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ALLERGIES AND THE ENVIRONMENT (M HERNANDEZ, SECTION EDITOR)

Environmental Exposures and Asthma in Active Duty Service Members

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Abstract

Purpose of Review Reports of respiratory symptoms, including asthma and hyper-reactive airway disease, have been more numerous in the media and medical literature since active duty service members (SM) began to support campaigns in South West Asia (SWA). Numerous environmental exposures have been reported and this review assesses the available evidence surrounding exposures, confounding conditions, and attempts to develop screening mechanisms.

Recent Findings While particulate matter exposures and particularly exposure to burn pits have garnered much attention, a 2010 Armed Forces Health Surveillance Center report and 2011 Institute of Medicine publication did not identify a link between exposure to particulate matter with SM respiratory disease. The "Study of Active Duty Military for Pulmonary Disease related to Environmental Deployment Exposure," (STAMPEDE) and STAMPEDE II have not identified effective forms of routine screening and these and other sources point to the importance of other factors in SM respiratory disease. These include higher than anticipated rates of tobacco use in deployed settings, impacts of obesity, recurrence of childhood asthma, and of confounding conditions such as Paradoxical Vocal Fold Motion.

Summary As with the general population, a complex set of clinical inputs and environmental exposures surround asthma and similar respiratory processes in SM. Concrete relationships and mechanisms for assessment continue to be assessed and refined, but clear associations and pathways have remained elusive.

Keywords Asthma · Burn pit · Paradoxical vocal fold motion · Vocal cord dysfunction · Deployment-associated lung disease · Environmental exposure · Hypersensitivity · Military

Abbreviations

GWOT	Global War on Terrorism
IED	Improvised explosive device
PM	Particulate matter
PVFM	Paradoxical vocal fold motion
SM	Service members
SWA	South West Asia

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There are approximately 1.3 million active duty and 800,000 reservist service members (SM) in the armed services of the USA and over 3.5 million US SM have deployed to the South West Asian (SWA) theater since 2001 [1••, 2]. Due to the physical standards requisite for military service, the active duty population is considered to be generally healthy [3]. Despite this, reports of respiratory symptoms, including asthma and hyper-reactive airway disease, have been more numerous in the media and medical literature since SM began to support campaigns in SWA [4, 5]. These observations are not novel to recent military conflicts as attested to by accounts of respiratory processes affecting combatants in varied theaters of operation stretching into the past [6]. Although recent operations in SWA have directed military medicine's attention towards evaluating, diagnosing, and treating the long-term effects of blast injuries, burn wounds, and post-traumatic stress disorder (PTSD), non-traumatic injury such as respiratory disease, has been an increasing medical symptom of both combat and non-combat military veterans [3]. Respiratory complaints are one of the most common medical symptoms in returning military personnel serving abroad, and recent literature has suggested that particular and specific elements of deployment-related respiratory exposures may be a driving force in the onset of respiratory disease, including asthma [2].

Concern surrounding environmental exposures prompted a 2010 Armed Forces Health Surveillance Center report and a 2011 publication by the Institute of Medicine, neither of which was able to link exposure to particulate matter with SM respiratory disease [7, 8•]. Also in 2010, the Department of Defense developed a Pulmonary Working Group to better understand the different respiratory diseases seen in the post-deployment setting [9]. From this, the original "Study of Active Duty Military for Pulmonary Disease related to Environmental Deployment Exposure," (STAMPEDE) study was published in 2014, a seminal work that sought to provide a comprehensive pulmonary evaluation to SM returning from deployment in SWA with respiratory symptoms [Table 1] [10••].

As these and other concerted efforts have begun to closely examine respiratory processes amongst SM, the complexity of the numerous and varied factors associated with reported illness presents a daunting challenge. Data surrounding late-onset asthma in the general population, including recurrent asthma, obesity, and gender influences; and confounders such as paradoxical vocal fold motion and comorbid psychiatric diagnoses, mirror effects observed in the military population [11, 12••]. Early efforts to effectively screen SM and identify those at increased risk of developing respiratory processes have met with little success [1••]. The expanding understanding of immune effects and of molecular endotypes, as well as emerging sophisticated approaches, such as machine-learning based analysis, may represent future pathways of inquiry [13–15]. We review the most pertinent of the complex network of clinical inputs and exposures to provide an updated understanding of the myriad factors that impact reported asthma and other reactive airway disease in US military service members.

Environmental Exposures

Although US SM are deployed across the globe at all times, the focus of combat deployments since the 9/11 terrorist attacks has been in Afghanistan and Iraq (SWA). Reported respiratory irritants that may be risks for development of asthma or exacerbation of underlying quiescent reactive airway disease in this desert combat environment are numerous. Ambient particulate matter (PM) in the air with augmentation in PM during dust storms is common. Indigenous peoples in SWA use the terms "shamal" and "sharqui" to refer to the northern and eastern seasonal dust storms, which are commonplace [16]. Particulate matter less than 10 μm may cause respiratory injury with symptoms like asthma [16]. This is even more of a concern with PM that is less than 2.5 μm [3]. A 2009 study by Engelbrecht et al. showed that the primary composition of geologic dusts was quartz grains and other sharp mineral grains that were coated with clay particulate iron oxides [17]. Moreover, a 2011 study by King et al. demonstrated that biopsy samples obtained from soldiers deployed in SWA, and undergoing evaluation for subsequent pulmonary

Table 1 Summary of STAMPEDE I and II [1••, 10••]

	STAMPEDE I	STAMPEDE II
Primary objective	- Evaluate new respiratory complaints in service members returning from deployments from SWA to determine potential etiologies.	-Comparison of pre- and post-deployment lung function In service members deployed to SWA.
Method	Prospective study. Standardized evaluation to include OFT, high-resolution chest CT, methacholine challenge testing, fiberoptic bronchoscopy with lavage.	-Prospective study. -Participants completed survey on respiratory health, and performed spirometry and impulse oscillometry pre-and post-deployment.
Results	-50 patients completed all study procedures. • 42% remained undiagnosed. - Airway hyperreactivity was most prevalent finding (40%) - 65% had underlying mental health and sleep disorders.	-1693 personnel completed baseline exam. 443 completed post-deployment exam. -Post-deployment values with no statistical change In spirometry in regard to FEV_1, FVC, or FEV_1/FVC.
Conclusion	In service members returning from SWA with new respiratory symptoms, focus should be placed on airway hyperreactivity.	Routine use of spirometry not recommended before or after deployment in the absence of respiratory symptoms.

Morris Ml. Study of active duty military for pulmonary disease related to environmental deployment exposure (STAMPEDE) American Journal of Respiratory and Critical Care Medicine. 2014;190 (1):7744

Morris MI. Study of active duty military personnel for environmental deployment exposures: pre- and post-deployment spirometry (STAMPEDE II). Respiratory Care. 2019;64 (5):536–544 symptoms, showed polarizable material consistent with inhalation of particulate matter [18]. In 2009, the US Army Public Health Command asserted that the average deployed US SM would have been exposed to levels of ambient PM that exceeded the suggested safe levels as determined by occupational medicine guidelines [5, 19].

The risk of geologic PM as potential driving factor for development of pulmonary disease and asthma is not limited to the most recent US military presence in SWA. During the Gulf War in 1991, concentrations of PM less than 10 μm exceeded the Environmental Protection Agency 24-h exposure maximum threshold by twofold to fivefold on a consistent basis [20]. Moreover, service members exposed to blast injuries, especially improvised explosive devices (IEDs), can have higher levels of exposure to these dusts, and IEDs have been responsible for 36.3% of combat injuries during OIF/OEF [21]. Such findings in SM deployed to SWA is not limited to the US military. NATO allies from across the globe have participated in the Global War on Terrorism (GWOT). A 2017 study on Swedish soldiers serving in Afghanistan showed that not only was there an association between SWA service and respiratory symptoms like asthma, but that there was a dose-dependent relationship with higher prevalence of symptoms with longer time spent deployed in the SWA environment [22]. Interestingly, this same study found that vehicle-borne troops were twice as likely to have respiratory symptoms of wheezing and chest tightness when compared with non-vehicle-borne service members, and suggests that this signal may be due to the increased dusts that are made airborne by the disturbance of the vehicle tires/tracks on the topsoil [22]. It is possible that vehicle-borne troops have higher exposure to combustible fuel exhaust as well, which we address later [23]. Geologic dusts, however, are merely one of the many deployed environmental exposures of concern.

Burn Pits

Emissions from burn pits have been a target of inquiry as an exposure risk for development of pulmonary disease, including asthma [24]. As discussed earlier, in the 2014 STAMPEDE prospective study, Morris et al. evaluated 50 US SM returning from deployment to SWA. Forty-two of 50 participants completed a post-deployment survey and of them, 92% reported exposure to burn pit smoke at a regular to continuous frequency while deployed [10••]. Burn pits refer to the common means of military waste removal used during combat operations in SWA. Waste discarded in these pits included paints, chemicals, human excrement, metals, ordinance, petroleum, rubbers, plastics, food, and ammunition. Often JP-8, or jet fuel, was used as incendiary for these pits. [VA] JP-8 fuel combustion in burn pits releases benzene and other toxins that are readily inhaled [21, 25]. The aerosolized materials that have been identified in burn pit emissions are diverse, will vary based on what is being burned, and include metals, hydrocarbons, aldehydes, and dioxins [Table 2] [8•, 26–28]. Notably and complicating this assessment, there was a correlation in rate of decline in spirometry and concomitant tobacco use, which suggests a benefit of tobacco cessation in these, and all, patients [29].

Small Arms Fire and Explosive Ordinance

US service members serving in the Global War on Terrorism (GWOT) have, similar to other armed conflicts, experienced protracted exposure to explosive materials, mostly in the form of exhaust from small arms fire. The primary infantryman weapon of the US armed forces is the M4 Carbine, a 5.56×45-mm gas-operated weapon. A similar gas-operated carbine, the HK416, was recently evaluated and suggested as a possible cause of respiratory symptoms in soldiers using the firearm in the Norwegian armed forces. In this study, exhaust fumes from the weapon were associated with acute declines in lung function regardless of the type of ammunition used in the rifle [27]. It is conceivable that small arms fire, as well as exhaust from other weapon systems employed by the U.S. military, such as heavy machine guns, mortars, rockets, grenade launchers, and artillery, produces compounds that could contribute to similar effects on lung function, but this has not been rigorously evaluated. A key difference between the GWOT and previous engagements is length. The GWOT is the longest American war and as a result many SM have experienced multiple deployments leading to increased frequency of exposure to many of these

Table 2 Burn pit emissions [8•, 26–28]

Acetaldehyde	Formaldehyde
Acrolein	Furans
Benzene	Lead
Bismuth	Nitrogen dioxide
Carbon monoxide	Polyaromatic hydrocarbons
Copper	Sulfur dioxide
Crystalline silica	Tin
Dioxins	Zinc

Compounds and elements detected in emissions from burn pits. Generated by the burning of products such as paints, chemicals, human excrement, metals, ordinance, petroleum, rubbers, plastics, food, and ammunition environmental risks, such as gunfire emissions. Additionally, urban warfare in SWA has led to close quarters exposure of SM to small-arms exhaust fumes, unlike exposures during past, more conventional military conflicts.

Vehicle Emissions Exposure

During earlier American conflicts, armies walked where they needed to go, and then engaged in direct combat on foot. World War I introduced vehicles directly into combat on a broad scale and the use of vehicles only grew with ensuing conflicts. The modern US military uses vehicles for almost all means of moving forces. Exposure to the products of the combustion engines in these vehicles has been cited as an exposure risk for the development of pulmonary disease, including asthma [30]. In 2008, an observational study was published on a cohort of 40 US Navy sailors who were exposed to 9 continuous hours of contained air circulation exposure to diesel exhaust due to faulty ventilation on a US ballistic missile submarine performing a training exercise under conventional combustible fuel power. The majority of the patients experienced short-term symptoms of reactive airway disease (RAD). In this cohort, corticosteroids were used post-exposure and long-term RAD symptoms were not observed [26]. Though an exposure like on this submarine is an uncommon occurrence, protracted lower dose exposures to diesel and other fuel exhausts are a risk factor for development of asthma and other pulmonary disease. Such effects have also been noted in the broader medical literature with observational and experimental studies demonstrating a link between diesel exhaust particles and asthma in the general population [31, 32]. As with other populations, SM exposed to exhaust leaks should be evaluated and monitored for adverse respiratory outcomes.

Diving

The diving community in the US Navy is a small one, but anecdotal reports of respiratory symptoms, including asthma symptoms, as well as reports from the civilian diving community, have raised the concern that military divers may be at increased risk for gradual reduction in pulmonary function and asthma [33]. It is known that the hyperbaric environment of diving challenges the lung through increased ambient pressure, changes in pulmonary circulation, and changes in characteristics of inhaled gasses. Hyperoxia can cause oxidative stress and increased density and pressure of other gasses, including nitrogen, both of which can lead to airway inflammation [34]. In contrast, a 2017 review of 18 longitudinal studies on lung function in both military and civilian divers was unable to demonstrate a risk for accelerated loss of long function, including FEV1 [34]. This finding was consistent with earlier assertions that diving does not appear to have a significant deleterious effects on SM's lung function [33]. Nonetheless, exposure to diving, represents a small subpopulation and merits continued attention to reported symptoms and respiratory effects.

Tobacco Use

A relevant exposure risk for pulmonary disease and asthma in the general population that is found at higher prevalence in the military is tobacco use. The most recent CDC estimates suggest that 14% of Americans over the age of 18 currently smoke cigarettes, with 15.8% of men and 12.2% of women reporting that they actively smoke [35]. This rate is significantly higher in military veterans, with 21.6% of SM reporting cigarette use [36]. The most recent Department of Defense Health Related Behaviors Survey of Active-Duty Service Members reported that the rate of smoking in active duty SM has decreased, to 13.9%, and is closer to the most recent general civilian population rate. While this may be true of the military as a whole, the reported rate of regular cigarette smoking during deployment was found to be 28%, more than double the rates reported in the civilian and general military SM populations [37]. The rate of smoking amongst military SM was greatest in the Army, when compared with other branches of service [38]. Although the overall rates of smoking and tobacco use in the military are declining with the general population, the use of these products at a substantially increased rate is unique to SM during deployment and represents a significant risk factor for the development or exacerbation of pulmonary disease and asthma in SM.

Clinical Confounders

As noted above, the average deployed SM has many occupational risks that may contribute to the diagnosis of asthma and reactive airway disease. Proper identification of these risk factors is paramount when reviewing the clinical history of the recently deployed SM. Asthma is a heterogeneous disease and it is now commonly understood that this disease state has many phenotypic presentations [14, 39]. Similar to the evaluation for asthma in the non-deployed and general population, there are many mimickers of the disease that make proper diagnosis sometimes difficult [40]. There is an extensive list of potential confounders, but when the diagnosis of asthma is blurred, or if a patient with asthma has symptoms despite appropriate therapy, these diagnoses should be considered [40]. We present some of the more common forms of these conditions.

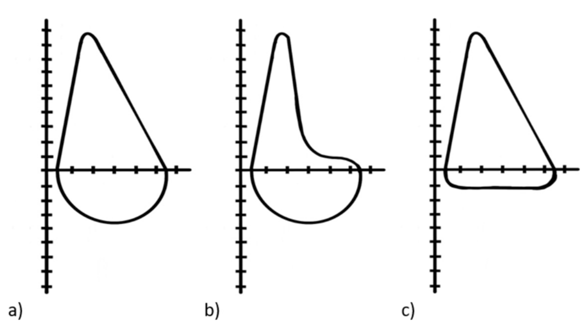
Paradoxical vocal fold motion

Paradoxical vocal fold motion (PVFM), also commonly referred to as vocal cord dysfunction, is a disorder characterized by the paradoxical adduction of the vocal cords during inspiration leading to airflow obstruction, due to a hyper-responsive larynx secondary to organic and irritant triggers [41]. This hyper-responsive larynx causes narrowing of the laryngeal airway which can manifest as a wheeze or stridor, commonly leading to a misdiagnosis of asthma and inappropriate therapy [42]. Clinical history should reveal dyspnea and noisy breathing, similar to asthma, and often times leads to formal spirometric testing [Fig. 1] [41]. To further complicate the clinical picture, asthma and PVFM can co-exist making clinical diagnosis difficult [43]. Although inspection of the flow-volume curve, obtained during spirometry, may reveal a truncated inspiratory limb suggesting PVFM, this is not always consistent with the diagnosis and should not preclude providers from pursuing laryngoscopy for direct assessment of the vocal cords [Fig. 2] [41]. The exact mechanism of this disease has not been completely described; however, common triggers of PVFM have been appreciated, to include but are not limited to exercise, environmental irritants, gastroesophageal reflux, psychiatric conditions, and stress [42]. Morris et al. published a retrospective study evaluating 48 active duty military personnel with a new diagnosis of PVFM post-deployment and found symptoms were secondary to stress/anxiety (35%), exercise (24%), or a combination of both (16%). There was environmental exposure present in 15/48 subjects, which create an environment to allow for PVFM to thrive, and this diagnosis should remain on the differential when SM return with respiratory symptoms following deployment [44]. In peace-time, SM are often placed under large amounts of stress due to the high demands/expectations of daily physical fitness requirements, high-intensity positions, and long working hours. These demands are exaggerated and largely exacerbated during deployments; which may cause respiratory symptoms mimicking asthma [42, 45]. Management of PVFM largely focuses on speech therapy, with training on special breathing techniques such as pursed-lip breathing and abdominal breathing [43]. Addressing the trigger is also a necessity such as treating the underlying GERD or post-nasal drip with medications and evaluation by psychiatry for behavioral processes [43].

Psychiatric Comorbidities

Asthma has been shown to be associated with higher rates of depression and anxiety as compared with the general population [46]. This was examined in depth in the Israeli Army in 2007, where nationals are required by law to serve in the military. They evaluated over 195,903 recruits; and found a 7.8% prevalence of asthma with an increased likelihood of mental disorder [47]. This association between mental health disorders and respiratory disease was also identified in the US military personnel. In a retrospective cohort study of 182,338 veterans returning from OEF/OIF, the odds of being diagnosed with any respiratory disease was significantly increased if the patient had a mental health diagnosis [48]. As noted above, many underlying psychiatric diagnoses can trigger PVFM, but also may cause other respiratory symptoms in the absence of PVFM.

Psychogenic cough has been described as a chronic cough that cannot be explained by a physiologic etiology, sometimes triggered by fatigue and sleep deprivation [46]. Patients with psychogenic cough have normal spirometry, and often have absence of symptoms at night when sleeping, a key differentiation as compared to asthma [46]. Treatment entails providing reassurance to the patient that there is no serious condition causing the cough, and removal of stressors that may trigger the cough [46]. This may be difficult at times in the deployed setting, when stressors are often increased.



Flow-Volume Loops	Key Features
Figure a) Normal	Graphical analysis of expiratory flow (above the x-axis) and inspiratory flow (below the x-axis).
Figure b) Obstructive Lung Disease	Classic scooping of the expiratory limb seen in obstructive lung disease due to increased airway resistance.
Figure c) Paradoxical Vocal Fold Motion	Truncation of the inspiratory limb.

Fig. 1 Review of spirometry and flow-volume loops. Modified from Pellegrino et al. [58]

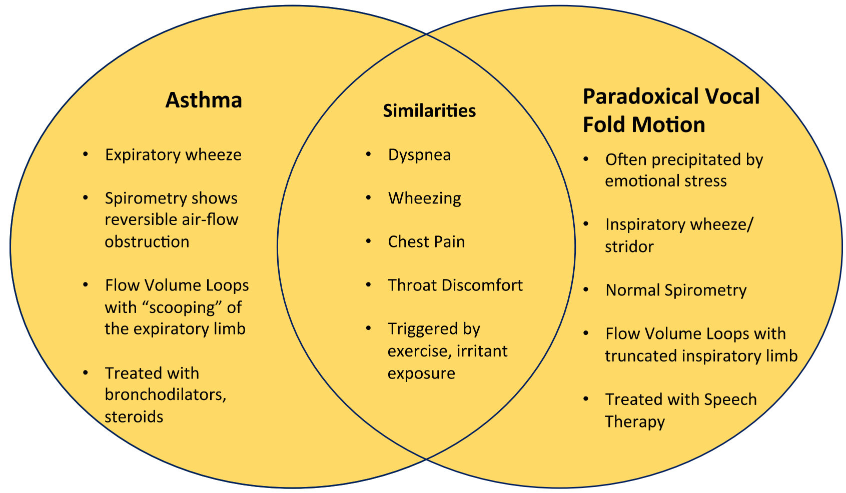


Fig. 2 Differentiation and overlap of paradoxical vocal fold motion and asthma. Data from Fretzayas et al.[58]

Hyperventilation syndrome is an entity described by tachypnea, often driven by a psychiatric process such as anxiety that leads to a respiratory alkalosis, hypocarbia, and subsequent symptoms [40]. Patients may experience tachypnea, chest discomfort, and sometimes syncope as a result. Diagnosis of this process is made by having the patient voluntarily hyperventilate for 90 seconds to assess if symptoms are provoked [46]. Treatment of this process includes but is not limited to cognitive behavioral therapy and psychotherapy and may require psychotropic medications [46].

Obesity

The active duty military requires their SM to remain in peak physical condition, maintaining physical appearance and height/weight standards. By design, it is not expected that obesity would be a commonplace in the military. However, in the original STAMPEDE study, the average body mass index was 28.6 ± 4.kg/m^2 [10••]. Elevated BMI alone can increase respiratory symptoms via reduced forced vital capacity and FEV1, but preserved FEV1/FVC ratio. Complicating the diagnostic and therapeutic picture even more, it is now appreciated that asthma has multiple phenotypic presentations, one of which is an entity of obesity-associated asthma with frequent exacerbations and that has been identified in disparate populations [49, 50]. Obesity has also been linked with late-onset asthma with evidence of increased mediators of the innate immune system, oxidative stress, and increased expression of IL-4 [12•]. Identifying symptoms related to obesity versus asthma and the complex interrelationship of these processes is challenging and should not be overlooked in the military population.

Deployment-Associated Lung Disease

Unlike the preceding conditions reviewed, diffuse lung disease is uncommon in SM returning from SWA, but there have been case series of deployment-associated lung disease. One such case series evaluated acute eosinophilic pneumonia (AEP) identified in 18 cases out of over 183,000 US military personnel deployed to SWA over a 13-month period [51]. As of 2016, the number of diagnosed AEP cases has climbed to 44 in patients deployed to SWA [9]. These patients reported a cough and/or dyspnea in the setting of a febrile illness. Their symptoms were acute in nature, with infiltrative process on chest radiograph and evidence of pulmonary eosinophilia present [51]. The majority of these cases were identified in new smokers, many required mechanical ventilation, and treatment included corticosteroids and tobacco cessation [51]. Fixed airway obstruction with distal airway fibrosis, termed constrictive bronchiolitis, was also identified in SM returning from SWA [9]. A case series of 80 patients with inhalational exposures during their SWA deployments were evaluated due to dyspnea on exertion. Of these, 49 underwent surgical lung biopsy which showed diffuse constrictive bronchiolitis [52].

Further evaluation of chronic pulmonary symptoms in SM that have returned from SWA is ongoing in the STAMPEDE III study [9].

Additional Considerations and Conclusions

As noted throughout, asthma is now recognized as a heterogeneous process, influenced and shaped by various clinical inputs, environmental exposures, predisposing genetic factors, and immune responses. Late-onset asthma is perhaps most germane to US SM, as recruits are heavily screened prior to entering service with up to 14% either discharged due to existing conditions or for failing initial training [53]. Factors associated with late-onset asthma include female gender, obesity, smoking, and recurrence of asthma that was previously present in childhood [11, 12•]. The importance of these associations can be seen in the under-appreciated prevalence of obesity amongst affected SM discussed above, the increased presence of active duty female SM in a variety of roles throughout the SWA theater of operations, increased prevalence of smoking while deployed, and the military services' screening approach to those with an apparently resolved history of childhood asthma. Additionally, the distinction between the immunologic mechanisms underpinning type 2 (T2) hypersensitivity and non-type 2 (non-T2) and the timing of asthma onset has both diagnostic and therapeutic implications.

The recent findings of the STAMPEDE II study highlight the importance of refining our understanding and identification of specific asthma subpopulations and these patients' differing risks and responses to treatments. In an effort to identify SM at risk for developing pulmonary disease, the STAMPEDE II study evaluated the utility of pre- and post-deployment pulmonary function testing in 843 SM deployed to SWA from 2012 to 2014. This study failed to demonstrate the utility of pre-deployment spirometry in the absence of any respiratory symptoms and also demonstrated a slight overall improvement in spirometric values despite reported increases in respiratory symptoms [1••]. Since such screening mechanisms have not shown promise in identifying at-risk SM, other diagnostic approaches are needed. Other biomarkers such as the fraction of exhaled nitric oxide (FeNO) and increasing research into T2 and non-T2 profiles remain active areas of research [54–56]. Furthermore, the exploration of the overlay and interactions between clinical factors and molecular endotypes through machine learning analysis may prove to be even more fruitful [15, 57]. The use of such sophisticated techniques appears necessary given the complex and variable predisposing factors, exposures, and expression of asthma and similar respiratory processes in both SM and the general population.

Much interest has been raised by the reports of respiratory symptoms in US SM who have returned from deployment, particularly with the operational experience over the past 18 years in SWA. Clear and generalizable connections or firm conclusions regarding specific environmental exposures have been and continue to prove elusive. A wide range of exposures and potentially contributory environmental irritants are present in environments such as SWA; however, the precise interaction of these exposures with predisposing genetic and immunologic responses as well as influence on known confounding conditions remains to be seen. Ongoing lines of inquiry through researchers such as the STAMPEDE group as well as increasingly sophisticated asthma analyses driven by machine learning techniques hold promise for the development of a more refined and concrete understanding in the future. At present, researchers, clinicians, and indeed patients confront a complex network of factors that both impact and also obscure and confuse the nature of reported respiratory processes in service members.

Compliance with Ethical Standards

Conflict of Interest The views expressed in this article are those of the authors and do not reflect the official policy of the Department of Army, Navy, Department of Defense, or US Government.

Additional Notification I am a military service member. This work was prepared as part of my official duties. Title 17 U.S.C. 105 provides that "Copyright protection under this title is not available for any work of the United States Government." Title 17 U.S.C. 101 defines a United States Government work as a work prepared by a military service member or employee of the United States Government as part of that person's official duties.

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- •• Of major importance

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