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STudy of Active Duty Military for Pulmonary Disease Related to Environmental Deployment Exposures (STAMPEDE)

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"At a Glance Commentary" – This study represents the first prospective evaluation of new onset respiratory symptoms in deployed military personnel. Most published literature currently describes increases in symptoms without determining underlying causes. It provides a more comprehensive evaluation of symptoms and determined that airway hyperreactivity is the most common finding identified in this population. Many individuals did not have a readily identifiable cause during their initial evaluation. Sleep and/or mental health disorders may play a role in their underlying respiratory symptoms.

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ABSTRACT

Rationale: Due to increased levels of airborne particulate matter in Southwest Asia, deployed military personnel are at risk for developing acute and chronic lung diseases. Increased respiratory symptoms are reported, but limited data exists on reported lung diseases.

Objective: To evaluate new respiratory complaints in military personnel returning from Southwest Asia to determine potential etiologies for symptoms.

Methods: Returning military personnel underwent a prospective standardized evaluation for deployment-related respiratory symptoms within six months of returning to their duty station.

Measurements: Prospective standardized evaluation to include full pulmonary function testing, high resolution chest tomography, methacholine challenge testing, and fiberoptic bronchoscopy with bronchoalveolar lavage. Other procedures to include lung biopsy were performed if clinically indicated.

Main Results: Fifty patients completed the study procedures. A large percentage (42%) remained undiagnosed including 12% with normal testing and an isolated increase in lavage neutrophils or lymphocytes. Twenty (40%) patients demonstrated some evidence of airway hyperreactivity to include eight who met asthma criteria and two with findings secondary to gastroesophageal reflux. Four (8%) additional patients had isolated reduced diffusing capacity and the remaining six had other miscellaneous airway disorders. No patients were identified with diffuse parenchymal disease on the basis of computed tomography imaging. A significant number (66%) of this cohort had underlying mental health and sleep disorders.

Conclusions: Evaluation of new respiratory symptoms in military personnel after service in SWA should focus on airway hyperreactivity from exposures to higher levels of ambient particulate matter. These patients may be difficult to diagnose and require close follow-up.

Word Count = 250

INTRODUCTION

Concerns have been raised about health effects related to deployment of military personnel to Southwest Asia (SWA) in support of combat operations during Operations Iraqi Freedom/Enduring Freedom (OIF/OEF). The effect of deployment on the respiratory health of military personnel remains an active issue[1]. These conflicts are unique due to environmental exposures from suspended geologic dusts, burn pits for waste disposal, and localized exposures such as the Al-Mishraq sulfur fire. United States Army environmental sampling demonstrated that military personnel were exposed to increased levels of airborne particulate matter (PM) consisting primarily of geologic dusts exceeding current exposure guidelines[2]. Based on limited evidence, the Armed Forces Health Surveillance Center concluded there was no increased risk for respiratory diseases associated with exposure to burn pits[3]. The 2011 Institute of Medicine report also concluded increased PM was a concerning issue, but there was insufficient evidence of an association between exposures and disease outcomes[4].

Documented increases in non-specific respiratory symptoms have been reported during SWA deployments. Survey research five years after the conclusion of the First Gulf War identified a modest correlation in self-reported symptoms of asthma and bronchitis in 1560 veterans, but findings did not correlate with modeled oil fire exposures[5]. Initial results from a Navy survey of 15,000 military personnel estimated that 69% of deployed personnel experienced respiratory illnesses, of which 17% required medical care[6]. Additional data from the Millennium Cohort Study found deployed personnel had higher rates of newly reported respiratory symptoms than non-deployed personnel (14% vs. 10%), with similar rates of chronic lung disease[7].

A 2011 case series reported unusual findings among deployed soldiers from Fort Campbell with varied exposures to the Al-Mishraq sulfur fire; 78% (38/49) of patients who underwent surgical lung biopsy were reported to have pathologic evidence of constrictive

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bronchiolitis (CB) described to involve a significant percentage of the small airways[8]. Despite these findings, spirometry was generally normal with only 16% having obstructive or restrictive indices; chest radiography (CXR) was normal in 37/38 patients while high resolution computed tomography (HRCT) showed "mild air trapping" in 16%. An epidemiologic cohort study of 191 exposed soldiers, however, demonstrated no increase in post-deployment medical encounters among personnel exposed to the sulfur fire[9].

A 2010 Working Group on post-deployment respiratory issues recommended pulmonary referral for chronic symptoms, reduction in exercise tolerance, abnormal pulmonary function testing, comprehensive evaluation; and potential consideration for lung biopsy in patients on an individualized basis[10]. Due to predominantly retrospective studies and surveys with limited data on post-deployment respiratory disease, the Department of Defense initiated clinical research studies to examine respiratory effects of deployment. The objective of this study was to conduct a preliminary evaluation of returning military personnel to establish etiologies for new onset respiratory symptoms after service in SWA.

METHODS

This prospective evaluation was approved by the Brooke Army Medical Center Institutional Review Board (#363715) and all study participants provided written informed consent. Subjects were active duty military personnel recruited after deployment to Iraq/Afghanistan beginning in July 2010. All individuals had returned in the previous six months and reported new onset pulmonary symptoms. Individuals with a pre-deployment medical history of pulmonary or cardiac disease were not enrolled. Participants first completed a deployment questionnaire detailing deployment history, airborne exposures, smoking, pulmonary symptoms, and medical treatment. Initial laboratory examination consisted of a complete blood

count to evaluate for anemia and eosinophilia. Radiographic imaging included a standard posteroanterior and lateral CXR and chest HRCT (1 and 3 mm intervals) with expiratory and inspiratory views.

Participants performed a baseline spirometry exam using a VMax spirometer (CareFusion, Yorba Linda, CA). They underwent a standard forced expiratory maneuver from maximal inhalation to maximal exhalation to record the forced expiratory volume at one second (FEV_1), and forced vital capacity (FVC) in accordance with American Thoracic Society standards for spirometry. Reference values were taken from NHANES III[11]. All patients were given two puffs of levalbuterol to measure FEV_1 improvement post-bronchodilator (BD). Lung volumes were determined using VMax body plethysmography (CareFusion, Yorba Linda, CA) to determine total lung capacity (TLC) and residual volume (RV) values. The diffusing capacity for carbon monoxide (DLCO) was determined using the single breath technique on the VMax spirometer (Carefusion, Yorba Linda, CA) and interpreted according to 1993 European Respiratory Society reference values[12].

Three replicate measurements of oscillatory resistance were obtained using system software (CareFusion MasterScreen IOS, Jaeger/Toennies). For measurement of respiratory resistance, participants were asked to breathe quietly for 15 to 20 seconds using a rigid oval mouthpiece while supporting both cheeks. Measurements of R5 (total respiratory resistance), R20 (proximal resistance), X5 (distal capacitive reactance), Fres (resonant frequency), and AX (reactance area) were recorded. Post-BD values were also recorded after administration of an inhaled levalbuterol[13].

Participants undergoing methacholine challenge testing (MCT) were required to be off pulmonary medications for one week. Increasing doses of methacholine were administered at

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the following concentrations: normal saline, 0.0625 mg/ml, 0.25 mg/ml, 1.0 mg/ml, 4 mg/ml, 8 mg/ml, and 16 mg/ml. Each dose was administered via five breaths through a Salter model 0700 dosimeter (Salter Labs, Arvin, CA) using an inspiratory time of 0.6 seconds. After each dose, the subject waited three minutes and performed two FVC maneuvers. This was repeated for all methacholine concentrations until maximal concentration or a 20% drop in the FEV_1. If there was a 20% decrease in FEV_1, patients received two puffs of levalbuterol followed by repeat FVC maneuvers. The bronchoprovocation test was considered positive with 20% decrease in FEV_1 at a dose of 4 mg/ml or less[14].

Participants underwent flexible fiberoptic bronchoscopy (FOB) with conscious sedation to examine the airways and obtain a bronchoalveolar lavage (BAL) sample. After standard airway preparation with topical and nebulized lidocaine, patients were given conscious sedation with intravenous midazolam and fentanyl. Fiberoptic bronchoscopy (Olympus 160, Olympus America, Center Valley, PA) entailed an airway survey, BAL of the right middle lobe with three 60 ml aliquots of isotonic saline. From the collected BAL, a 10 ml aliquot was sent for standard cell count independently conducted by two cytopathologists at study completion to provide a mean population of cells (macrophages, lymphocytes, neutrophils, and eosinophils). Normal ranges were identified from published values[15]. Thirty ml of BAL fluid were sent for flow cytometry to identify lymphocyte subpopulations. The remaining BAL supernatant (along with serum and urine samples) was centrifuged and stored at -70º C for future analysis.

The primary investigators in this study (MM, PL) reviewed all available clinical data provided to determine the clinical diagnosis. This included cardiopulmonary exercise testing (CPET), exercise laryngoscopy, and additional imaging studies when indicated. A diagnosis of asthma was established with baseline obstructive spirometry, a 12% increase in post-BD FEV_1,

or reactive MCT in accordance with current asthma guidelines[16]. A diagnosis of nonspecific airway hyperreactivity (AHR) was established in patients with normal baseline spirometry, BD response less than 12%, reactive MCT above 4 mg/ml, or evidence increased airway resistance based on IOS criteria (R5 greater than 150% predicted and X5-X5 predicted less than -1.5). In those patients with normal full PFTS, lack of AHR, normal imaging studies, and normal BAL cell count, a specific diagnosis was not established.

Statistical analysis was performed using commercially available software (SPSS, version 16). Data are expressed as mean ± SD, unless otherwise noted. Statistical comparison for gender differences was performed with a t-test for the following variables, FVC (% predicted), FEV_1 (% predicted), FEV_1/FVC (actual), RV (% predicted), TLC (% predicted) and DLCO (% predicted). Post hoc analysis was performed if the primary analysis failed to reach significance. Impulse oscillometry values (pre and post bronchodilator) were compared using a paired t-test. Cell count differentials were compared using the Kruskal-Wallis test. P values less than 0.05 were considered significant.

RESULTS

Fifty consecutive patients who met inclusion criteria completed the protocol. The group was 80% male (n=40) and 20% female (n=10) and race consisted of 58% Caucasians, 24% Hispanics and 18% African-Americans. Mean age was 31.9 ± 8.4 years and body mass index was measured at 28.6 ± 4.3 kg/m^2. The majority of the group (58%) never smoked and 26% were previous smokers. Active smokers comprised 16% and averaged 0.5 packs per day. Mean cigarette use for all smokers was 5.3 ± 6.6 pack years.

Deployment surveys were completed by 42 of 50 (84%) participants. Deployment

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location included Iraq (64%), Afghanistan (24%), and both countries (9.5%) with mean deployment of 11.7 ± 3.6 months. Less than half (45%) reported previous military deployments in support of OIF/OEF with an average of 1.6 ± 0.7 deployments per individual with multiple deployments. General types of airborne hazard exposures included sandstorms and blowing dust (97%), burn pit smoke (92%), smoke/vehicle exhaust (86%) and various chemicals (52%). Thirty-four (81%) individuals responded to questions on frequency and severity of exposures (Exposure: 1-occasionally, 2-regularly and 3-continuously; Severity: 0-none, 1-mild, 2-moderate, 3-severe) and is shown in Table 1. Airborne dust/sand had the highest frequency (2.55 ± 0.50) and severity (1.71 ± 0.68) of exposure. The percentage who reported exposure-related respiratory symptoms and medical evaluations is also detailed.

During deployment, 14% reported evaluation and treatment for "asthma" symptoms, 14% upper respiratory infections, 10% acute bronchitis, 5% influenza symptoms, and 21% rhinitis. The study cohort reported 1.4 ± 2.0 medical visits while deployed. Prior to study evaluation, seven patients reported asthma medication use and 11 used daily allergy medications. There were continuous increases in all symptoms during deployment that continued post-deployment until study evaluation (Figure 1). Additional confounding sleep and psychiatric medical issues were identified. Fifty percent of patients were evaluated for insomnia and 22% were diagnosed with obstructive sleep apnea based on objective testing. Sixty-eight percent of patients were evaluated for a mental health disorder and 54% had multiple diagnoses. Frequency of diagnoses included anxiety (42%), depression (42%), adjustment disorder (42%), post-traumatic stress disorder (32%) and traumatic brain injury (12%).

All patients completed full pulmonary function testing (PFT) (except two patients without lung volumes and DLCO) as shown in Table 2. A significant difference between males

and females was shown for FEV_1 (% predicted), p = 0.03, and FVC (% predicted), p = 0.006. Baseline obstruction was present in eight (16%) patients. Two patients had moderate obstruction (FEV_1 < 70%) and six with mild obstruction (FEV_1 > 70%). In three patients, the FEV_1 > 90% predicted. A total of 37 patients completed post-BD testing (mean FEV_1% change = 5.5 ± 6.8) and five (14%) had an FEV_1 response above 12%. Lung volume testing identified 13 patients (27%) with a reduction in TLC; 11 had mild severity above 70% and two with moderate severity below 70%. Measurement of residual volume identified three patients with hyperinflation and normal TLC. When interpreted by 1993 reference values and corrected for hemoglobin, 11 patients (23%) had a reduction in DLCO; 10 were mild > 60% and one was moderate.

Laboratory studies identified all patients with normal complete blood counts with white blood cell count of 6.8 ± 2.3 x 10^3, hemoglobin of 14.8 ± 1.2 g/dL, hematocrit of 43.2 ± 3.4% and platelets of 238 ± 41 x 10^3. Cell counts obtained from BAL (n=47) are shown in Table 3 based on diagnosis category. Of the 8 active smokers in the study, only one patient had an elevated neutrophil count of 21% on BAL and was included in the elevated cell count group.

Methacholine challenge testing was performed in 44/50 (88%) of patients to establish the presence of AHR. Thirty-two had negative MCT studies, seven were positive and the remaining five patients had borderline hyperreactivity with a 20% decrease in FEV_1 above 4 mg/ml. Impulse oscillometry data is shown in Table 4. Baseline IOS values were obtained in 46 patients with 23 also obtaining post-BD values. Significant differences were found between measurements of X5, R5, and R20 pre and post-BD. Fourteen patients (30%) were identified with elevated R5 greater than 150% and increased X5 as measured by X5(measured) – X5(predicted) less than -1.5. The majority (86%) of these correlated with diagnoses of asthma and AHR from conventional measures; two patients had slightly elevated R5 or X5 values post-

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BD.

Chest imaging was obtained in all patients with 49/50 (98%) obtaining a HRCT examination. In 37 patients (76%), the HRCT were read as normal. None of the cohort had any diffuse infiltrates or parenchymal changes that warranted lung biopsy. Three patients had focal air trapping on expiratory views only. Incidental pulmonary nodules or calcified granulomata were identified in an additional four patients while two patients also had several subcentimeter mediastinal nodes. Other findings included a left upper lobe nodule, mild peribronchial thickening while another scan had several dilated bronchiectatic airways and parenchymal emphysematous changes consistent with COPD.

Additional studies included exercise laryngoscopy in 11 patients based on spirometry findings (truncated inspiratory FVL) and one patient was diagnosed with vocal cord dysfunction. Cardiopulmonary exercise testing (CPET) was completed in another 11 patients; six patients had a normal study, four had ventilatory limitation to exercise (three diagnosed with AHR, one undiagnosed), and one performed a submaximal study. Results of testing are shown in Table 5 and compared to the symptomatic military cohort evaluated in the 2002 Morris study[17].

From these testing modalities, a preliminary diagnosis was established for the entire patient cohort as shown in Figure 2. The largest percentage of patients remained undiagnosed in 42% of the cohort. This included seven of 21 patients with normal testing and an isolated increase in either neutrophils or lymphocytes on BAL. Thirty-six percent (n=18) of the patients demonstrated evidence of AHR; 16% met criteria for asthma based on baseline obstruction, BD response or a reactive MCT while the remaining 20% had nonspecific AHR. Two patients had symptoms, upper airway and PFT findings consistent with AHR secondary to gastroesophageal reflux. Four additional patients (8%) had an isolated reduced DLCO without other findings (one

current smoker, two former). Miscellaneous causes were identified in six patients as shown in Figure 2. Distribution of diagnoses for identified sleep disorders was similar for both undiagnosed (62%) and diagnosed (52%) patients. Similarly, mental health disorders were evenly divided between both groups, 69% vs. 67% respectively.

DISCUSSION

Military personnel deployed to Iraq/Afghanistan have been exposed to numerous airborne hazards due to higher levels of ambient PM^2. Reports have implied a direct relationship between deployment PM exposure and development of serious and debilitating chronic pulmonary disease[18]. The current medical literature clearly shows increases in respiratory symptoms in deployed military, but provides minimal longitudinal data on development of chronic lung disease[7]. The 2011 Institute of Medicine report reached a similar conclusion and noted the lack of PFT data in deployed individuals[4].

This study represents a preliminary systematic evaluation of deployed military personnel for deployment-related respiratory symptoms and evidence of lung disease. A large percentage (42%) had a non-diagnostic evaluation suggesting that symptoms may be non-specific and not necessarily indicate underlying lung disease. The majority of patients with a clinical diagnosis had evidence of asthma or nonspecific AHR. Whether this was a transient mild AHR caused by airborne exposures or chronic asthma merely aggravated by deployment exposures is beyond the study objective and requires more longitudinal data. There was also no evidence of any diffuse interstitial changes to suggest an ongoing subacute interstitial process. Furthermore, none of this cohort had CB based on the established the clinical definition of fixed airway obstruction with hyperinflation and mosaicism on chest imaging[19]. There is a possibility that some patients with isolated findings may have had pathological evidence of CB if a surgical lung biopsy was

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performed. However, we chose to clinically follow these patients for worsening symptoms and/or evidence of physiologic or radiographic changes.

There were reported increases in respiratory symptoms during deployment in Operations Desert Shield/Storm. Investigators found increases in reported symptoms of airway irritation, dyspnea, and cough associated with proximity to Kuwaiti oil fires. Symptoms generally resolved exposure ceased; no long term follow-up was conducted[20]. Further survey research in a cohort of 1560 veterans did not find correlation in self-reported symptoms of asthma and bronchitis with modeled proximity exposures[5]. Another evaluation of Gulf War veterans 10 years post conflict did not show an increased prevalence of clinically significant pulmonary abnormalities[21].

The current military deployments are very unique in terms of different PM exposures, longer in duration, and repeated deployments required of military personnel. Identification of specific individual PM exposures is difficult due to deployment locations, movement, and job tasks related to exposures. Survey results from 15,000 redeploying personnel estimated 69.1% report experiencing respiratory illnesses, of which 17% required medical care[6]. Millennium Cohort Study data of follow-up surveys of 46,077 military personnel (10,753 deployed) found higher rates of newly reported respiratory symptoms in deployed personnel (14% vs. 10%), with similar rates of chronic bronchitis/emphysema and asthma. Deployment was associated with increased respiratory symptoms independently of smoking status[7]. Short term respiratory health effects have not been identified. Epidemiologic research of PM surveillance sites found no association with increased PM exposures and acute cardiorespiratory events requiring medical encounters[22].

Notably, a significant percentage of our patients remained undiagnosed despite a thorough evaluation. The normal finding in 30% parallel the findings in the 2002 Morris study

where 25% remained undiagnosed despite a more comprehensive evaluation[17]. Additionally, these findings are consistent with other studies in patients who have undergone a similar systematic workup including with clinically unremarkable findings[23]. Dyspnea can be very subjective and may be multi-factorial to include underlying lung disease, physical conditioning, smoking, and other factors such as anxiety and hyperventilation[24]. Persons characterized by elevated anxiety may also present with medically unexplained dyspnea[25]. Important in the evaluation of deployed military personnel are underlying mental health and sleep disorders that may contribute to symptoms. Two-thirds of our overall patient cohort and those with unexplained dyspnea were diagnosed with these disorders. The contribution of these disorders to chronic respiratory symptoms in our cohort was undetermined and not readily identified during a pulmonary evaluation. Another potentially confounding factor in evaluating respiratory symptoms in deployed service members is the higher rate of tobacco use in the military and its increased use during deployment[26, 27]. However, our limited cohort did not report the same levels of cigarette smoking as previously reported.

Despite accession standards which exclude individuals with an established diagnosis of asthma over the age of 12 from military service, asthma remains a common finding in the military population[28, 29]. While asthma may be a disqualifying diagnosis, some asthma patients are given a medical waiver to enter military service, while other asthmatics are retained. Data obtained from new Army recruits identified 14% with asymptomatic AHR based on spirometric findings and exercise testing[30]. Several deployment studies have noted asthma to be a common finding. A survey of deploying Army personnel identified 5% deployed to SWA reported a previous diagnosis of asthma[31]. A limited ICD-9 review of over 6000 VA medical records noted higher rates of asthma (6.6% versus 4.3%) in deployed military between 2004 and 2007

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compared to non-deployed personnel[32]. An in-depth review on asthmatics undergoing fitness for duty evaluations identified 25% of patients were diagnosed post-deployment with no differences in PFT or asthma severity shown[33]. The significant percentage of patients with either asthma or nonspecific AHR in this study concurs with previous findings[17]. Given the effects of geologic dusts and increased smoking associated with deployment, any evaluation of deployed individuals should begin with testing to identify asthma.

The 2011 publication by King et al. reported significant numbers of returning military personnel with respiratory symptoms and CB was the leading cause of respiratory illness in these individuals[8]. It is a rare diagnosis associated with environmental and occupational inhalation exposures such toxic fumes, irritant gases (sulfur dioxide), dusts, or volatile flavoring agents[34]. Constrictive bronchiolitis has been characterized by fixed airways obstruction and fibrosis of the distal airways or bronchioles[19], with irreversible obstruction and hyperinflation on PFTs, and HRCT evidence of air trapping and mosaicism[35, 36]. In the King series, evaluation in these patients was primarily limited to full PFTs, HRCT, and CPET. Methacholine challenge testing was only performed in 32% and no post-bronchodilator testing was reported. Computed tomography imaging likewise only showed "mild air trapping" in 16% and the typical radiographic mosaicism pattern was not described. Additionally, since this histopathologic description of CB did not match physiologic findings and was not responsive to therapy, we could not justify performing biopsies in the absence of HRCT changes.

Military physicians remain aware of the cluster of acute eosinophilic pneumonia cases identified at Landstuhl Regional Medical Center associated with new-onset smoking[37]. Our study did not identify any subacute lung disease such as hypersensitivity pneumonitis despite the increased PM exposure in the deployed military population. Due to the lack of isolated HRCT

findings in our study population, use of HRCT should be generally reserved for patients with PFT abnormalities or indeterminate CXR findings. Furthermore, the use of bronchoscopy and BAL in this study was of very limited value in the absence of HRCT findings. It did allow us to visual the upper airway for evidence of laryngeal disorders or evidence of gastroesophageal reflux, but the mild elevation of cell counts in few patients was of little clinical value. It may represent a resolving subacute process and further testing is planned for the collected BAL to identify inflammatory markers.

CONCLUSION

This study represents the first step in determining various etiologies of pulmonary symptoms in deployed military personnel and focused on those patients with new onset symptoms. While symptoms may be multi-factorial in nature, most post-deployment patients should first be evaluated for evidence of AHR given its prevalence in military populations. With numerous airborne exposures, patients may have aggravated pre-existing asthma or developed new airways disease. Further evaluation should be pursued when the diagnosis remains elusive, but there is little evidence for interstitial or bronchiolar diseases. It may be difficult to establish a specific diagnosis in some patients; additional testing and close follow-up is warranted. Longitudinal studies are being conducted with deployed military to define the potential for chronic pulmonary disorders. Finally, the role of mental health and sleep disorders on symptoms of dyspnea in this population needs further investigation.

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REFERENCES

1. Morris MJ, Zacher LL, Jackson DA. Investigating the respiratory health of deployed military personnel. *Mil Med* 2011; 176 (10):1157-61.
2. Weese CB, Abraham JH. Potential health implications associated with particulate matter exposure in deployed settings in southwest Asia. *Inhal Toxicol* 2009; 21(4):291–96.
3. Armed Forces Health Surveillance Center. Epidemiological studies of health outcomes among troops deployed to burn pit sites. Silver Spring, MD; 2010.
4. Institute of Medicine. Long-term health consequences of exposure to burn pits in Iraq and Afghanistan. Washington, DC: The National Academies Press; 2011.
5. Lange JL, Schwartz DA, Doebbeling BN, Heller JM, Thorne PS. Exposures to the Kuwait oil fires and their association with asthma and bronchitis among Gulf War veterans. *Environ Health Perspect* 2002; 110(11):1141–46.
6. Sanders JW, Putnam SD, Frankart C, et al. Impact of illness and non-combat injury during Operations Iraqi Freedom and Enduring Freedom (Afghanistan). *Am J Trop Med Hyg* 2005; 73(4):713-19.
7. Smith B, Wong CA, Smith TC, Boyko EJ, Gacksetter GS, Ryan MAK. Newly reported respiratory symptoms and conditions among military personnel deployed to Iraq and Afghanistan: A prospective population-based study. *Am J Epidemiol* 2009; 170(11):1433-42.
8. King MS, Eisenberg R, Newman JH, et al. Constrictive bronchiolitis in soldiers returning from Iraq and Afghanistan. *N Engl J Med* 2011; 365(3):222-30.
9. Baird CP, Debakey S, Reid L, Hauschild VD, Petruccelli B, Abraham JH. Respiratory health status of US Army personnel potentially exposed to smoke from 2003 Al-Mishraq sulfur plant fire. *J Occup Environ Med* 2012; 54(6):717–23.

AJRCCM Articles in Press. Published on 12-June-2014 as 10.1164/rccm.201402-0372OC

10. Rose C, Abraham J, Harkins D, et al. Overview and recommendations for medical screening and diagnostic evaluation for post-deployment lung disease in returning US warfighters. *J Occup Environ Med* 2012; 54(6):746-51.
11. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. *Am J Respir Crit Care Med* 1999; 159(1):179-87.
12. Coles JE, Chinn DJ, Quanjer PH, Roca J, Yernault JC. Standardization of the measurement of transfer factor (diffusing capacity). Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. *Eur Respir J* 1993; 16:41-52.
13. Vink GR, Arets HG, van der Laag J, van der Ent CK. Impulse oscillometry: a measure for airway obstruction. *Pediatr Pulmonol* 2003; 35(3):214-19.
14. American Thoracic Society. Guidelines for methacholine and exercise challenge testing, 1999. *Am J Respir Crit Care Med* 2000; 161(1):309–29.
15. Meyer KC, Raghu G, Baughman RP, et al. An official American Thoracic Society clinical practice guideline: The clinical utility of bronchoalveolar lavage cellular analysis in interstitial lung disease. *Am J Respir Crit Care Med* 2012; 185(9):1004-1014.
16. National Heart, Lung, and Blood Institute. Expert panel report 3: guidelines for the diagnosis and management of asthma—full report 2007. August 28, 2007. Available at: www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf.
17. Morris MJ, Grbach VX, Deal LE, Boyd SY, Johnson JE, Morgan JA. Evaluation of exertional dyspnea in the active duty patient: The diagnostic approach and the utility of clinical testing. *Mil Med* 2002; 167(4):281-88.

18. Risen J. Veterans sound alarm over burn pit exposure. New York Times, Aug 6, 2010. Accessed 19 Sept 2010 at http://www.nytimes.com/2010/08/07/us/07burn.html.

19. Epler GR. Constrictive bronchiolitis obliterans: the fibrotic airway disorder. *Exp Rev Respir Med* 2007; 1(1):139-47.

20. Petruccelli BP, Goldenbaum M, Scott B, et al. Health effects of the 1991 Kuwait oil fires: A survey of US army troops. *J Occup Environ Med* 1999; 41(6):433–39.

21. Karlinsky JB, Blanchard M, Alpern R, et al. Late prevalence of respiratory symptoms and pulmonary function abnormalities in Gulf War I veterans. *Arch Intern Med* 2004; 164(22):2488-91.

22. Abraham JH, Baird CB. A case-crossover study of ambient particulate matter and cardiovascular and respiratory medical encounters among U.S. military personnel deployed to Southwest Asia. *J Occup Environ Med* 2012; 54(6):733–39.

23. Wan L, Stans L, Bogaerts K, Decramer M, Van den Bergh O. Sensitization in medically unexplained dyspnea. *Chest* 2012; 141(4):989-95.

24. Parshall MB, Schwartzstein RM, Adams L, et al. American Thoracic Society Committee on Dyspnea. An official American Thoracic Society statement: update on the mechanisms, assessment, and management of dyspnea. *Am J Respir Crit Care Med* 2012; 185(4):435-52.

25. Reid S, Wessely S, Crayford T, Hotopf M. Medically unexplained symptoms in frequent attenders of secondary health care: retrospective cohort study. *BMJ* 2001; 322 (7289):767-69.

26. Bray RM, Pemberton MR, Hourani LL, et al. 2008 Department of Defense survey of health related behaviors among active duty military personnel. *RTI International* 2009/10940-FR.

27. DiNicola, AF, Seltzer DM. Tobacco product usage in deployed male and female military personnel. *Mil Med* 2010; 175(9):vii-viii.

AJRCCM Articles in Press. Published on 12-June-2014 as 10.1164/rccm.201402-0372OC

28. Nish WA, Schwietz LA. Underdiagnosis of asthma in young adults presenting for USAF basic training. *Ann Allergy* 1992; 69(3):239-42.

29. Carson J, Winfield CR. Exercise testing in servicemen with asthma and its application to the assessment of potential recruits. *J R Army Med Corps* 1983; 129(1):14-18.

30. Morris MJ, Schwartz D, Nohrenberg JA, Dooley SN. Asymptomatic airway hyperreactivity in military personnel. *Mil Med* 2007; 172(11):1194-97.

31. Roop SA, Niven AS, Calvin BE, Bader J, Zacher LL. The prevalence and impact of respiratory symptoms in asthmatics and non-asthmatics during deployment. *Mil Med* 2007; 172(12):1264–69.

32. Szema AM, Peters MC, Weissinger KM, Gagliano CA, Chen JJ. New-onset asthma among soldiers serving in Iraq and Afghanistan. *Allergy Asthma Proc* 2010; 31(5):67-71.

33. Delvecchio S, Zacher L, Morris M. Correlation of asthma with deployment in active duty military personnel. *Chest* 2010; 138:145A;doi:10.1378/chest.10873.

34. Myers JL Colby TV. Pathologic manifestations of bronchiolitis, constrictive bronchiolitis, cryptogenic organizing pneumonia, and diffuse panbronchiolitis. *Clin Chest Med* 1993; 14(4):611-22.

35. Parambil JG, Yi ES, Ryu JH. Obstructive bronchiolar disease identified by CT in the non-transplant population: analysis of 29 consecutive cases. *Respirology* 2008; 14(3):443-48.

36. Akpinar-Elci M, Travis WD, Lynch DA, Kreiss K. Bronchiolitis obliterans syndrome in popcorn production plant workers. *Eur Respir J* 2004; 24(2):298-302.

37. Shorr AF, Scoville SL, Cersovsky SB, et al. Acute eosinophilic pneumonia among U.S. military personnel deployed in or near Iraq. *JAMA* 2004; 292(24):2997-3005.

TABLE 1: Reported Frequency and Duration of Airborne Exposures

	Exposure (1-3)	Severity (0-3)	Health Effects	Treatment Visits
Dust/Sand	2.55 ± 0.50	1.71 ± 0.68	17/34 (50%)	7/34 (20.6%)
Burn Pits	2.00 ± 0.85	1.30 ± 0.85	14/34 (41.2%)	4/34 (11.2%)
Vehicle Exhaust	1.85 ± 0.83	0.72 ± 0.77	5/34 (14.7%)	0/34 (0%)
Smoke/Fumes	1.32 ± 1.01	0.80 ± 0.87	6/34 (17.6%)	4/34 (11.2%)

Self-reported exposures and severity based on the following scale. Exposure: 1 - occasionally, 2 - regularly, 3 – continuously; Severity: 0 - none, 1 - mild, 2 - moderate, 3 - severe

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TABLE 2: Pulmonary Function Testing

	ALL	Diagnosed	Undiagnosed	P value	Smoking History	No Smoking History	P value
	N = 50	N = 29	N = 21		N = 21	N = 29	
FEV_1 (% pred)	87.7 ± 12.7	82.2 ± 11.1	94.8 ± 11.7	0.001	85.7 ± 10.7	88.8 ± 14.2	0.20
FVC (% pred)	91.0 ± 13.4	87.0 ± 12.8	96.0 ± 12.8	0.03	90.2 ± 11.4	91.2 ± 14.9	0.39
FEV_1/FVC	79.6 ± 5.8	78.5 ± 6.3	81.0 ± 4.9	0.17	78.1 ± 5.9	80.6 ± 5.6	0.07
TLC (% pred)	90.8 ± 13.1	90.4 ± 14.5	92.0 ± 11.0	0.83	95.3 ± 10.7	87.8 ± 14.0	0.02
RV (% pred)	82.1 ± 31.9	86.0 ± 37.1	75.8 ± 20.4	0.20	93.0 ± 39.1	73.3 ± 21.6	0.02
DLCO (% pred)	89.7 ± 15.2	85.1 ± 15.6	96.1 ± 11.1	0.007	90.5 ± 17.9	88.1 ± 12.2	0.30

FEV_1 – forced expiratory volume at one second; FVC – forced vital capacity; TLC – total lung capacity; RV – residual volume; DLCO – diffusing capacity for carbon monoxide. Comparison of groups (diagnosed vs. undiagnosed; smoking vs. no smoking) was performed using a student's t test.

TABLE 3: Impulse Oscillometry

	Pre-Bronchodilator (N=23)	Post-Bronchodilator (N=23)	P value
R5	4.72 ± 2.44	3.87 ± 2.16	< 0.001
R5 (% pred)	162.4 ± 72.1%	133.1 ± 61.6%	< 0.001
R20	3.83 ± 1.74	3.16 ± 1.33	< 0.001
R20 (% pred)	155.5 ± 59.4%	129.4 ± 46.0%	< 0.001
R5-R20 (% pred)	8.9 ± 24.7	4.1 ± 20.6	0.48
X5	-1.63 ± 0.66	-1.33 ± 0.72	0.003
X5 – X5 Pred	-1.70 ± 0.67	-1.39 ± 0.73	0.004
Fres	17.85 ± 6.63	14.26 ± 4.63	0.007
AX	9.4 ± 8.41	6.26 ± 9.84	0.171

R5 – total airway resistance; R20 – proximal airway resistance, X5 – reactance, Fres - resonant frequency, AX – reactance area. Statistical analysis performed with paired t-test for patients with both pre and post-bronchodilator values (n=23). P values < 0.05 are considered significant.

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TABLE 4: Bronchoalveolar Lavage Cell Counts

	All (n=46)	Diagnosed (n=26)	Undiagnosed (n=13)	Isolated Cell Count (n= 7)	p value
Macrophages	79.2 ± 12.9%	77.2 ± 15.9%	85.6 ± 3.5%	73.9 ± 4.2%	0.004
Lymphocytes	14.2 ± 11.4%	15.5 ± 14.4%	10.8 ± 3.6%	17.0 ± 7.2%	0.19
Neutrophils	5.0 ± 5.8%	5.0 ± 6.2%	3.0 ± 2.4%	8.4 ± 8.0%	0.67
Eosinophils	1.6 ± 4.6%	2.3 ± 6.0%	0.6 ± 1.1%	0.6 ± 0.7%	0.48

Cell counts from bronchoalveolar lavage based on final diagnosis. Undiagnosed includes 13 patients with normal testing and 7 patients with normal testing and an isolated cell count abnormality. Cell count differentials were compared using the Kruskal-Wallis test.

TABLE 5: Cardiopulmonary Exercise Testing

	Current Study (n=11)	Mil Med, 2002[17] (n=104)
Exercise time (min)	11.7 ± 1.3	13.0 ± 2.5
VO_2 Max (% predicted)	111.6 ± 22.4	89.6 ± 15.5
Maximum HR (% predicted)	96.1 ± 8.5	92.7 ± 7.2
VAT (%VO_2 Max)	77.3 ± 20.4	69.9 ± 16.6
HRR (beats/min)	37.7 ± 9.3	39.4 ± 13.0
VE/MVV	89.2 ± 15.4	73.1 ± 13.8
RR (breaths/min)	42.0 ± 6.1	50.2 ± 12.4
VE/VCO_2	30.8 ± 4.3	34.8 ± 5.4
TV/IC	76.4 ± 13.7	82.5 ± 21.8

VO_2 max – maximum oxygen consumption; HR – heart rate; VAT – ventilatory anaerobic threshold; HRR – heart rate response; VE – ventilatory equivalent; MVV – maximal voluntary ventilation; RR – respiratory rate; VE/VCO_2 – ventilatory equivalent for carbon monoxide; TV/IC – Tidal volume/inspiratory capacity

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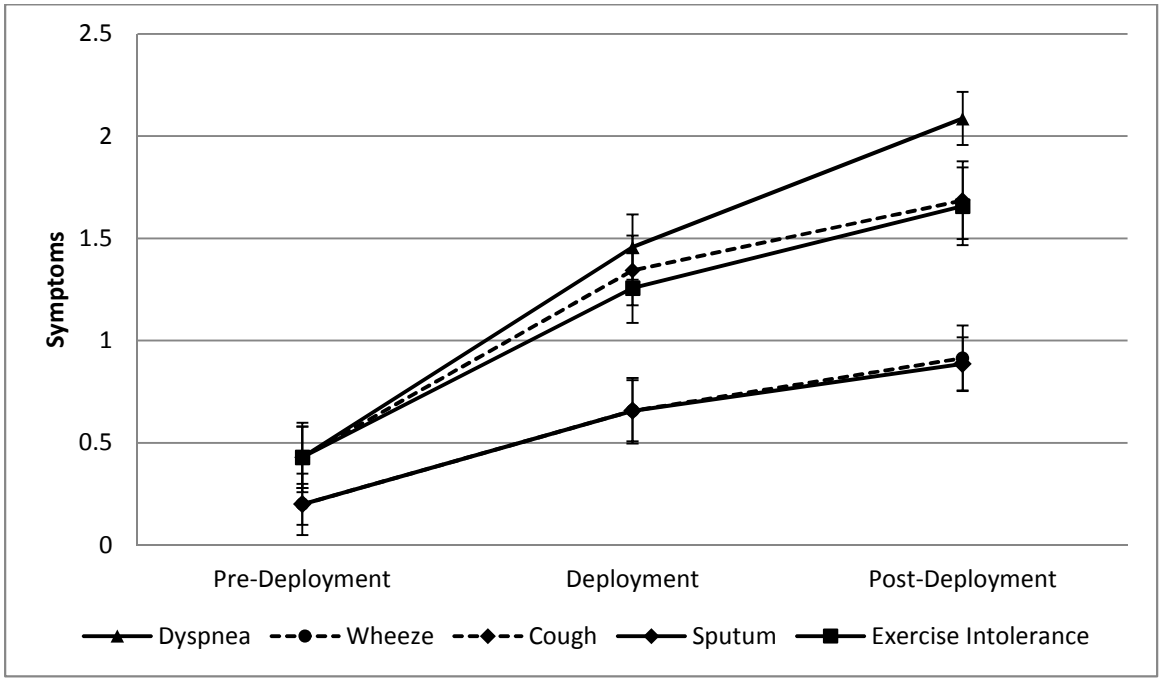

Figure 1: Frequency of self-reported symptoms pre, during and post-deployment reported on the following scale: 0 – Never, 1 - 2x weekly, 2 - 2-5x weekly, 3 – Daily

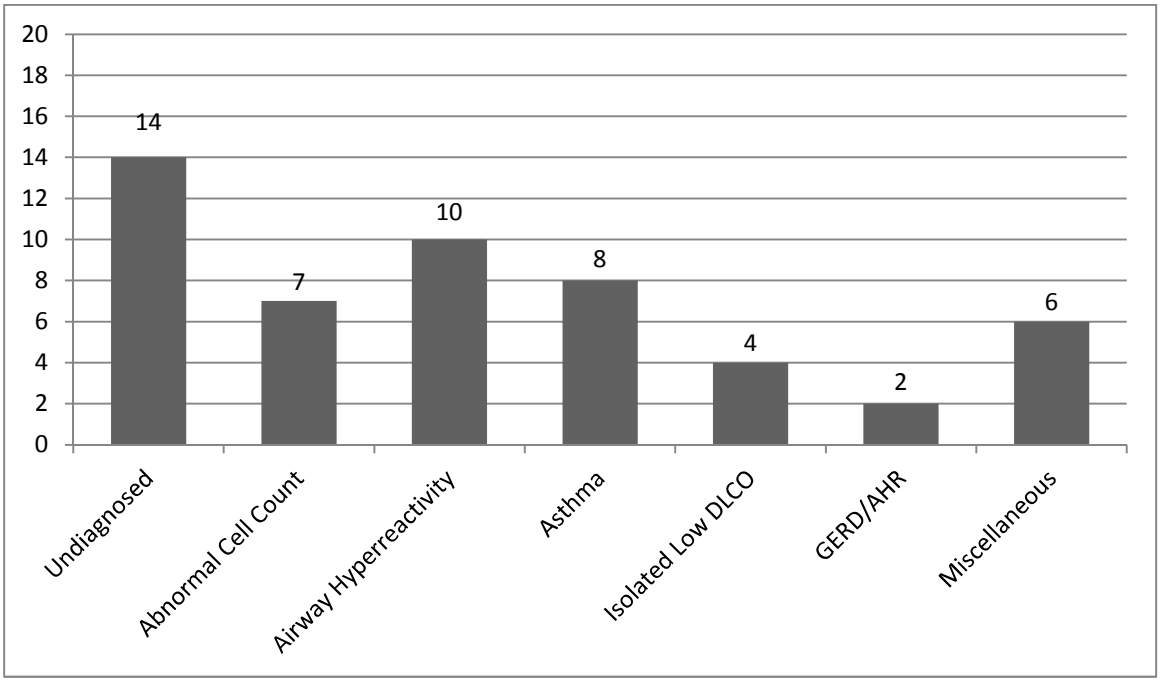

Figure 2: Final Diagnosis

Number of patients with specified clinical diagnoses based on protocol evaluation. Miscellaneous category includes individual patients with the following diagnosis: vocal cord dysfunction (also diagnosed with asthma), chronic obstructive pulmonary disease, lung nodule, fixed airway obstruction, inhalational injury, and isolated air trapping.