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Original Research

Longitudinal changes in lung function following post-9/11 military deployment in symptomatic veterans

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ABSTRACT

Rationale: Exposure to burn pit smoke, desert and combat dust, and diesel exhaust during military deployment to Southwest Asia and Afghanistan (SWA) can cause deployment-related respiratory diseases (DRRDs) and may confer risk for worsening lung function after return.
Methods: Study subjects were SWA-deployed veterans who underwent occupational lung disease evaluation (n = 219). We assessed differences in lung function by deployment exposures and DRRD diagnoses. We used linear mixed models to assess changes in lung function over time.
Results: Most symptomatic veterans reported high intensity deployment exposure to diesel exhaust and burn pit particulates but had normal post-deployment spirometry. The most common DRRDs were deployment-related distal lung disease involving small airways (DDLD, 41%), deployment-related asthma (DRA, 13%), or both DRA/DDLD (24%). Those with both DDLD/DRA had the lowest estimated mean spirometry measurements five years following first deployment. Among those with DDLD alone, spirometry measurements declined annually, adjusting for age, sex, height, weight, family history of lung disease, and smoking. In this group, the forced expiratory volume in the first second/forced vital capacity (FEV1/FVC) ratio declined 0.2% per year. Those with more intense inhalational exposure had more abnormal lung function. We found significantly lower estimated FVC and total lung capacity five years following deployment among active duty participants (n = 173) compared to those in the reserves (n = 26).
Conclusions: More intense inhalational exposures were linked with lower post-deployment lung function. Those with distal lung disease (DDLD) experienced significant longitudinal decline in FEV1/FVC ratio, but other DRRD diagnosis groups did not.

1. Introduction

Over the past two decades, United States (US) military men and women have been deployed to conflicts in Iraq, Afghanistan, and other parts of Southwest Asia (SWA). Deployment to these areas is associated with exposure to inhalational hazards such as particulate matter (PM) from sandstorms, combat, local polluting industries, burn pit combustion products, and diesel exhaust, and to vapors, gases, dusts, and fumes (VGDF, e.g., paints and solvents) during job tasks [1–6]. Many previously deployed service members and contractors have developed persistent and sometimes career-ending respiratory symptoms including cough, dyspnea on exertion, and chest tightness or wheezing, and some have been diagnosed with deployment-related respiratory diseases (DRRDs) [7–18].

A 2019 American Thoracic Society (ATS) workshop report concluded that, although there is a known link between PM exposure in the general US population and decrements in pulmonary function, there were no long-term studies in military personnel nor studies on the natural history of DRRDs [8]. A 2020 National Academy of Sciences Report on the Health Effects of Airborne Hazards Exposures in Southwest Asia Theater

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of Military Operations emphasizes the need for surveillance lung function measurements and studies that address the long-term or chronic impacts of military exposures on lung function [5]. Much of the existing literature on lung function in this population is limited by small sample size [9,19], lack of pre-deployment baseline pulmonary function testing (PFT) data [16], lack of appropriate control groups (e.g., asymptomatic deployed service members) [20], spirometry collected at only a single time point [20], or analytical approaches that precluded assessment of within-subject changes [10].

While normal declines in lung function are anticipated with aging [21,22], abnormally rapid declines due to workplace exposures have been documented in cement production workers [23], cotton textile workers [24], woodworkers [25], welders [26], firefighters [27,28], and those in flavor manufacturing [29]. Firefighters who responded immediately after the 2001 attacks on the World Trade Center have particular relevance to previously deployed military personnel regarding exposure-related respiratory health outcomes. Firefighters and other rescue workers had sharp declines in forced expiratory volume in the first second (FEV1) following exposure to World Trade Center dust that persisted over the next six years [30]. While less is known about long term health outcomes in previously deployed military personnel, there is "limited/suggestive evidence for an association between exposure to combustion products and decreased pulmonary function" and evidence that adverse "pulmonary function effects can be observed even in the absence of clinical symptoms or disease" [31]. A recent study comparing pre-and post-deployment spirometry between Air Force firefighters who deployed (n = 184) to those who had not (n = 84) found no significant differences between groups, but those who deployed had decreased lung function after deployment [32].

Our previous work has characterized the spectrum of non-malignant DRRDs including deployment-related distal lung disease (DDLD), deployment-related asthma (DRA), expiratory central airway collapse (ECAC), rhinitis, sinusitis, and exertional mitochondrial dysfunction [16,33,34]. Surgical lung biopsies showed a spectrum of histopathologic findings in those diagnosed with DDLD, including constrictive/obliterative bronchiolitis, peribronchiolar metaplasia, and both granulomatous and lymphocytic inflammation [35]. Further efforts have focused on identifying sensitive non-invasive markers of large and small airways disease using multiple breath washout (MBW) testing and quantitative imaging analysis [36–38]. To address the paucity of information on long-term lung health outcomes in those with DRRDs, we analyzed longitudinal changes in lung function in previously deployed military veterans and contractors. Utilizing PFT data collected after deployment in a cohort of symptomatic patients followed clinically over several years, we explored whether longitudinal changes in lung function differ among diagnosis and exposure groups and whether some groups have accelerated declines in lung function.

2. Materials and methods

2.1. Study population

In 2010, National Jewish Health (NJH) established the Center for Deployment-Related Lung Disease to focus on the diagnosis and treatment of active duty military personnel, veterans, and contractors with respiratory illnesses following post-9/11 deployment missions. As of August 31, 2023, 295 previously deployed symptomatic military personnel consented to participate in research (Institutional Review Board [IRB] Protocol HS-2689). Many have been followed clinically and have serial PFTs available for analysis. As shown in Fig. 1, to be eligible for this analysis, participants had to have deployed to SWA since September 11, 2001, developed respiratory symptoms after deployment, had one or more acceptable PFT, and had complete covariate information, as detailed below.

2.2. Deployment exposures

Questionnaires administered to study subjects by trained personnel via REDCap elicited timing and location of each deployment as well as specific inhalational hazards encountered. We collected self-reported

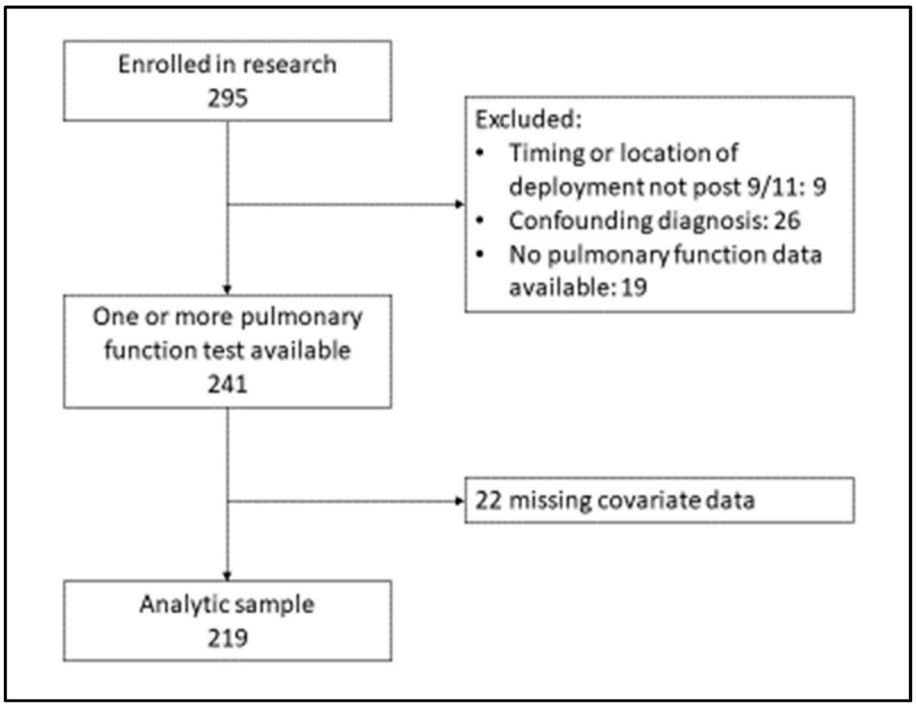

Fig. 1. Study flow diagram. Confounding diagnoses that led to exclusion included: sarcoidosis (n = 7), autoimmune disease (n = 6), cancer (n = 2), dendriform pulmonary ossification (n = 2), Birt-Hogg-Dubé (n = 2), pulmonary embolism (n = 2) and one of each of acute respiratory distress syndrome, eosinophilia syndrome, familial pulmonary fibrosis, recurrent diaphragm paralysis, and childhood asthma. Covariates that were missing and led to exclusion included family history of lung disease (n = 22), of which two were also missing smoking history.

frequency, proximity, and/or intensity of exposure to PM generated from sandstorms, burn pits, diesel exhaust, and combat dust (including controlled detonations, improvised explosive devices [IEDs], and mortar fire) for each deployment, as well as deployment duration. Using a modification of our previously developed inhalational exposure matrix [6], we calculated weighted individual respiratory hazard scores [34] based on cumulative exposure intensity and duration of deployment and classified these scores into tertiles of low, medium, and high overall exposure. Additionally, we defined high intensity exposure to each of the hazards as those reportedly occurring more than once weekly during any deployment.

Self-reported service as a military contractor, active duty, or a member of the reserves was collected via questionnaire and used to compare participants' lung function by service status. Additionally, participants reported their current or most recent military pay grade, and we classified those reporting E1-E9 as enlisted and those reporting O1–O7 as officers. Those reporting warrant officer paygrades were grouped with the enlisted group if they moved to warrant officer after the majority of their deployments, otherwise they were grouped with the officers.

2.3. Diagnosis groups

Study subjects had been clinically characterized as having DRA, DDLD, ECAC, rhinitis, sinusitis, and/or mitochondrial dysfunction, with a small proportion in whom evaluation of respiratory symptoms did not lead to diagnosis. Case definitions for deployment-related respiratory diseases have been detailed elsewhere [16,33,34]. Briefly, for all diagnoses, respiratory symptoms developed during or after post-9/11 deployment. DRA diagnosis was defined based on a post-bronchodilator increase in FEV1 $\geq$ 12 % and increase in FEV1 $\geq$ 200 mL or methacholine-induced change with provocative concentration (PC20) FEV1 $\leq$ 4 mg/mL (definite) or PC20 FEV1 $>$ 4 and $\leq$ 16 mg/mL (probable) [16]. Additionally, a significant post-exercise fall in FEV1 ($>$10 % and $>$200 mL) was included [39]. A diagnosis of definite DDLD was based on surgical lung biopsy findings of hyperinflation, emphysema, bronchiolitis, small airways inflammation, peribronchiolar fibrosis, or granulomatous pneumonitis [16,35]. Probable DDLD diagnosis required high-resolution chest computed tomography (HRCT) findings of two or more of the following: centrilobular nodularity, air trapping or mosaicism, or bronchial wall thickening [16,40] ECAC was defined as $\geq$ 70 % reduction in the cross-sectional area of the trachea at dynamic expiration on HRCT [33]. Rhinitis and/or sinusitis was diagnosed based on findings on sinus CT and/or direct laryngoscopy [16]. Finally, mitochondrial dysfunction was defined based on five metabolic exercise testing abnormalities including arterial peak exercise lactate exceeding 12 mEq/L [34].

2.4. Pulmonary function testing

Pre-bronchodilator pulmonary function testing was conducted by experienced and certified respiratory therapists and technicians. A pulmonary physician with specialized training in physiology reviewed all tests to exclude those that did not meet American Thoracic Society (ATS)/European Respiratory Society (ERS) criteria for reproducibility and acceptability [41–43]. We calculated predicted values for each parameter based on the race-neutral Global Lung Initiative (GLI) reference values (GLI-Global) with the exception of forced mid-expiratory flow (FEF25-75) [44] where race-neutral values have not yet been derived [44–48]. For comparison to previous studies, we also calculated predicted values for spirometry using National Health and Nutrition Examination Survey (NHANES) III reference equations [49]. PFT data were downloaded for analysis from the NJH Research Database (Data Set Identifier: 901-16803-04,212,023). A small number of participants provided outside testing that was included in analysis if it met ATS/ERS criteria.

Spirometry patterns were classified based on the 2005 ATS/ERS guidelines [50]. An obstructive pattern abnormality was defined as FEV1/forced vital capacity (FVC) ratio $<$ lower limit of normal (LLN), and restrictive pattern abnormality was defined as FEV1/FVC $\geq$ LLN and FVC $<$ LLN. All other spirometry was classified as normal. Using lung volume measurements, air trapping was defined based on percent predicted residual volume (RVpp) $>$ 120 % and restriction was based on percent predicted total lung capacity (TLCpp) $<$ 80 %. For comparability, we also present abnormal RV and TLC based on the upper limit of normal (ULN) and LLN per the 2022 ATS/ERS guidelines [51]. Abnormal diffusion capacity for carbon monoxide (DLCO) was defined as DLCO $<$ LLN.

2.5. Covariate selection

We collected information for as many relevant covariates as possible via REDCap questionnaire including demographics, smoking/vaping histories, medical histories, and family history of lung disease (asthma and/or emphysema/chronic obstructive pulmonary disease [COPD]). We used the NJH Research Database to review all asthma medications ever prescribed to each participant (Supplemental Table 1), characterizing anyone with a prescription as being "treated." We developed a conceptual model (Fig. 2) for the relationship between inhalational exposures during deployment and accelerated lung function decline after returning from deployment, and adjusted all models for the minimally sufficient adjustment set (confounding variables that would allow for assessment of the total effect) which included age, height, sex, smoking, and family history of lung disease. Further, we included time varying body weight in all models as a precision variable that improved model fit. Where percent predicted values are presented instead of measured values, sex, age and height were not included as covariates. Variables that were unmeasured in our study and could not be adjusted for included lung function before deployment, respiratory infections, and asthma exacerbations. Variables such as development of lung disease and treatment that are on the pathway between exposure and outcome (mediators) were not adjusted for as we aimed to estimate the total effect.

2.6. Statistical analysis

Before proceeding with statistical analyses, we reviewed all variables for outliers and examined their distributions. Based on each variable's distribution and data type (e.g., categorical vs. continuous), we summarized the mean $\pm$ standard deviation (SD), number and percent (n, %), or median and range. For PFTs that occurred on the same day, we took the highest value for each parameter.

To examine any potential demographic, deployment, or clinical characteristics that may differ among participants with longer follow-up duration, we split participants into groups by quartile of follow-up and compared categorical variables via Cochran-Mantel-Haenszel test, reporting the p-value from the row mean scores difference, and compared continuous variables via ANOVA test or Kruskal-Wallis test based on their distribution. Statistical significance was evaluated after adjusting for multiple comparisons via Bonferroni correction.

To examine any potential demographic, deployment, or clinical characteristics that may differ among participants according to service status, we compared categorical variables via Chi-Square or Fisher Exact test and compared continuous variables via ANOVA test or Kruskal-Wallis test based on their distribution. Statistical significance was evaluated after adjusting for multiple comparisons via Bonferroni correction.

We used a linear mixed model with a random intercept for each subject and for group (diagnosis, exposure) by time interactions as well as a spatial power covariance structure to assess changes in lung function parameters over time. To account for differences in time between when participants deployed and when they were evaluated for DRRDs,

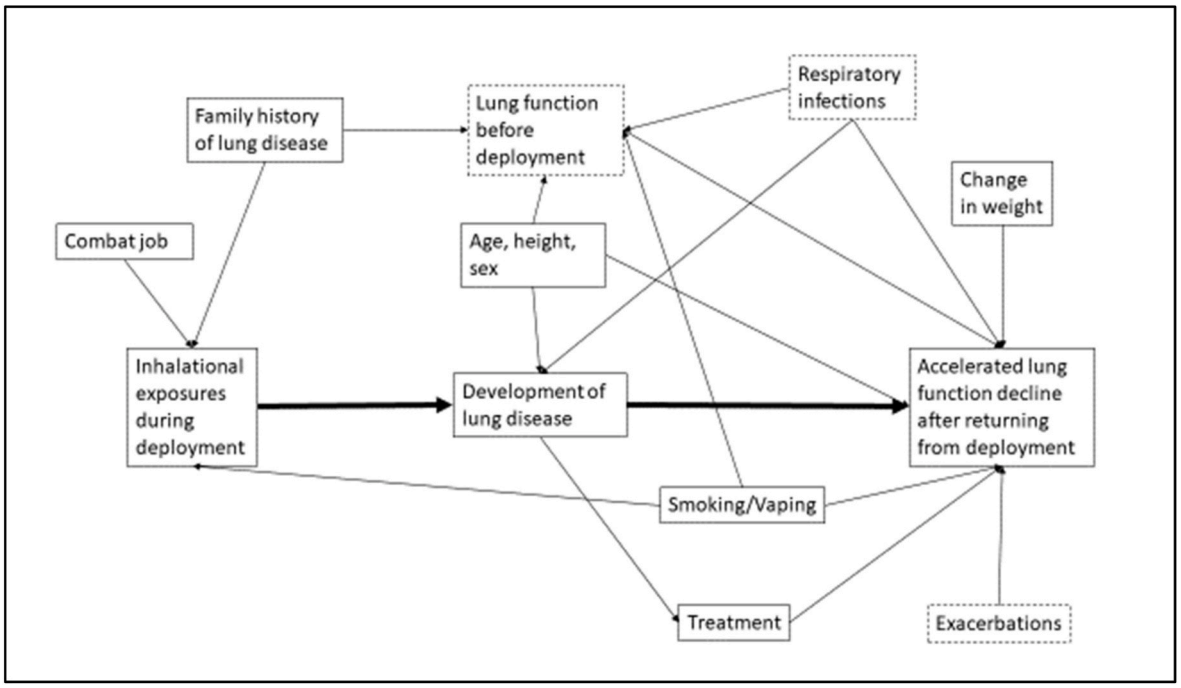

Fig. 2. Conceptual model for the relationship between inhalational exposures during deployment and accelerated lung function decline after returning from deployment. Dashed lines indicate unmeasured variables.

we used the number of days since initial deployment as the time variable in all models. We present all estimates from longitudinal models at a time point of five years following first deployment [52]. Means were compared between groups at fixed levels of covariates, applying the Tukey-Kramer method for multiple comparisons. Additionally, we used similar mixed models to examine differences in pulmonary function measurements among service groups (active duty, contractors, and reserves), service branches (Army and Marine vs. Air Force), and between those who reported being an officer in their last job during deployment vs. those who did not. All models were adjusted for family history of lung disease, smoking, sex, and time varying age, height, and weight.

To examine differences in lung function changes over time among those with large and/or small airways disease between younger participants whose lungs likely were still growing and those with mature lungs, we divided participants based on those who first deployed before age 30 vs. on or after age 30 [53]. In this model covariates were allowed to vary by group by including additional interaction terms for all covariates (sex, height, weight, age, smoking pack-years, and family history of lung disease) with time (days since start of first deployment).

All analyses were performed in SAS.v.9.4.

3. Results

In this analytical cohort of 219 participants with respiratory symptoms (Table 1), the majority were male (88 %) with mean age at first PFT of 40 years. Thirty-seven percent (n = 81) reported ever smoking cigarettes, with mean pack-years of 8.6, and 22 % (n = 33/150) reported smoking other products including cigars, pipes, water pipes, e-cigarettes, or marijuana. The median total deployment duration was 18 months (range 2–99 months), with the vast majority deploying to Iraq (41 %), Afghanistan (19 %), or both (31 %). The median age at first deployment was 28 years (range 19–59 years old) and 34 years at last deployment (range 20–60 years). High intensity exposure to diesel exhaust was nearly ubiquitous (95 %) during deployment, followed by high intensity exposure to burn pits, sandstorms, and combat dust reported by 78 %, 19 %, and 16 %, respectively.

The most common DRRD diagnosed in this group was distal lung disease or DDLD involving the small airways and interstitium (41 %). An additional 24 % had both DDLD and deployment-related asthma, and 13 % had DRA alone. Among those with DDLD, 65 had findings confirmed on surgical lung biopsy (19 in the group with both DDLD/DRA, and 46 in the group with only DDLD) while the remainder were diagnosed based on HRCT findings and did not undergo surgical lung biopsy. The remaining 22 % had other DRRDs including rhinitis and/or sinusitis (n = 11), ECAC (n = 5), rhinitis and/or sinusitis plus ECAC (n = 4), mitochondrial dysfunction (n = 1), or had respiratory symptoms only (n = 27). A family history of lung disease, including asthma and/or emphysema/COPD, was reported by 21 %. At initial visit the mean weight was 94 kg and body mass index (BMI) was 30 kg/m^2.

Sixty-six percent were prescribed asthma medications at some point during clinical follow-up. While we do not know whether participants were taking their medications or the timing of treatment onset in relation to lung function measurements, the majority (91 %) of those with DRA were prescribed at least one asthma medication, and 51 % with other DRRDs reported treatment with inhaled medications.

At initial visit, spirometry measurements on average were normal (Table 2), with 8 % (n = 18) meeting criteria for obstruction and 5 % (n = 12) for a restrictive pattern (via spirometry). Percent predicted spirometry values were similar among cohorts of deployed military personnel across comparable published studies, despite widely varying intervals between last deployment and spirometry measurement (range 1 week–7 years). The majority (91 %) of our study participants also had lung volumes available. Among those, 60 % (n = 119) had air trapping defined based on RVpp>120 % while 6 % (n = 11) had restriction defined based on TLCpp<80. Using the ULN for RV, 16 % (n = 31) would be classified as having air trapping; using the LLN for TLC, 8 % (n = 16) would be classified as restricted. One participant had decreased DLCO. Among those with more than one spirometry (n = 192), the median number of tests per participant was 3 (range 2–18) with median clinical follow-up duration of 5.7 months (range 0.03–163 months). Twenty-seven participants had only a single PFT available.

Comparing demographic, deployment, and clinical characteristics among participants by quartile of clinical follow-up duration (Supplemental Table 2), we did not observe any significant differences after

Table 1
Characteristics of previously deployed participants with respiratory symptoms, n = 219.

Demographics	Mean ± SD or n (%)
Male	193 (88 %)
Age at first test (years)	40.1 ± 9.6
Ever smoked cigarettes	81 (37 %)
Smoking pack-years	8.6 ± 13.1
Ever smoked other products[a]	33/150 (22 %)
Initial visit weight (kg)	94.5 ± 19.2
Initial visit height (cm)	176.9 ± 8.4
Initial body mass index (BMI) (kg/m^2)	30.1 ± 5.0
Service Branch	
Army	131 (60 %)
Air Force	44 (20 %)
Marine	9 (4 %)
Navy	4 (2 %)
Multiple	21 (10 %)
Service Status	
Contractor	20 (9 %)
Active Duty	173 (79 %)
Reserves	26 (12 %)
Officer	48/177 (27 %)
Deployment Information	
Number of deployments, median (range)	2 (1–11)
Total deployment duration (months), median (range)	18 (2–99)
Deployment location	
Iraq	90 (41 %)
Afghanistan	41 (19 %)
Both	69 (31 %)
Other	19 (9 %)
Reported high intensity (more than weekly) exposure	
Sandstorms	38/199 (19 %)
Burn pits	157/201 (78 %)
Diesel exhaust	178/187 (95 %)
Combat dust	31/189 (16 %)
Deployment-Related Respiratory Disease Group	
Distal lung disease	89 (41 %)
Asthma	29 (13 %)
Both asthma and distal lung disease	53 (24 %)
Other DRRDs[b] (or respiratory symptoms only)	48 (22 %)
Treated with inhaled medications	144/217 (66 %)
Reported family history of asthma or emphysema	46 (21 %)

Abbreviations: DRRDs = deployment-related respiratory diseases.
[a] Other products includes cigars, a pipe, water pipe, e-cigarettes, or marijuana.
[b] Other DRRDs include rhinitis and/or sinusitis (n = 11), expiratory central airway collapse (n = 5), rhinitis and/or sinusitis plus expiratory central airway collapse (n = 4), and mitochondrial dysfunction (n = 1). The remainder (n = 27) had respiratory symptoms only.

adjusting for multiple comparisons. Those with the shortest follow-up reported a higher prevalence of ever-smoking cigarettes, while those in the longest follow-up group reported smoking other products most frequently. Additionally, those in the longest follow-up group were more likely to be in the reserves and to have been treated with asthma medications compared to those with shorter follow up duration.

Further, comparing demographic, deployment, and clinical characteristics among participants by service status (Supplemental Table 3), we observed several differences between active duty, contractor, and reserve groups. Contractors were unique in that they were older at first visit (p = 0.0006), reported more intense cigarette smoking (p = 0.05), longer total deployment duration (p = 0.02), and were more likely to report high intensity exposures to sandstorms (p = 0.07) and combat dust (p = 0.002). Additionally, contractors and those in the reserves were more likely to be female (p = 0.02).

3.1. Findings by diagnosis groups

Adjusting for age, sex, height, weight, family history of lung disease, and smoking, we examined whether participants in the four different diagnosis groups had significant differences in lung function parameters five years following first deployment (Table 3a and Fig. 3). Those with distal lung disease (but without asthma) had significantly lower DLCO than those with asthma or other deployment-related respiratory diseases.

Among those with deployment-related asthma (but without distal lung disease), FEV1 and FVC were significantly higher than in those with both DDLD/DRA five years following first deployment. Additionally, DLCO was higher in those with DRA alone compared to those with DDLD alone and both DDLD/DRA.

Those with both DDLD/DRA had the lowest estimated mean spirometry measurements five years following first deployment, adjusting for age, sex, height, weight, family history of lung disease, and smoking. Specifically, military personnel diagnosed with both post-deployment asthma and distal lung disease had significantly lower FEV1 compared with all other diagnosis groups. FVC was significantly lower in this group than in those with DRA alone or with other DRRDs. Similarly, estimated mean FEV1/FVC ratio was significantly lower in the DRA/DDLD group than in those with DDLD alone. DLCO also was reduced compared to those with DRA alone. Taken together, these findings show that, over time, veterans with clinical diagnoses of both DDLD and DRA have significantly lower spirometry and DLCO compared to those with only deployment-related asthma or those with upper airway disorders that do not involve the distal lung parenchyma and small airways. Not surprisingly, RV was higher among participants with asthma (either alone or in combination with DDLD), which may be an indicator of hyperinflation, though this finding was not statistically significant.

We also examined longitudinal changes in lung function parameters among the different diagnosis groups. Based on these same models, the mean change per year in pre-bronchodilator lung function (Table 3b) was generally stable, with some modest improvements among participants with DRA (either alone or in combination with DDLD). Notably, among those with small airways disease/DDLD alone, spirometry measurements were generally declining over time, and the FEV1/FVC ratio declined significantly in this diagnosis group (0.2 % per year, [95 % confidence interval: 0.4 %, −0.03 %).

As a sensitivity analysis, we examined whether those with biopsy proven deployment-related distal lung disease (definite DDLD, n = 65) vs. probable DDLD (n = 77) based on HRCT findings had different estimated mean lung function measurements five years after first deployment or whether the annual rates of change were significantly different. Mean lung function measurements (Supplemental Table 4) were similar between groups, with those in the biopsy proven DDLD group having a higher mean FEV1/FVC than those with probable DDLD (p = 0.01). None of the annual changes were statistically significantly different between groups.

Focusing on those with large or small airways disease alone or in combination (DRA and/or DDLD, n = 171), the annual changes in measured lung function (Table 4) were generally stable or declining over time after adjusting for age, sex, height, weight, family history of lung disease, and smoking. The exception was RV which increased with time, suggesting increasing hyperinflation. Among those that first deployed before age 30 (n = 101), spirometry measurements generally increased at a faster rate compared to the overall group with large and/or small airways disease with the exception of FEV1/FVC ratio which significantly declined. Those that first deployed at or after age 30 (n = 70) had generally declining spirometry measurements with no statistically significant changes. As a sensitivity analysis, we examined annual changes in lung function among all participants with five or more years of follow-up (Supplemental Table 5). Annual changes were generally stable but had greater variability and could not be grouped by age due to the limited sample size (n = 21). Annual changes in those with five or more years of follow-up were not statistically significant for any of the examined parameters.

Table 2
Pre-bronchodilator pulmonary function testing (using GLI-Global and NHANES reference values) from 219 veterans' initial clinic visit for evaluation of respiratory symptoms following deployment, with comparison to other published studies.

Study Population	Current n = 219		Morris 2014 n = 50	Morris 2019 n = 843		Holley 2016 n = 267	Falvo 2016 n = 114
Timing	Post-deployment		Post-deployment	Pre-deployment	Post-deployment	Post-deployment	Post-deployment
Reference value source	Race-Neutral GLI-Global	NHANES III	NHANES III, Cotes	NHANES III	NHANES III	NHANES III, Miller	NHANES III
Spirometry							
FEV1pp	95.8 ± 16.9	91.4 ± 16.0	87.7 ± 12.7	95.2 ± 12.6	96.1 ± 12.4	91.9 ± 16.0	90.3 ± 14.6
FVCpp	97.9 ± 15.0	91.6 ± 13.7	91.0 ± 13.4	95.9 ± 11.8	96.4 ± 11.9	92.1 ± 15.0	94.2 ± 14.8
FEV1/FVC	79.9 ± 7.4	79.9 ± 7.4	79.6 ± 5.8	81.5 ± 5.9	81.8 ± 6.1	77.3 ± 6.7	77.1 ± 6.5
FEF25–75pp	93.9 ± 31.5	95.1 ± 31.6	N/A	96.5 ± 25.5	98.1 ± 25.9	N/A	87.5 ± 27.5
Lung Volumes							
RVpp (n = 199)	131.7 ± 32.4	N/A	82.1 ± 31.9	N/A	N/A	N/A	87.3 ± 31.8
TLCpp (n = 199)	99.5 ± 12.4	N/A	90.8 ± 13.1	N/A	N/A	N/A	91.7 ± 17.9
Diffusion							
DLCOpp unadjusted (n = 192)	118.9 ± 18.0	N/A	89.7 ± 15.2	N/A	N/A	97.8 ± 17.7	N/A
Other							
Time since last deployment, median (range)	4 (−7.6[a] to 20.6) years		<6 months	N/A	1–2 weeks	27.9 (13.1–55.2) months	6.9 (0.7–13.1) years

Note: Results are the mean ± standard deviation unless otherwise noted.
Abbreviations: pp = percent predicted; FEV1 = forced expiratory volume in the first second; FVC = forced vital capacity; FEF25-75 = forced mid-expiratory flow; RV = residual volume; TLC = total lung capacity; DLCO = diffusion capacity for carbon monoxide; N/A = not available or not applicable; NHANES = National Health and Nutrition Examination Survey; GLI = Global Lung Initiative.
[a] Three participants in our cohort deployed again after their initial visit.

Table 3a
Mean [95 % confidence interval] pre-bronchodilator lung function measurements by diagnosis group five years after first deployment adjusted for age, sex, height, weight, family history of lung disease, and smoking, n = 219.

Group	DDLD only, n = 89	DRA only, n = 29	DDLD/DRA, n = 53	Other DRRDs, n = 48	P-value[a]
FEV1 (L)	3.9 [3.8, 4.1]	3.9 [3.7, 4.2]	3.5 [3.3, 3.7]	4.1 [3.8, 4.3]	0.0002[abc]
FVC (L)	4.8 [4.6, 4.9]	5.0 [4.7, 5.3]	4.5 [4.2, 4.7]	5.0 [4.8, 5.3]	0.003[ac]
FEV1/FVC (%)	83.4 [81.7, 85.1]	80.0 [76.9, 83.0]	77.5 [75.3, 79.6]	81.0 [78.4, 83.7]	<0.0001[b]
FEF25-75 (L/s)	4.3 [4.0, 4.5]	3.8 [3.3, 4.3]	3.2 [2.8, 3.6]	3.9 [3.4, 4.3]	<0.0001[b]
RV (L)	1.9 [1.8, 2.0]	2.2 [1.9, 2.5]	2.1 [2.0, 2.3]	2.1 [1.9, 2.4]	0.05
TLC (L)	6.8 [6.6, 7.1]	7.4 [6.9, 7.8]	6.8 [6.5, 7.1]	7.3 [6.9, 7.8]	0.03
DLCO (mL/min/mmHg)	35.2 [33.7, 36.7]	40.9 [38.1, 43.7]	36.0 [34.1, 38]	39.2 [36.5, 41.9]	0.0008[adf]

Notes: Estimates are presented for males with no family history of lung disease that never smoked at the average baseline height (176.9 cm), weight (94.5 kg) and age (40.1 years) for the cohort.
Abbreviations: DDLD = deployment-related distal lung disease; DRA = deployment-related asthma; DRRDs = deployment-related respiratory diseases; FEV1 = forced expiratory volume in the first second; FVC = forced vital capacity; FEF25-75 = forced mid-expiratory flow; RV = residual volume; TLC = total lung capacity; DLCO = diffusion capacity for carbon monoxide.
[a] Pairwise comparison <0.05 after Tukey-Kramer adjustment: a = DDLD/DRA vs. DRA only, b = DDLD/DRA vs. DDLD only, c = DDLD/DRA vs. other DRRDs, d = DRA only vs. DDLD only, e = DRA only vs. other DRRDs, f = DDLD only vs. other DRRDs.

3.2. Findings by exposure

We analyzed whether lung function varied by weighted exposure intensity group five years following first deployment. For all lung function parameters examined, those in the medium/high inhalational exposure group generally had lower lung function (Table 5). Specifically, FEV1, FVC, FEV1/FVC and FEF25-75 were all statistically significantly lower among those in the medium/high exposure group compared to the lowest exposure group. Mean values are presented as percent predicted values across all three tertiles in Fig. 4 for comparison. FEV1pp was significantly more abnormal among those in the medium group compared to the lowest exposure group. FEV1/FVC ratio and FEF25–75pp were significantly lower in the medium exposure group compared to the lowest exposure group. FEV1pp, RVpp, TLCpp and DLCOpp were not significantly different between exposure groups.

We examined the utility of deployment duration in months as a simplified estimate of exposure (Table 6). All spirometry parameters decreased with increasing duration of deployment while lung volume and diffusion parameters were unchanged. FEV1, FEV1/FVC ratio, and FEV25-75 all declined significantly (p = 0.04, 0.01, 0.02, respectively).

We analyzed for differences in lung function potentially related to exposure variability among active duty personnel, reservists, and military contractors, between enlisted and officer service members, and among service branches. We found significantly lower estimated FVC and TLC among active duty participants (n = 173) compared to those in the reserves (n = 26) five years following deployment (Supplemental Table 6). Notably, contractors (n = 20) had significantly lower estimated DLCO compared to active duty participants five years following deployment (Supplemental Table 6). Additionally, contractors had decreasing FEV1, FVC, and FEF25-75 over time while active duty and reserve participants had stable or increasing measurements over time. Among those for whom information about current or most recent pay-grade was available (n = 177), those holding officer positions (n = 48) had generally higher (with the exception of RV) lung function measurements than those in enlisted jobs (n = 129), but none of the estimated mean values were significantly different (Supplemental Table 7). Among those that served in the Army or Marines (n = 155) compared to those that served in the Air Force (n = 45), land based troops generally had lower lung function measurements (with the exception of RV and TLC), but none of the estimated mean values were significantly different (Supplemental Table 8).

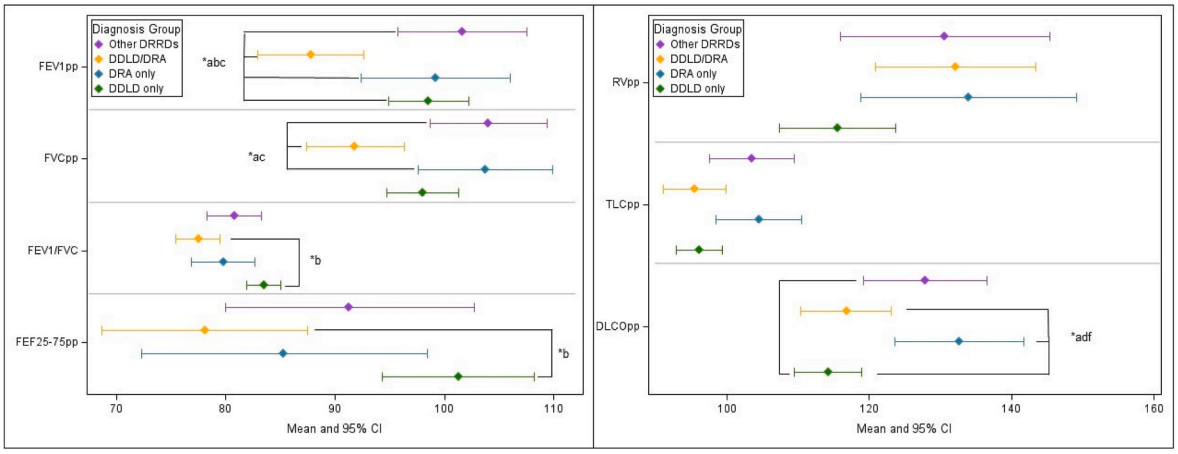

Fig. 3. Comparison of mean pre-bronchodilator lung function measurements by diagnosis group five years after first deployment adjusted for smoking, family history of lung disease, and weight.
*Pairwise comparison <0.05 after Tukey-Kramer adjustment: a = DDLD/DRA vs. DRA only, b = DDLD/DRA vs. DDLD only, c = DDLD/DRA vs. other DRRDs, d = DRA only vs. DDLD only, e = DRA only vs. other DRRDs, f = DDLD only vs. other DRRDs.
Abbreviations: pp = percent predicted; FEV1 = forced expiratory volume in the first second; FVC = forced vital capacity; FEF25-75 = forced mid-expiratory flow; RV = residual volume; TLC = total lung capacity; DLCO = diffusion capacity for carbon monoxide.

Table 3b
Annual mean change [95 % confidence interval] in pre-bronchodilator lung function measurements by diagnosis group adjusted for age, sex, height, weight, family history of lung disease, and smoking, n = 219.

Group	DDLD only, n = 89	DRA only, n = 29	DDLD/ DRA, n = 53	Other DRRDs, n = 48	P-value
FEV1 (mL)	−8.6 [-24.1, 6.9]	24.2 [-4.2, 52.6]	9.8 [-14.6, 34.2]	6.4 [-21.1, 34.0]	0.13
FVC (mL)	−1.4 [-18.2, 15.3]	25.1 [-5.5, 55.7]	**30.7 [4.2, 57.1]**	10.0 [-20.1, 40.1]	0.09
FEV1/FVC (%)	**−0.2 [-0.4, -0.03]**	−0.01 [-0.3, 0.3]	−0.1 [-0.4, 0.1]	−0.1 [-0.4, 0.2]	0.64
FEF25-75 (mL/s)	−17.9 [-47.0, 11.1]	31.8 [-21.7, 85.3]	−10.8 [-57.7, 36.1]	20.2 [-31.1, 71.4]	0.24
RV (mL)	16.4 [0.1, 32.6]	27.6 [-1.1, 56.4]	**48.4 [22.7, 74.1]**	1.9 [-28.1, 32.0]	0.07
TLC (mL)	0.8 [-24.9, 26.4]	−5.0 [-52.8, 42.7]	**45.8 [2.6, 88.9]**	0.2 [-52.1, 52.6]	0.26
DLCO (mL/min/mmHg)	0.1 [-0.02, 0.3]	−0.1 [-0.4, 0.2]	0.2 [-0.1, 0.4]	−0.1 [-0.4, 0.3]	0.31

Note: Values in bold are statistically significant.
Abbreviations: DDLD = deployment-related distal lung disease; DRA = deployment-related asthma; DRRDs = deployment-related respiratory diseases; FEV1 = forced expiratory volume in the first second; FVC = forced vital capacity; FEF25-75 = forced mid-expiratory flow; RV = residual volume; TLC = total lung capacity; DLCO = diffusion capacity for carbon monoxide.

Table 4
Annual mean change [95 % confidence interval] in lung function measurements among all participants with DDLD and/or DRA and by younger vs older age group, adjusted for age, sex, height, weight, family history of lung disease, and smoking, n = 171.

Parameter	Annual change [95 % CI]		
	All n = 171	First deployed before age 30 n = 101	First deployed age 30 or after n = 70
FEV1 (mL)	0.9 [-26.5, 28.3]	4.0 [-39.6, 47.5]	−3.6 [-26.7, 19.6]
FVC (mL)	14.9 [-14.3, 44.0]	30.4 [-16.0, 76.8]	−7.4 [-32.0, 17.1]
FEV1/FVC (%)	−0.3 [-0.6, 0.01]	**−0.5 [-1.0, -0.04]**	0.03 [-0.2, 0.3]
FEF25-75 (mL/s)	−23.8 [-75.2, 27.6]	−47.4 [-129.1, 34.3]	10.1 [-33.2, 53.5]
RV (mL)	**38.1 [13.3, 63.0]**	**50.3 [10.8, 89.7]**	20.7 [-0.7, 42.0]
TLC (mL)	20.2 [-19.1, 59.5]	47.6 [-15.0, 110.1]	−19.2 [-52.2, 13.8]
DLCO (mL/min/mmHg)	0.2 [-0.01, 0.5]	0.4 [-0.05, 0.8]	0.1 [-0.1, 0.3]

Note: Values in bold are statistically significant.
Abbreviations: FEV1 = forced expiratory volume in the first second; FVC = forced vital capacity; FEF25-75 = forced mid-expiratory flow; RV = residual volume; TLC = total lung capacity; DLCO = diffusion capacity for carbon monoxide.

4. Discussion

Little is known about the long-term respiratory sequelae of exposure to inhalational hazards that occurred with post-9/11 military deployment to Southwest Asia. In our cohort of 219 previously deployed veterans with respiratory symptoms and DRRDs, we observed significantly lower lung function among those with both DRA and DDLD as well as in those with longer deployment duration and those reporting more intense cumulative exposure to inhalational hazards.

Specifically, spirometry parameters were lowest in those with both DRA and DDLD while those with DDLD alone had the most substantial annual declines. Importantly, we do not have lung function data preceding deployment to use as a pre-exposure baseline, so observed declines and lower lung function may have important clinical implications for previously deployed military personnel even if percent predicted values are within the normal range for the general population. This is similar to the declines in FEV1 that were observed among World Trade Center rescue workers where declines in lung function were substantial, but often still within the normal range [30]. In our study, among those with DRA alone or both DRA/DDLD, we observed modest increases in most lung function measurements over time, which could be attributed in part to the use of asthma medications and/or to avoidance of ongoing exposures that could sustain inflammatory airway responses. Additionally, the higher DLCO values observed in our cohort could be related in part to higher asthma prevalence compared to other previously

Table 5
Mean [95 % confidence interval] lung function measurements by exposure intensity five years after first deployment adjusted for age, sex, height, weight, family history of lung disease, and smoking, n = 183.

Exposure Group	Low, n = 60	Medium/High, n = 123	P-value
FEV1 (L)	4.0 [3.9, 4.2]	3.7 [3.6, 3.9]	**0.004**
FVC (L)	4.9 [4.7, 5.1]	4.7 [4.5, 4.9]	**0.04**
FEV1/FVC (%)	82.7 [80.5, 84.8]	79.5 [77.6, 81.4]	**0.01**
FEF25-75 (L/s)	4.2 [3.8, 4.5]	3.6 [3.3, 3.9]	**0.005**
RV (L)	2.0 [1.8, 2.2]	2.0 [1.8, 2.2]	0.93
TLC (L)	7.0 [6.7, 7.3]	6.9 [6.7, 7.2]	0.70
DLCO (mL/min/mmHg)	37.5 [35.6, 39.4]	36.5 [34.7, 38.2]	0.40

Note: Values in bold are statistically significant.
Estimates are presented for males with no family history of lung disease that never smoked at the average baseline height (176.9 cm), weight (94.5 kg) and age (40.1 years) for the cohort.
Abbreviations: FEV1 = forced expiratory volume in the first second; FVC = forced vital capacity; FEF25-75 = forced mid-expiratory flow; RV = residual volume; TLC = total lung capacity; DLCO = diffusion capacity for carbon monoxide.

deployed cohorts, as well as to using the GLI-Global reference set for determining the lower limit of normal.

Among participants with DRA or DDLD, FEV1/FVC significantly decreased among those that first deployed before the age of 30, while those who were older and had more mature lungs when they first deployed were less impacted. Interestingly, RV measurements became significantly higher among participants with DRA or DDLD, indicating increasing air trapping/hyperinflation with time since first deployment and perhaps contributing to persistent exertional dyspnea in this group.

Based on weighted measures of exposure intensity, we found a link between more intense deployment exposures and worse lung function. Using self-reported estimates of exposure to sandstorms, burn pit smoke, diesel exhaust, and combat dust, those with medium or high inhalational exposure scores generally had more abnormal spirometry. A number of previous studies have examined changes in respiratory symptoms, describing increases during and after deployment [9,10]. Our study is the first to examine lung function measurements in relation to weighted multi-hazard exposure intensity and is an important step in understanding potential dose-response relationships for deployment inhalational hazards and post-deployment lung function.

Deployment duration also was associated with a more rapid decline in spirometric measures of obstruction in DRA and DDLD in our cohort. We observed statistically significant declines in FEV1, FEV1/FVC and FEV25-75 for every additional month of deployment after adjusting for age, sex, height, weight, family history of lung disease, and smoking. The median deployment duration in our cohort was 18 months, substantially longer than two other studies that examined trends in post-deployment lung function measurements based on total deployment duration [19,20]. Falvo et al., 2016 observed a trend toward greater airflow limitation (reduced FEV1/FVC) for each additional month of

Table 6
Annual mean change in pre-bronchodilator lung function measurements per additional month of deployment adjusted for age, sex, height, weight, family history of lung disease, and smoking, n = 219.

Parameter	Change per Month	p-value
FEV1 (mL)	**−5.5**	**0.04**
FVC (mL)	−2.3	0.45
FEV1/FVC (%)	**−0.1**	**0.01**
FEF25-75 (mL/s)	**−12.4**	**0.02**
RV (mL)	3.7	0.13
TLC (mL)	5.1	0.20
DLCO (mL/min/mmHg)	0.01	0.68

Note: Values in bold are statistically significant.
Abbreviations: FEV1 = forced expiratory volume in the first second; FVC = forced vital capacity; FEF25-75 = forced mid-expiratory flow; RV = residual volume; TLC = total lung capacity; DLCO = diffusion capacity for carbon monoxide.

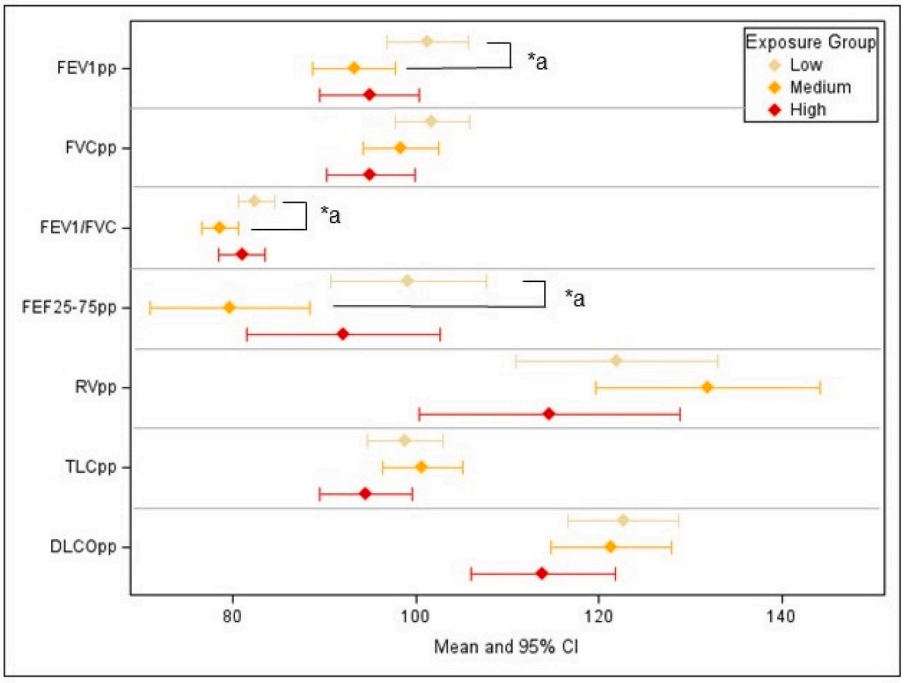

Fig. 4. Comparison of mean lung function measurements by exposure intensity five years after first deployment adjusted for smoking, family history of lung disease, and weight
*Pairwise comparison <0.05 after Tukey-Kramer adjustment: a = Low vs. Medium, b = Low vs. High, c = Medium vs. High.
Abbreviations: pp = percent predicted; FEV1 = forced expiratory volume in the first second; FVC = forced vital capacity; FEF25-75 = forced mid-expiratory flow; RV = residual volume; TLC = total lung capacity; DLCO = diffusion capacity for carbon monoxide.

deployment (mean duration 11.9 months) after adjusting for smoking ($p = 0.059$) [20]. Holley et al., 2016 observed a non-statistically significant negative correlation between deployment duration and lung function measurements among service members with unexplained cough or dyspnea who had deployed to Iraq or Afghanistan (median duration 11.7 months) [19]. Of note, their analysis used simple Spearman's correlations that did not account for important covariates such as age, sex, height, weight, family history of lung disease, and smoking history. In a group of Air Force firefighters followed for approximately one year, those who had deployed generally had lower lung function upon return compared to those who did not deploy, but analyses did not examine deployment duration [32].

Differences between enlisted service members compared to officers, among military contractors, active duty personnel and reservists, and among service branches might be expected based on differences in job duties and other deployment-specific exposure variables. The population examined by Holley et al. described significantly lower FEV1pp and FVCpp in 193 enlisted/warrant service members compared to 74 officers [19]. Our exploratory analysis comparing 48 officers and 129 enlisted service members, informed by differences in age, sex, height, weight, family history of lung disease, and smoking, showed findings of similar magnitude and direction though they were not statistically significant. Additionally, we found significantly lower FVC and TLC among active duty participants (n = 173) compared to those in the reserves (n = 26), and further, that contractors (n = 20) had significantly lower DLCO compared to active duty participants. In simple univariable analyses, Holley et al. observed lower FEV1pp, FVCpp, FEV1/FVC and DLCOpp among active duty (n = 245) participants compared to guard/reserve (n = 22) participants, but none of the differences were statistically significant. While the number of contractors in our cohort is small, some important differences in exposure characteristics (longer deployment duration and more frequent exposure to sandstorms and combat dust) were observed that may confer risk for declines in lung function; this group should not be overlooked for clinical evaluation and follow-up care.

Lacking longitudinal data in other deployed cohorts for comparison, we considered our findings relative to studies of lung function over time in populations characterized by exposures to known occupational hazards. Using a job exposure matrix for two large population-based cohorts (n = 17,833) in Europe and Switzerland with nearly two decades of follow-up, investigators observed accelerated declines in FEV1 and FEV1/FVC among participants with exposure to biological dust, mineral dust, and metals [54]. The declines were similar to those observed among chronic cigarette smokers. Values are presented per 25 intensity-years of exposure so are not directly comparable to our results. In two population-based cohorts in Copenhagen (n = 16,144) with a mean follow-up of 9 years, exposure to mineral dusts, biological dusts, gases and fumes was not associated with FEV1 decline. Specifically, these investigators noted a decline of 2 ml/year (95 % CI: 5.3, 1.3) in one cohort vs. an increase of 0.7 ml/year (95 % CI: 0.8, 2.3) in the other. When using an indexed exposure, gases and fumes were associated with an accelerated decline in FEV1 in one cohort (−5.8 ml/unit/year) [55]. Similarly, in the US Framingham Heart Study (n = 1332) with multiple spirometry measurements and mean follow-up of 17 years, subjects more likely to have been exposed to workplace dust had -4.5 ± 1.7 ml/year excess loss in FEV1 compared to those less likely to have workplace dust exposure based on estimates from an established job exposure matrix. No significant difference in FEV1/FVC was observed [56]. A recent systematic review and meta-analysis found that exposures to vapors, gases, dusts, fumes (VGDF) and aromatic solvents were significantly associated with FEV1 decline in population-based cohort studies while other occupational exposures had less consistent findings. The effect for VGDF was −3.31 ml/year (95 % CI: 6.12, −0.49) across five cohorts [57]. Future studies of lung health risks from common military exposures should include efforts to better quantify occupational VGDF.

Studies to date examining lung function following deployment have had varying intervals between most recent deployment and lung function testing. Morris et al. measured lung function just one to two weeks after return from deployment [10]. In Holley et al. measurements were collected at a median of 30 months after deployment [19]. Falvo et al. collected data 7 years after deployment [20]. In our cohort the median time since deployment was four years for the initial measurement. These differences in timing likely explain some of the variability among studies (Table 2). Further, only two previous studies [10,32] describe lung function testing at multiple time points. In both, follow-up duration is less than five years, too short to reliably estimate an individual's true rate of decline [52]. The median length of follow-up thus far in our cohort is 5.7 months (range 0.03–163 months), but in those with five or more years of follow-up (n = 21,Supplemental Table 5), annual changes were similar to participants with DRA and/or DDLD. Continued follow-up of our study participants will be important to better understand trends among the different lung disease groups and identify those with accelerated lung function decline for targeted clinical care.

Our study has several strengths. First, this is a well-characterized cohort based on standardized case definitions and comprehensive diagnostic evaluation that enabled analysis of longitudinal changes in the major nonmalignant respiratory disease groups affecting previously deployed military personnel. Additionally, we had access to high quality lung function testing that included lung volumes and diffusion capacity as well as pre- and post-bronchodilator spirometry. Moreover, we used the most current recommended predicted equations for analyzing lung function data and were able to adjust for relevant covariates including weight, smoking, family history of lung disease and considered treatment with asthma medications. Most participants had multiple PFT measurements, diminishing problems of within subject variability, and many had adequate follow-up duration to assess trends in lung function reliably. Further, our study population included service members and contractors from multiple military branches, occupational specialties, and varying deployment exposure intensities. While exposures were self-reported, we observed consistency between different measures of exposure. Finally, our analysis methods allowed us to look at within subject changes rather than simply comparing means between groups, enabling assessment of both individual and group changes in lung function over time.

Our study has several limitations. First, all pulmonary function testing was collected after deployment exposures occurred. While pre-deployment spirometry has been recommended by a number of experts, this baseline information is not obtained routinely for military service members. Second, exposure measurements were not available, and we had to rely on self-reported exposures that may suffer from recall and awareness bias. Third, information from asymptomatic or non-deployed control groups was unavailable for comparison. Fourth, there was no information about specific timing of use or compliance with prescribed asthma medication. Duration of follow-up for some participants was short, limiting our ability to detect changes over time and likely reducing statistical power in our study. Finally, there is also potential for selection bias since some participants may have been referred for assessment of benefits eligibility, while others may have left our clinical program to seek follow up medical care elsewhere (e.g., the Veterans Administration).

5. Conclusion

Among previously deployed military personnel with respiratory symptoms and deployment-related respiratory diseases, we observed significantly lower lung function among those with both asthma and distal lung disease and in those reporting more intense exposure to inhalational hazards during deployment. Those with DDLD alone had the most substantial annual lung function declines. Continued monitoring of pulmonary function in those with deployment-related respiratory diseases is important for detecting accelerated declines in lung

function, especially among those with the most intense hazardous inhalational exposures during deployment, including military contractors. Further, the dose-response findings observed with both exposure intensity and deployment duration highlight the importance of baseline lung function testing and ongoing medical surveillance to help identify opportunities for expedient diagnosis and treatment.

CRediT authorship contribution statement

Lauren M. Zell-Baran: Writing – original draft, Methodology, Funding acquisition, Formal analysis, Conceptualization. **Silpa D. Krefft:** Writing – review & editing, Supervision. **Matthew Strand:** Writing – review & editing, Methodology, Formal analysis. **Cecile S. Rose:** Writing – original draft, Supervision, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Cecile Rose receives research grant funding from the U.S. Department of Defense. Silpa Krefft is employed by the U.S. Department of Veterans Affairs (DVA) and receives research grant funding from the DVA. Dr. Rose has participated in medicolegal depositions to provide expert testimony on patients for whom she has rendered medical opinions; however, she have received no personal income or compensation for these medicolegal efforts, all of which have been reimbursed to National Jewish Health. Dr. Krefft has received payment for medicolegal consulting in occupational lung disease.

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Appendix A. Supplementary data

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