP, Goranson EN, Sattler AL, Colbenson KM, Elamin MB, Seime RJ, Prokop LJ, Zirakzadeh A (2009) Sexual abuse and lifetime diagnosis of somatic disorders: a systematic review and meta-analysis. Jama 302(5):550–561

9. Perona M, Benasayag R, Perello A, Santos J, Zarate N, Zarate P, Mearin F (2005) Prevalence of functional gastrointestinal disorders in women who report domestic violence to the police. Clin Gastroenterol Hepatol 3(5):436–441

10. Gold AR, Dipalo F, Gold MS, O'Hearn D (2003) The symptoms and signs of upper airway resistance syndrome: a link to the functional somatic syndromes. Chest 123(1):87–95

11. Rains JC, Poceta JS, Penzien DB (2008) Sleep and headaches. Curr Neurol Neurosci Rep 8(2):167–175

12. Wahner-Roedler DL, Olson EJ, Narayanan S, Sood R, Hanson AC, Loehrer LL, Sood A (2007) Gender-specific differences in a patient population with obstructive sleep apnea-hypopnea syndrome. Gend Med 4(4):329–338

13. Gold AR, Broderick JE, Amin MM, Gold MS (2009) Inspiratory airflow dynamics during sleep in irritable bowel syndrome: a pilot study. Sleep Breath 13(4):397–407

14. Germanowicz D, Lumertz MS, Martinez D, Margarites AF (2006) Sleep disordered breathing concomitant with fibromyalgia syndrome. J Bras Pneumol 32(4):333–338

15. Gold AR, Dipalo F, Gold MS, Broderick J (2004) Inspiratory airflow dynamics during sleep in female fibromyalgia patients. Sleep 27(3):459–466

16. Donta ST, Clauw DJ, Engel CC Jr, Guarino P, Peduzzi P, Williams DA, Skinner JS, Barkhuizen A, Taylor T, Kazis LE, Sogg S, Hunt SC, Dougherty CM, Richardson RD, Kunkel C, Rodriguez W, Alicea E, Chiliade P, Ryan M, Gray GC, Lutwick L, Norwood D, Smith S, Everson M, Blackburn W, Martin W, Griffiss JM, Cooper R, Renner E, Schmitt J, McMurtry C, Thakore M, Mori D, Kerns R, Park M, Pullman-Mooar S, Bernstein J, Hershberger P, Salisbury DC, Feussner JR (2003) Cognitive behavioral therapy and aerobic exercise for Gulf War veterans' illnesses: a randomized controlled trial. JAMA 289(11):1396–1404

17. Broadbent DE, Cooper PF, FitzGerald P, Parkes KR (1982) The Cognitive Failures Questionnaire (CFQ) and its correlates. Br J Clin Psychol 21(Pt 1):1–16

18. Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD (1989) The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. Arch Neurol 46(10):1121–1123

19. Rechtschaffen, A, Kales, A (1968). A manual of standardized terminology, techniques and scoring system for sleep stages of human subjects. (Bethesda: US Dept of Health, Education and Welfare).

20. American Sleep Disorders Association Atlas Task Force (1992) EEG arousals: scoring rules and examples. Sleep 15(2):173–184

21. Hosselet JJ, Norman RG, Ayappa I, Rapoport DM (1998) Detection of flow limitation with a nasal cannula/pressure transducer system. Am J Respir Crit Care Med 157(5 Pt 1):1461–1467

22. Rowley JA, Zhou X, Vergine I, Shkoukani MA, Badr MS (2001) Influence of gender on upper airway mechanics: upper airway resistance and Pcrit. J Appl Physiol 91(5):2248–2254

23. Amin M, Broderick J, Gold M, Gold AR (2008) The effects of nasal continuous positive airway pressure on the symptoms of Gulf War Syndrome. Sleep 31(Abstract Supplement): A159.

24. Punjabi NM, Newman AB, Young TB, Resnick HE, Sanders MH (2008) Sleep-disordered breathing and cardiovascular disease: an outcome-based definition of hypopneas. Am J Respir Crit Care Med 177(10):1150–1155

25. Amin MM, Parisi JA, Gold MS, Gold AR (2010) War-related illness symptoms among Operation Iraqi Freedom/Enduring Freedom returnees. Mil Med 175(3):155–157

26. Hoge CW, McGurk D, Thomas JL, Cox AL, Engel CC, Castro CA (2008) Mild traumatic brain injury in US soldiers returning from Iraq. N Engl J Med 358(5):453–463

27. Hoge CW, Terhakopian A, Castro CA, Messer SC, Engel CC (2007) Association of posttraumatic stress disorder with somatic symptoms, health care visits, and absenteeism among Iraq war veterans. Am J Psychiatry 164(1):150–153

28. Chang L (2006) Neuroendocrine and neuroimmune markers in IBS: pathophysiological role or epiphenomenon? Gastroenterology 130 (2):596–600

29. Martinez-Lavin M, Vargas A (2009) Complex adaptive systems allostasis in fibromyalgia. Rheum Dis Clin North Am 35(2):285–298

30. Tanriverdi F, Karaca Z, Unluhizarci K, Kelestimur F (2007) The hypothalamo-pituitary-adrenal axis in chronic fatigue syndrome and fibromyalgia syndrome. Stress 10(1):13–25

31. Antelman SM, Eichler AJ, Black CA, Kocan D (1980) Interchangeability of stress and amphetamine in sensitization. Science 207(4428):329–331

32. del Rosario CN, Pacchioni AM, Cancela LM (2002) Influence of acute or repeated restraint stress on morphine-induced locomotion: involvement of dopamine, opioid and glutamate receptors. Behav Brain Res 134(1–2):229–238

33. Haney M, Maccari S, Le Moal M, Simon H, Piazza PV (1995) Social stress increases the acquisition of cocaine self-administration in male and female rats. Brain Res 698(1–2):46–52

34. Kawakami SE, Quadros IM, Takahashi S, Suchecki D (2007) Long maternal separation accelerates behavioural sensitization to ethanol in female, but not in male mice. Behav Brain Res 184 (2):109–116

35. Salzberg M, Kumar G, Supit L, Jones NC, Morris MJ, Rees S, O'Brien TJ (2007) Early postnatal stress confers enduring vulnerability to limbic epileptogenesis. Epilepsia 48(11):2079–2085

36. Bell IR, Miller CS, Schwartz GE (1992) An olfactory-limbic model of multiple chemical sensitivity syndrome: possible relationships to kindling and affective spectrum disorders. Biol Psychiatry 32(3):218–242