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Department of Medicine
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Looking Back, Moving Forward: Research on Deployment-Related Respiratory Diseases

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PACT Act Research Symposium for Veteran Health
Aurora, CO
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Disclosures

- Department of Defense (DoD): *Mechanisms and Treatment of Deployment-Related Lung Injury: Repair of the Injured Epithelium*
- DoD: *Innate Immunity and Deployment-Related Lung Disease*
- DoD: *Study to Improve Deployment-Related Asthma Using L-Citrulline Supplementation*
- Sergeant Sullivan Center

Since 1990, over 3.5 million people deployed to Southwest Asia & Afghanistan.

The first decade (2001 – 2011)

Iraq:

- Operation Iraqi Freedom:

  2003 – 2009

- Operation New Dawn:

  2010 – 2011

Afghanistan:

- Operation Enduring Freedom:

  2001 - 2014

Early reports of post-9/11 deployment respiratory diseases

- Increased respiratory symptoms

- *Helmer DA, Rossignol M, Blatt M, Agarwal R, Teichman R, Lange G. Health and exposure concerns of veterans deployed to Iraq and Afghanistan. J Occup Environ Med. 2007 May;49(5):475-80.*
- *Smith TC. The US Department of Defense Millennium Cohort Study: career span and beyond longitudinal follow-up. J Occup Environ Med. 2009 Oct; 51(10):1193-201.*

- Acute eosinophilic pneumonia

Shorr AF. Scoville SL, Cersovsky SB, Shanks GD, Ockenhouse CF, Smoak BL, Carr WW, Petruccelli BP. Acute eosinophilic pneumonia among US Military personnel deployed in or near Iraq. JAMA. 2004 Dec 22; 292(24):2997-3005.

- New onset asthma/asthma aggravation

Roop SA, Niven AS, Calvin BE, Bader J, Zacher LL. The prevalence and impact of respiratory symptoms in asthmatics and nonasthmatics during deployment. Military Medicine. 2007; 172(12):1264–1269.

- Constrictive bronchiolitis

King MS, Eisenberg R, Newman JH, Tolle JJ, Frank E. Harrell FEJ, Nian H, Ninan M, Lambright ES, Sheller JR, Johnson JE, Miller RF. Constrictive bronchiolitis in soldiers returning from Iraq and Afghanistan. N Engl Med. July 2011; 365:222-230.

Deployers reported exposure to multiple, poorly characterized inhalational hazards.

- Burn pit smoke
- Desert dust particulates
- Diesel exhaust
- Industrial fires/pollutants
- Combat dust
- Cigarette smoke
- IED blasts/mortar fire
- Temperate extremes
- Microbial/allergenic agents
- Job-specific VDGF (solvents, welding fumes, concrete, paints)

https://www.military.com/equipment/high-mobility-multipurpose-wheeled-vehicle-hmmwv

Other relevant exposures and outcomes

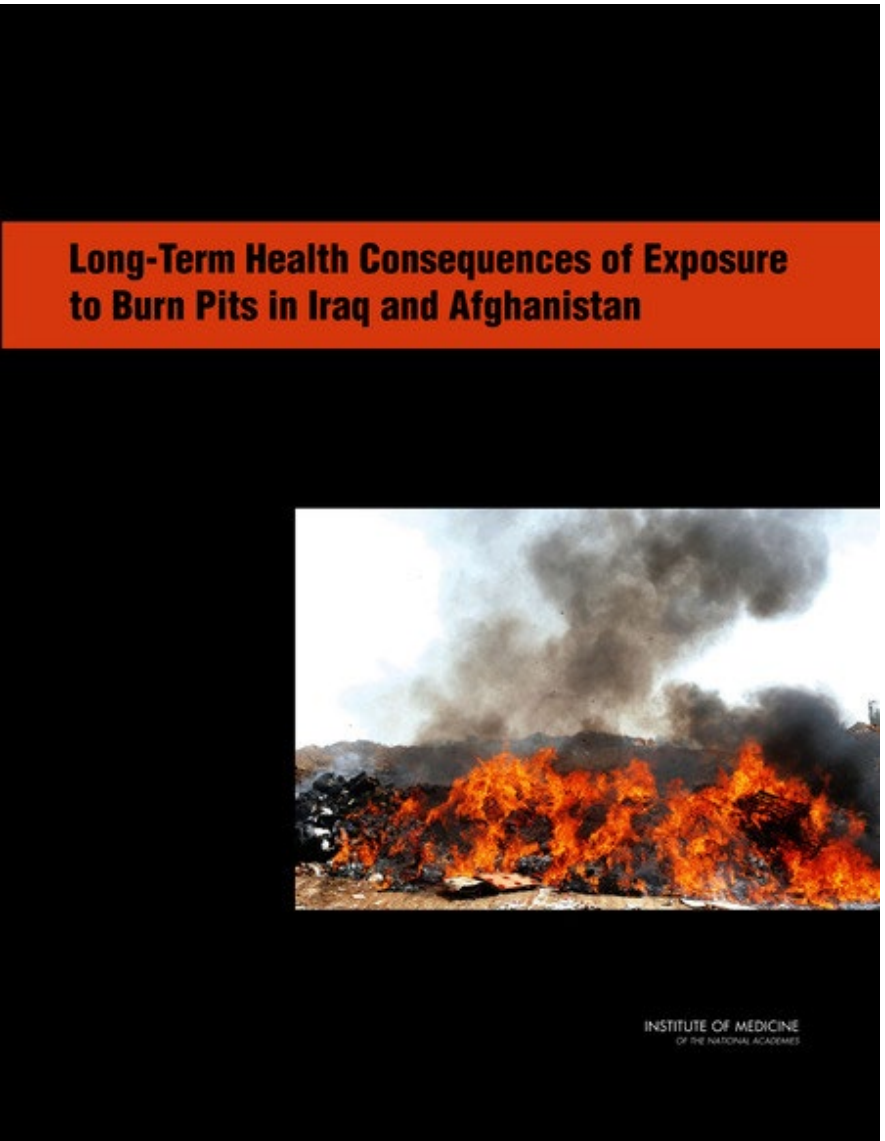
- First Persian Gulf War
  - Oil well fire smoke, dust storms
- World Trade Center first responders
  - Smoke from smoldering pile, other airborne PM
  - Significant decline in FEV1 in NYC firefighters *Aldrich TK, Gustave J, Hall CB, Cohen HW, Webber MP, Zeig-Owens R, Cosenza K, Christodoulou V, Glass L, Al-Othman F, Weiden MD, Kelly KJ, Prezant, DJ. Lung function in rescue workers at the World Trade Center after 7 years. N Engl J Med 2010; 362:1263-1272*
  - WTC cough, asthma, COPD, GERD, rhinosinusitis, sarcoidosis, PTSD

Enhanced Particulate Matter Surveillance Program

- 15 locations in SWA (Iraq 6, Afghanistan 2)
- >3000 filter samples – TSP, PM10, PM2.5
- All sites exceeded the Military Exposure Guideline (MEG) of 15 *u*g/m3 for PM2.5
- 3 main air pollutants:
  - Geological dust
  - Smoke from burn pits
  - Heavy metals (Al, Cd, Pb in PM2.5 fraction)

Engelbrecht JP, McDonald EV, Gillies JA, Jayanty RKM, Casuccio G, Gertler AW. Characterizing mineral dusts and other aerosols from the Middle East—Part 1: ambient sampling. Inhalation Toxicology 2009; 21:4, 297-326

2010 IOM Study on burn pits



Multiple studies document increased incidence of respiratory complaints in Veterans of the 1991 Gulf War and post-9/11 conflicts in Iraq and Afghanistan.

An unknown number returned from deployment unable to meet military physical fitness requirements.

- Dyspnea on exertion
- Cough
- Wheezing
- Chest Tightness

https://www.military.com/military-fitness/army-fitness-requirements/army-basic-training-pft

Working group & early approach to diagnosis

Overview and Recommendations for Medical Screening and Diagnostic Evaluation for Postdeployment Lung Disease in Returning US Warfighters

Cecile Rose, MD, MPH, Joseph Abraham, ScD, MS, Deanna Harkins, MD, MPH, Robert Miller, MD, Michael Morris, MD, Lisa Zacher, MD, Richard Meehan, MD, Anthony Szema, MD, James Tolle, MD, Matthew King, MD, David Jackson, PhD, John Lewis, PhD, Andrea Stahl, PhD, Mark B. Lyles, DMD, PhD, Michael Hodgson, MD, MPH, Ronald Teichman, MD, MPH, Walid Salihi, DO, Gregory Matwiyoff, MD, Gregory Meeker, MS, Suzette Mormon, MPH, RN, Kathryn Bird, MD, MSPH, and Coleen Baird, MD, MPH

Objective: To review inhalational exposures and respiratory disease risks in US military personnel deployed to Iraq and Afghanistan and to develop consensus recommendations for medical screening and diagnostic referral. **Methods:** A Working Group of physicians and exposure scientists from academia and from the Departments of Defense and Veterans Affairs was convened in February 2010. **Results:** Despite uncertainty about the number of people affected and risk factors for adverse pulmonary outcomes in this occupational setting, the Working Group recommended: (1) standardized approaches to pre- and postdeployment medical surveillance; (2) criteria for medical referral and diagnosis; and (3) case definitions for major deployment-related lung diseases. **Conclusions:** There is a need for targeted, practical medical surveillance for lung diseases and for a standardized diagnostic approach for all symptomatic deployed personnel.

Learning Objectives

- Become familiar with published data on inhalational exposures and respiratory disease risks in U.S. military personnel deployed to Iraq and Afghanistan, as reviewed by the Working Group.
- Summarize the Working Group's recommendations on standardized pre- and post-deployment medical surveillance, criteria for medical referral and diagnosis, and case definitions for deployment-related lung diseases.
- Identify areas of disagreement with the Working Group recommendations in the accompanying "clarification" by the Department of Defense.

NJH Center for Deployment-Related Lung Disease

Center for Deployment-Related Lung Disease

Since 2001, more than 3 million United States military personnel and contractors have deployed to Iraq, Afghanistan and other sites in southwest Asia. In-theatre exposure to open air burn pits, sandstorms, combat dust, diesel exhaust and other workplace hazards may place deployers at risk for disabling respiratory symptoms and lung diseases. Our program at National Jewish Health is focused on diagnosis and treatment of deployers with these lung conditions and on research into their causes and prevention, identifying new and better diagnostic tools, and developing more effective treatment options.

Center for Deployment-Related Lung Disease

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njhealth.org/deploymentlung

National Jewish Health®

njhealth.org

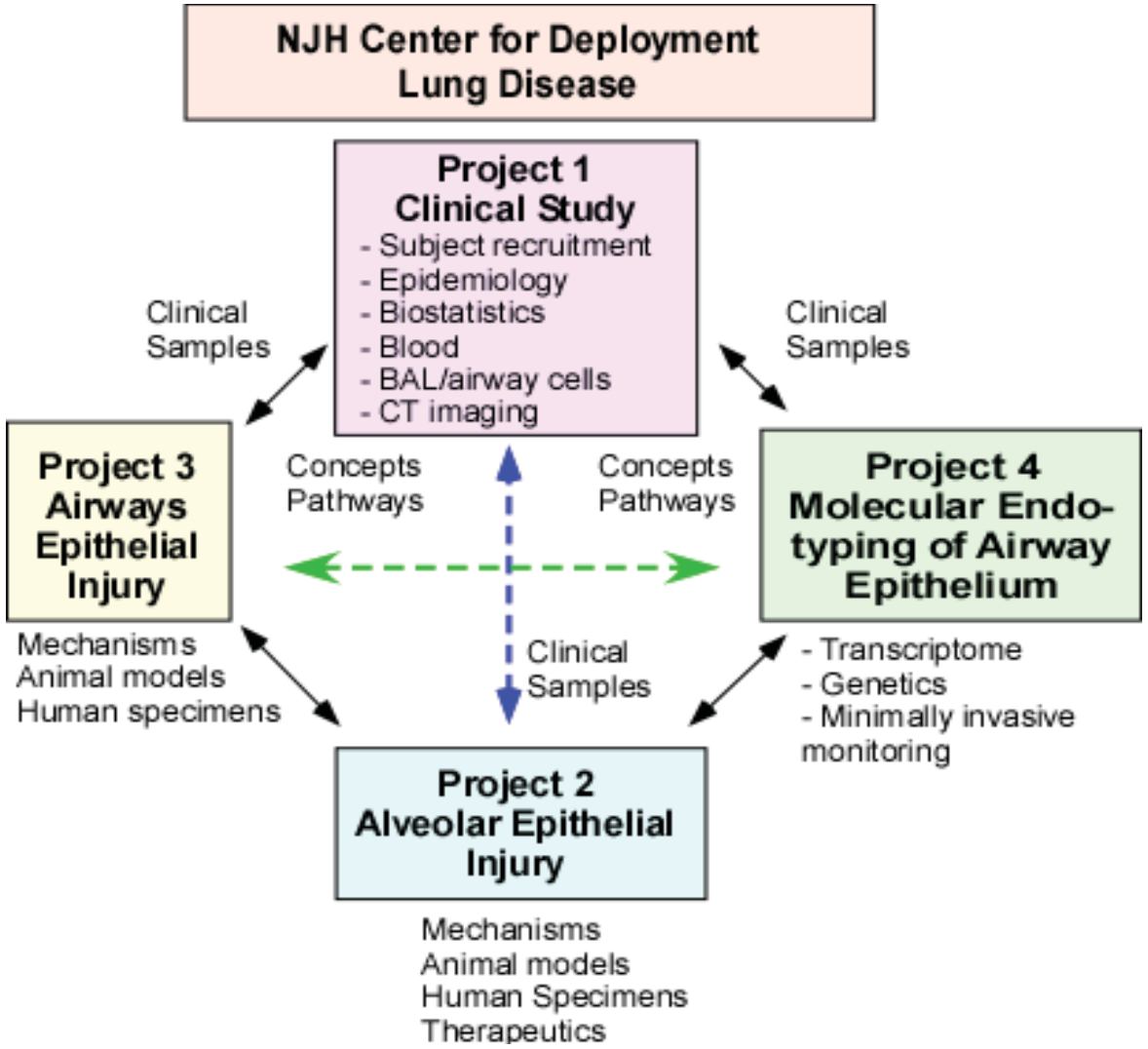
Center for Deployment-Related Lung Disease

at National Jewish Health

Standardized clinical case definitions

	Symptoms
Distal lung disease	
Deployment Distal Lung Disease (DDLD)	
Definite One or more of the following surgical lung biopsy findings: • Bronchiolitis, small airways inflammation, peribronchiolar fibrosis • Granulomatous pneumonitis • Hyperinflation or emphysema	• Cough • Shortness of breath • Chest tightness/ wheezing
Probable Two or more of the following chest CT findings: • Centrilobular nodularity • Air trapping or mosaicism • Bronchial wall thickening	
Proximal respiratory diseases	
Deployment-Related Asthma (DRA)	
Definite One or more of the following findings: • Post-bronchodilator ↑ in $FEV_1 \geq 12\%$ **and** ↑ in $FEV_1 \geq 200$ cc • Methacholine challenge with PC_{20} FEV1 ≤ 4 mg/mL	• Cough • Shortness of breath • Chest tightness/ wheezing
Probable • Methacholine challenge with PC_{20} FEV1 >4 and ≤16 mg/mL	
Deployment-Related Rhinosinusitis	
One or more of the following findings: • Sinus CT imaging with evidence of mucosal thickening, partial or complete opacification of the paranasal sinuses, rhinitis • Physician-diagnosed rhinosinusitis on laryngoscopy	• Cough • Runny Nose • Rhinorrhea • Sinus congestion • Sinus headache • Post nasal drip

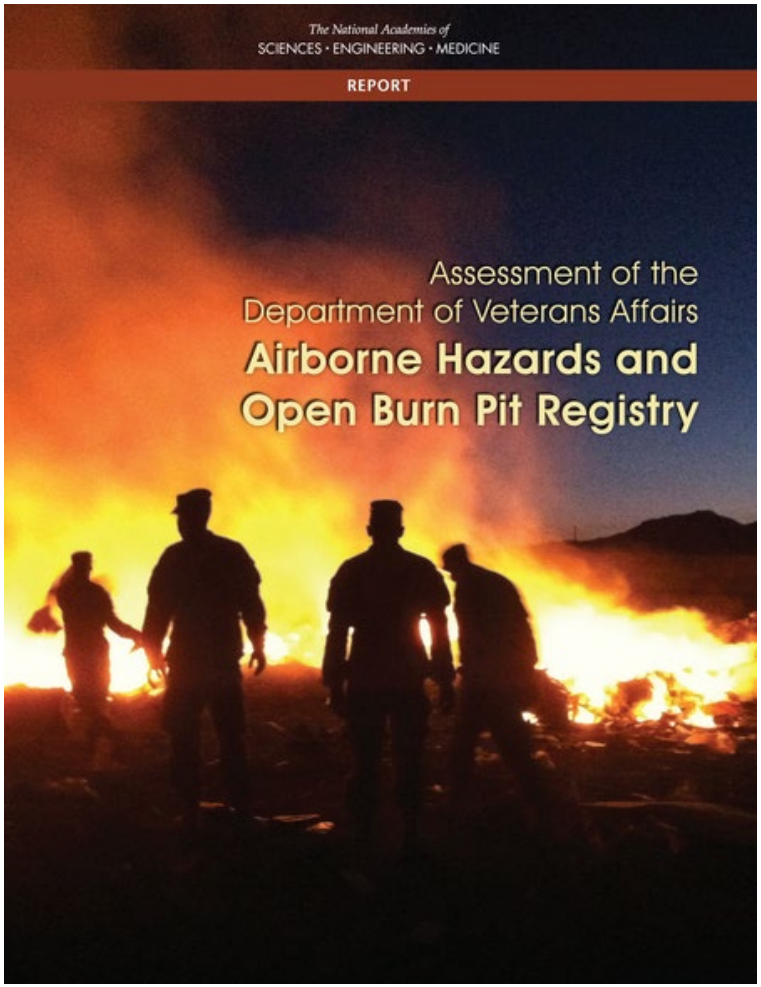
GLIDE: Multi-pronged investigation of lung disease mechanisms and prevention



VA Airborne Hazards and Open Burn Pit Registry

Eligible to participate if deployed to Southwest Asia theater of operations any time after August 2, 1990 or Afghanistan or Djibouti on or after September 11, 2001

https://www.publichealth.va.gov/exposures/burnpits/registry.asp



DRRD research: The 1st decade (2001 – 2011)

- Increased respiratory symptoms among previously deployed
- Complex and variable exposures
- General approach to diagnosis
- Standardized clinical case definitions
- Studies begin on mechanisms of airway injury
- VA Airborne Hazards and Open Burn Pit Registry

The second decade (2012 – 2022)

Iraq:
Operation Inherent
Resolve: 2014 - present

Afghanistan:
Operation Enduring
Freedom: 2001 - 2014
Operation Freedom's
Sentinel: 2015 – 2021

American Journal of Epidemiology

Vol. 187, No. 10
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June 11, 2018

Original Contribution

New-Onset Asthma and Combat Deployment: Findings From the Millennium Cohort Study

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Initially submitted January 4, 2018; accepted for publication May 23, 2018.

Key Findings:

- Military deployers with combat experience were 24%–30% more likely to develop asthma than those who did not deploy.
- This association was not seen in deployers without combat experience.

Military occupational specialty codes (MOS) assigned to all personnel by Dept. of Defense

Alpha numeric codes to describe job training & duties.

For example, Army 11 Bravo = Infantry

Job Duties

- Perform as a member of a fire team during drills and combat
- Aid in mobilization of vehicles, troops and weaponry
- Assist in reconnaissance missions
- Process prisoners of war and captured documents
- Use, maintain and store combat weapons (rifles, machine guns, antitank mines, etc.)

Source: https://www.goarmy.com/careers-and-jobs/browse-career-and-job-categories/combat/infantryman-11b.html

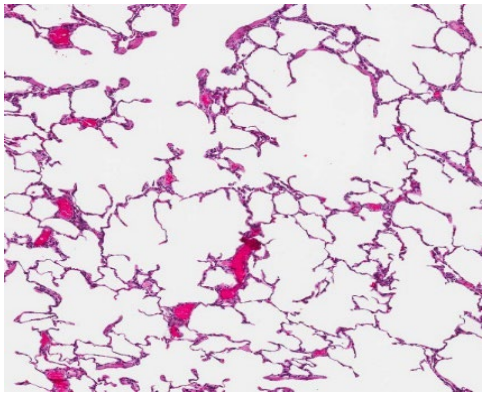
Combat MOS codes are linked to higher exposure risk, but have limitations.

- *Combat MOS codes* linked to the highest mean respiratory hazard exposure intensities and to likelihood of having undergone clinical evaluation for respiratory symptoms.
- Military deployment exposures may be related to variables such as deployment *location* (e.g., presence/absence of a burn pit), *timing* (before/after the drawdown), *season* (e.g., seasonal dust storms), and *job duties* during deployment (e.g., chaplain) that are not reflected in MOS code.

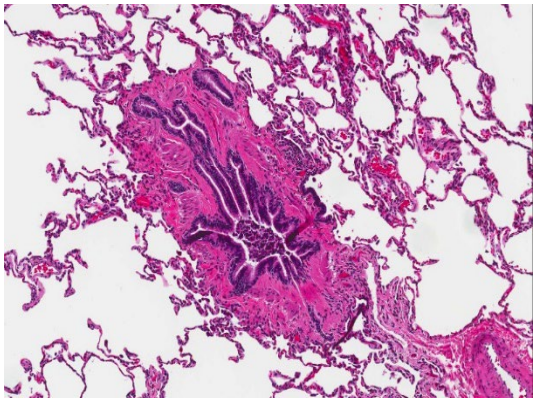
Zell-Baran LM, Meehan R, Wolff J, Strand M, Krefft SD, Gottschall EB, Macedonia TV, Gross JE, Sanders OL, Pepper GC, Rose CS. Military Occupational Specialty Codes: Utility in Predicting Inhalation Exposures in Post-9/11 Deployers. J Occup Environ Med. 2019 Dec;61(12):1036-1040.

Spectrum of lung histopathologic abnormalities

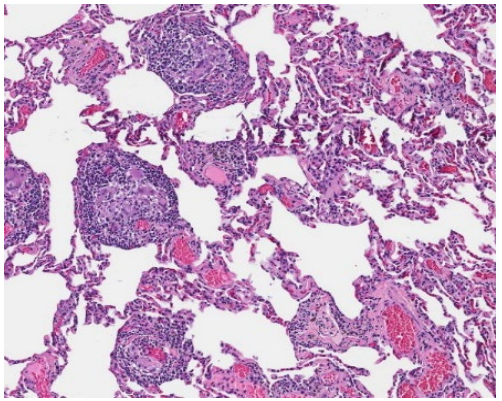
- Mod/severe emphysema/hyperinflation (46%)
- Constrictive/obliterative bronchiolitis (18.5%)
- Granulomatous pneumonitis (46%)
- Peribronchiolar metaplasia (68%)
- Pleuritis



Emphysema



Constrictive bronchiolitis



Granulomatous pneumonitis

- *Rose CS, Moore CM, Zell-Baran LM, Krefft S, Wolff J, Pang K, Parr J, Cool C. Small airways and airspace inflammation and injury distinguish lung histopathology in deployed military personnel from healthy and diseased lungs. Hum Pathol. 2022 Jun;124:56-66.*
- *Gutor SS, Richmond BW, Du RH, Wu P, Lee JW, Ware LB, Shaver CM, Novitskiy SV, Johnson JE, Newman JH, Rennard SI, Miller RF, Blackwell TS, Polosukhin VV. Characterization of Immunopathology and Small Airway Remodeling in Constrictive Bronchiolitis. Am J Respir Crit Care Med. 2022 Aug 1;206(3):260-270. doi: 10.1164/rccm.202109-2133OC. PMID: 35550018; PMCID: PMC9890264*

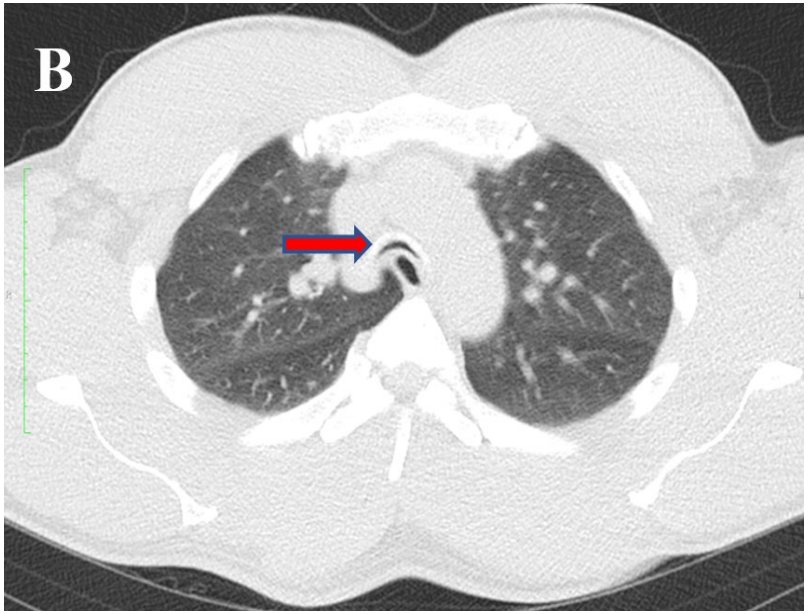
Noninvasive tests of distal lung disease

Deployers with DRA and DDLD significantly more likely than controls to have abnormal MBW/LCI.

- MBW/LCI is useful to detect global ventilation inhomogeneity from airways disease in symptomatic deployers.
- Deployers who reported more frequent exposure to explosive blasts had significantly higher LCI scores.

Zell-Baran LM, Krefft SD, Moore CM, Wolff J, Meehan R, Rose CS. Multiple breath washout: A noninvasive tool for identifying lung disease in symptomatic military deployers. Respir Med. 2021 Jan;176:106281.

Chest imaging in proximal & distal DRRD



Krefft SD, Oh A, Zell-Baran L, Wolff J, Moore CM, Macedonia TV, Rose CS. Semiquantitative chest computed tomography assessment identifies Expiratory Central Airway Collapse in symptomatic military personnel deployed to Iraq and Afghanistan. Journ Thoracic Imaging, 2021.

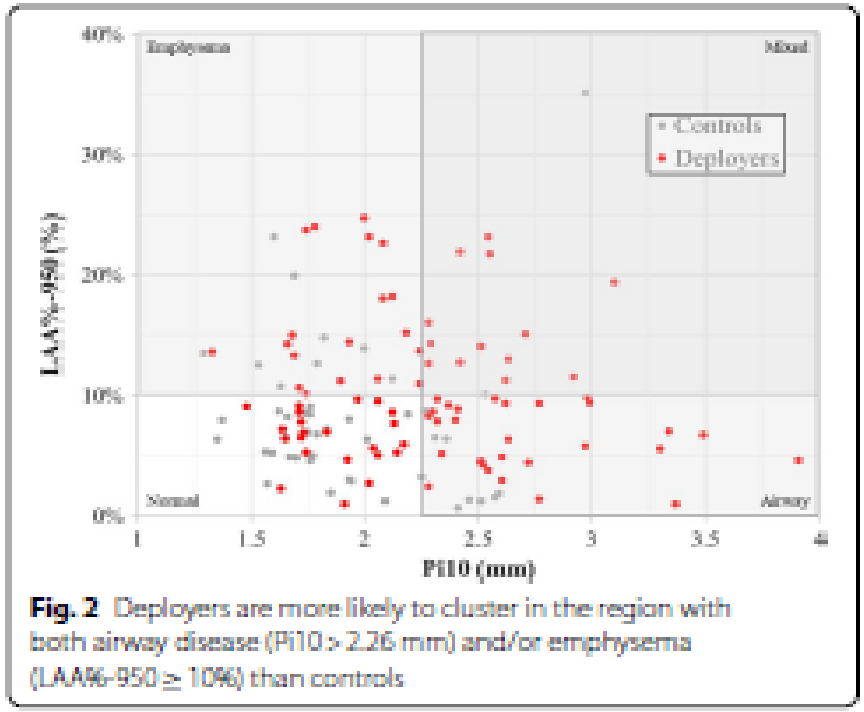


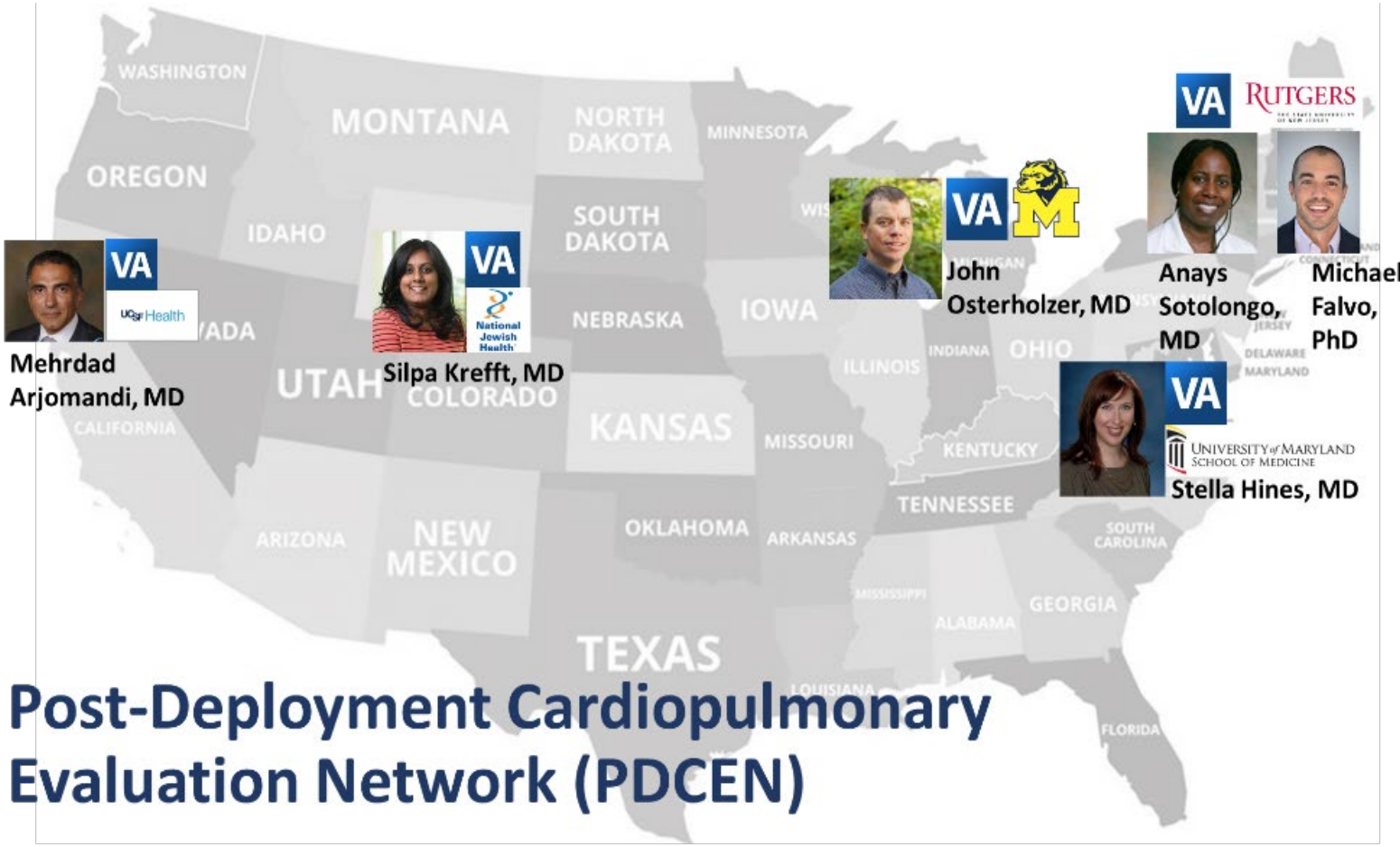
Fig. 2 Deployers are more likely to cluster in the region with both airway disease (Pi10 > 2.26 mm) and/or emphysema (LAA%-950 ≥ 10%) than controls

Zell-Baran L, Humphries SM, Moore CM, Lynch DA, Charbonnier JP, Oh AS, Rose CS. Quantitative imaging analysis detects subtle airway abnormalities in symptomatic military deployers. BMC Pulmonary Medicine. April 2022; 22:163.

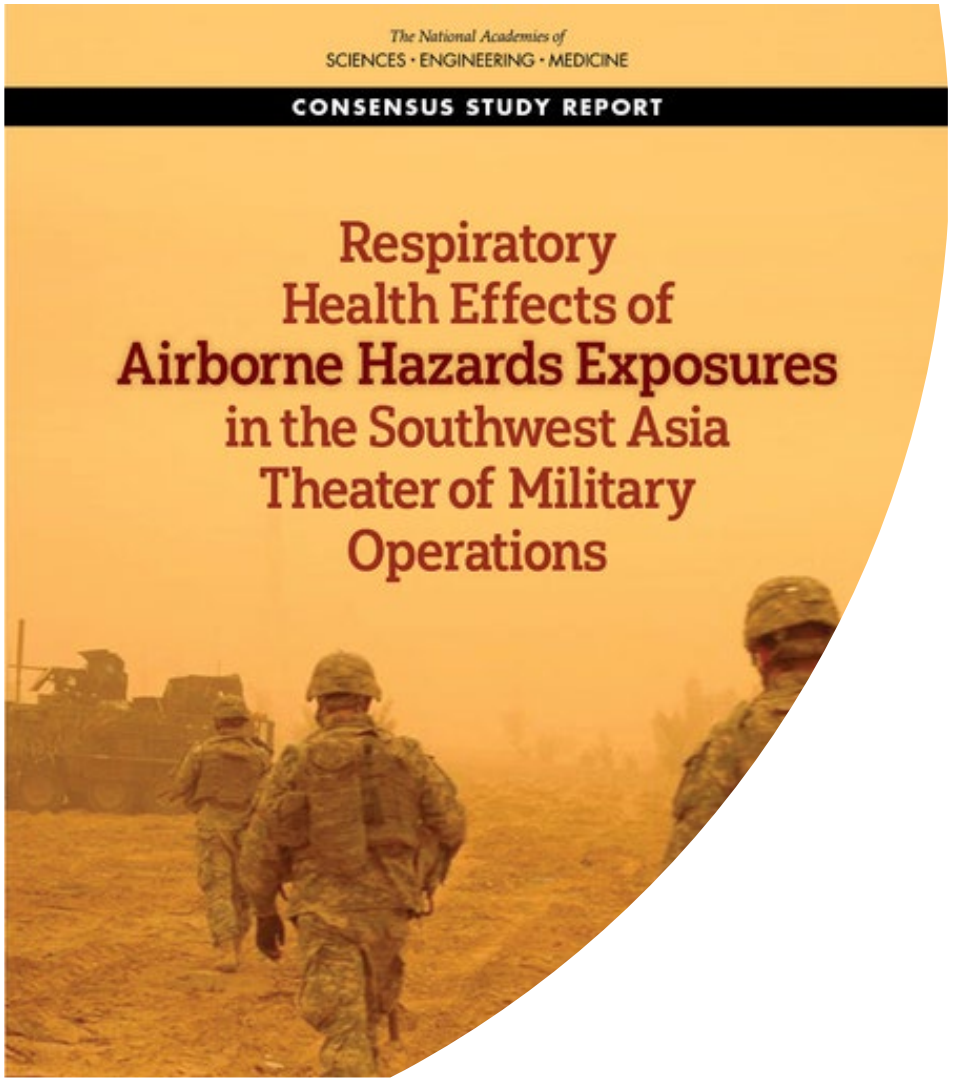
Expanding spectrum of deployment-related respiratory diseases

- Rhinitis and sinusitis
- Eosinophilic syndromes
- New onset asthma/aggravation of pre-existing asthma
- Bronchiolitis, granulomatous pneumonitis and emphysema
- Expiratory central airways collapse
- Intermittent laryngeal dysfunction *Morris MJ, Oleszewski RT, Sterner JB, Allan PF. Vocal Cord Dysfunction Related to Combat Deployment, Military Medicine. 2013 Nov;178(11): 1208-1212*
- Mitochondrial dysfunction as a cause of dyspnea *Onofrei CD, Gottschall EB, Zell-Baran L, Rose CS, Kraus R, Pang K, Krefft SD. Unexplained dyspnea linked to mitochondrial myopathy following military deployment to Southwest Asia and Afghanistan. Physiol Rep. 2023 Jan;11(2):e15520.*

VA Centers of Excellence



2020 NASEM Report



- Insufficient evidence of association
- Lack of good exposure characterization
- DoD-VA partnership ‘with free flow of information’

Emerging consensus on DRRD

- 3-tiered approach to diagnosis
- Injury in multiple lung compartments
- Terminology: DRRD

[Diffuse Lung Disease Guidelines and Consensus Statements]

CHEST

Consensus Statements on Deployment-Related Respiratory Disease, Inclusive of Constrictive Bronchiolitis

A Modified Delphi Study

Check for updates

Michael J. Falvo, PhD; Anays M. Sotolongo, MD; John J. Osterholzer, MD; Michelle W. Robertson, MD; Ella A. Kazerooni, MD; Judith K. Amorosa, MD; Eric Garshick, MD; Kirk D. Jones, MD; Jeffrey R. Galvin, MD; Kathleen Kreiss, MD; Stella E. Hines, MD; Teri J. Franks, MD; Robert F. Miller, MD; Cecile S. Rose, MD; Mehrdad Arjomandi, MD; Silpa D. Krefft, MD; Michael J. Morris, MD; Vasiliy V. Polosukhin, MD; Paul D. Blanc, MD; and Jeanine M. D'Armiento, MD, PhD

DRRD research: The 2nd decade (2012 – 2022)

- Expanding spectrum of deployment-related respiratory diseases
- Combat related risks
- Lung histopathology
- Noninvasive diagnostic tests
- VA Centers of Excellence
- PACT Act [Sergeant First Class Heath Robinson Honoring our **P**romise to **A**ddress **C**omprehensive **T**oxics Act]

PACT Act covered nonmalignant respiratory illnesses (‘presumptive’)

- Asthma that was diagnosed after service
- Chronic bronchitis
- Chronic obstructive pulmonary disease (COPD)
- Chronic rhinitis
- Chronic sinusitis
- Constrictive bronchiolitis or obliterative bronchiolitis
- Emphysema
- Granulomatous disease
- Interstitial lung disease (ILD)
- Pleuritis
- Pulmonary fibrosis
- Sarcoidosis

Moving forward: 2023 and beyond

"Scientific findings do not fall on blank minds that get made up as a result. Science engages with busy minds that have strong views about how things are and ought to be."

Sir Michael Marmot, 2004, Professor of Epidemiology at University College London

Research needs and priorities

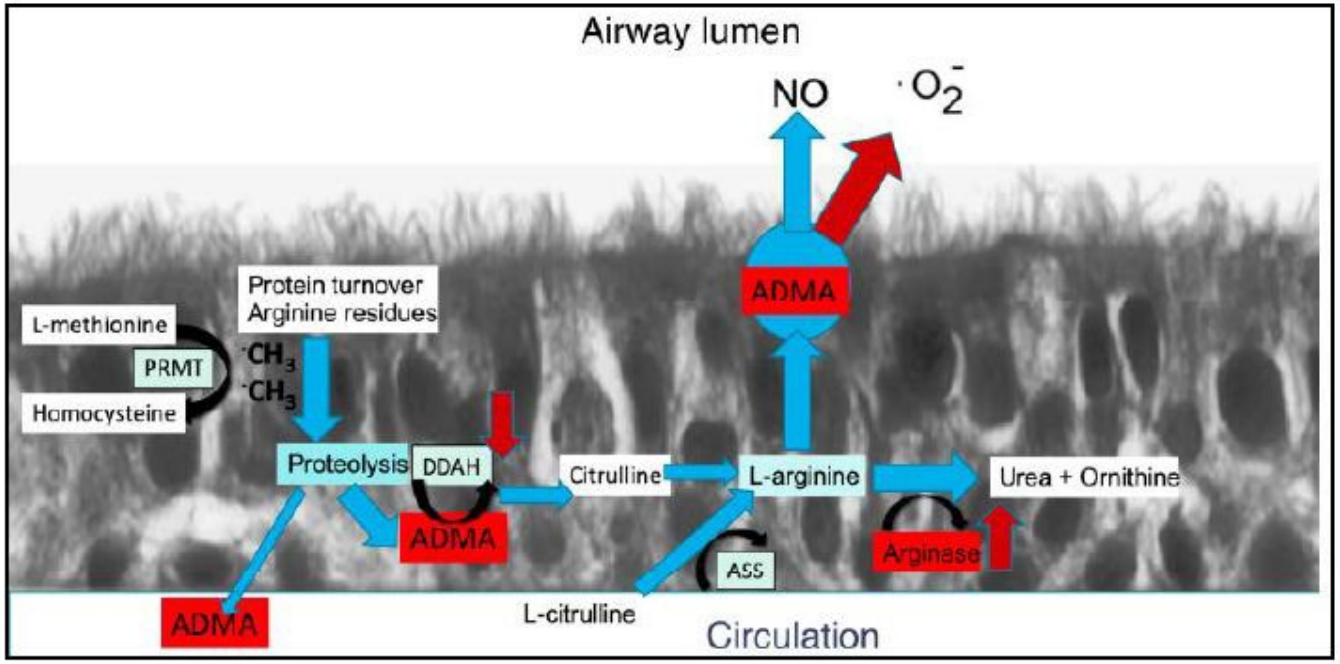
- Exposure assessment
- Large epidemiologic studies of respiratory outcomes
- Standardized questionnaires in multi-center studies
- Further validation of noninvasive markers of lung disease – eg, iOS, LCI, quantitative imaging
- Better understanding of DRRD pathogenesis to inform treatment
- Longitudinal follow up to assess prognosis
- Linkage of exposures to health outcomes
- Prevention: Targeting high risk settings for realistic exposure control

Longitudinal outcomes

- More intense deployment inhalational exposures linked with lower post-deployment lung function: *Significantly lower mean FEV1pp (88.8%) in highest vs lowest (97.2%) exposure tertile (p=0.004) [adjusted for cigarette smoking and family history asthma/COPD]*
- Consider baseline spirometry for those likely to face combat and those involved in infrastructure (burn pit duties) where risks appear highest.

Evidence-based treatment

SEALS: L-citrulline supplementation for deployment-related asthma



Exposure assessment and control

- Exposure assessment in military theaters
  - Portable, real-time, mixed/variable
  - Biomarkers
- Exposure priorities for PACT Act research
  - PM2.5, burn pit smoke, jet fuels, DEP, allergens/bioaerosols
  - Occupational VDGF
  - Effect modifiers (eg, noise, stress, temperature extremes)
- Linkage of exposures to health outcomes
  - ILER (Individual Exposure Record)
  - VA Asthma Study

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Participating Military Personnel

https://atgbcentral.com/army-pic.html