

Psychological stress is an Associated Health Risk to Military Exposures

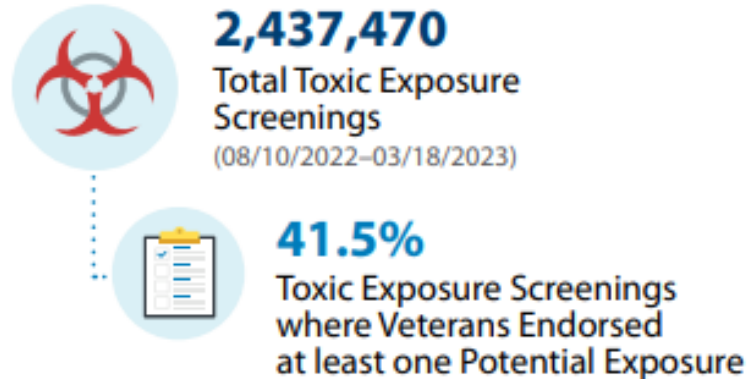
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PACT Act Screenings & Burn Pit Registry



[VA PACT Act Performance Dashboard](#)

- Over 300,000 Veterans have reported burn pit exposures on the AHOBPR as of March 2022
- 47.8% had respiratory disease
 - Greatest number of participants reporting symptoms are ages 35-44
 - most were in active duty army

❖ Veterans are experiencing respiratory diseases at an increasing rate, & with earlier onset than civilians

Chronic Stress and the Veteran Population

Malignant Neoplasms	
Brain Cancer	105
Lung and Bronchus Cancer	1,256
Bladder Cancer	732
Prostate Cancer	4,535
Kidney and Renal Pelvis Cancer	431
Non-Hodgkin Lymphoma	609
Endocrine/Metabolic Disorders	
Diabetes	19,367
Mental Disorders	
PTSD	12,520
Major Depressive Disorder	18,964
Anxiety Disorder	11,730
Substance Abuse Disorder	14,553

7,668

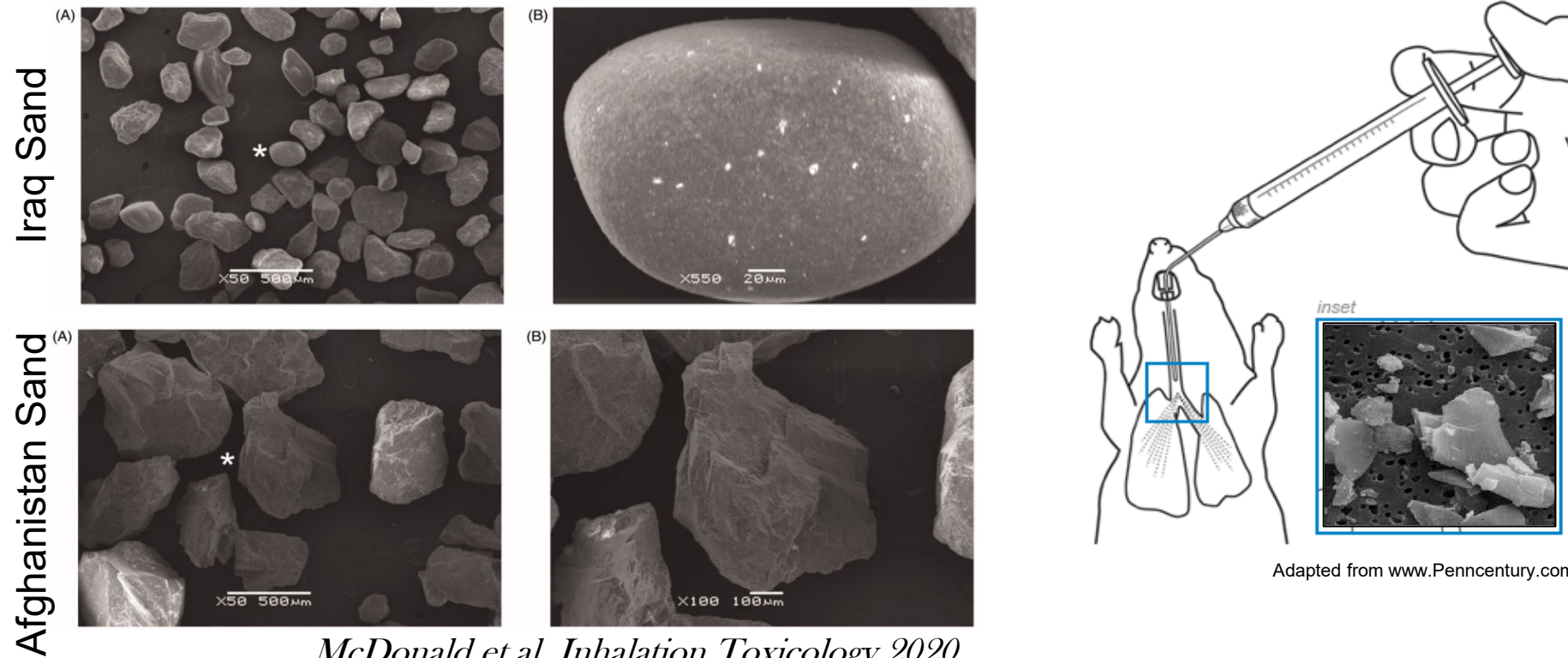
57,767

Source: Post-Deployment Surveillance Report 2019

- The second most reported condition among Veterans was Major Depressive Disorder (MDD) (*2019 Post-Deployment Surveillance Report* - data from over 12 million Veterans 2010-2019)
- MDD, anxiety disorder, and PTSD were among the conditions that consistently had the highest incidence from 2015-2019 over all VHA users
 - in OEF/OIF/OND Veterans these conditions were even more prevalent

❖ Stress and mental health are important co-morbidities in multiple diseases however, our understanding of the direct impact of psychological stress on disease is limited

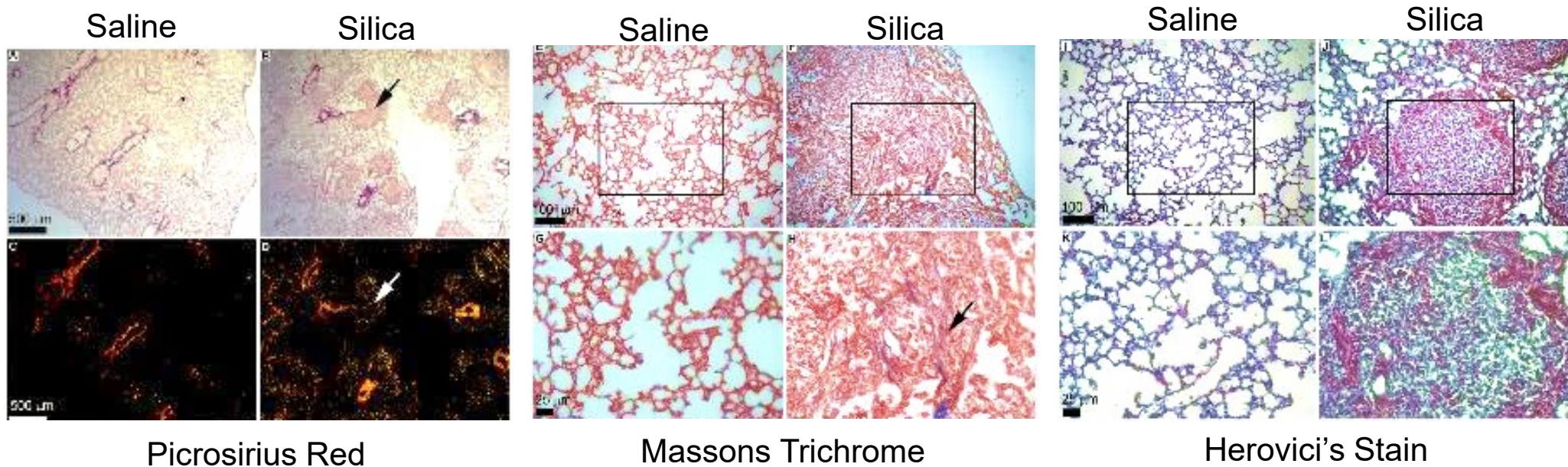
Veteran-centric Animal Model of Pulmonary Fibrosis



McDonald et.al. Inhalation Toxicology 2020

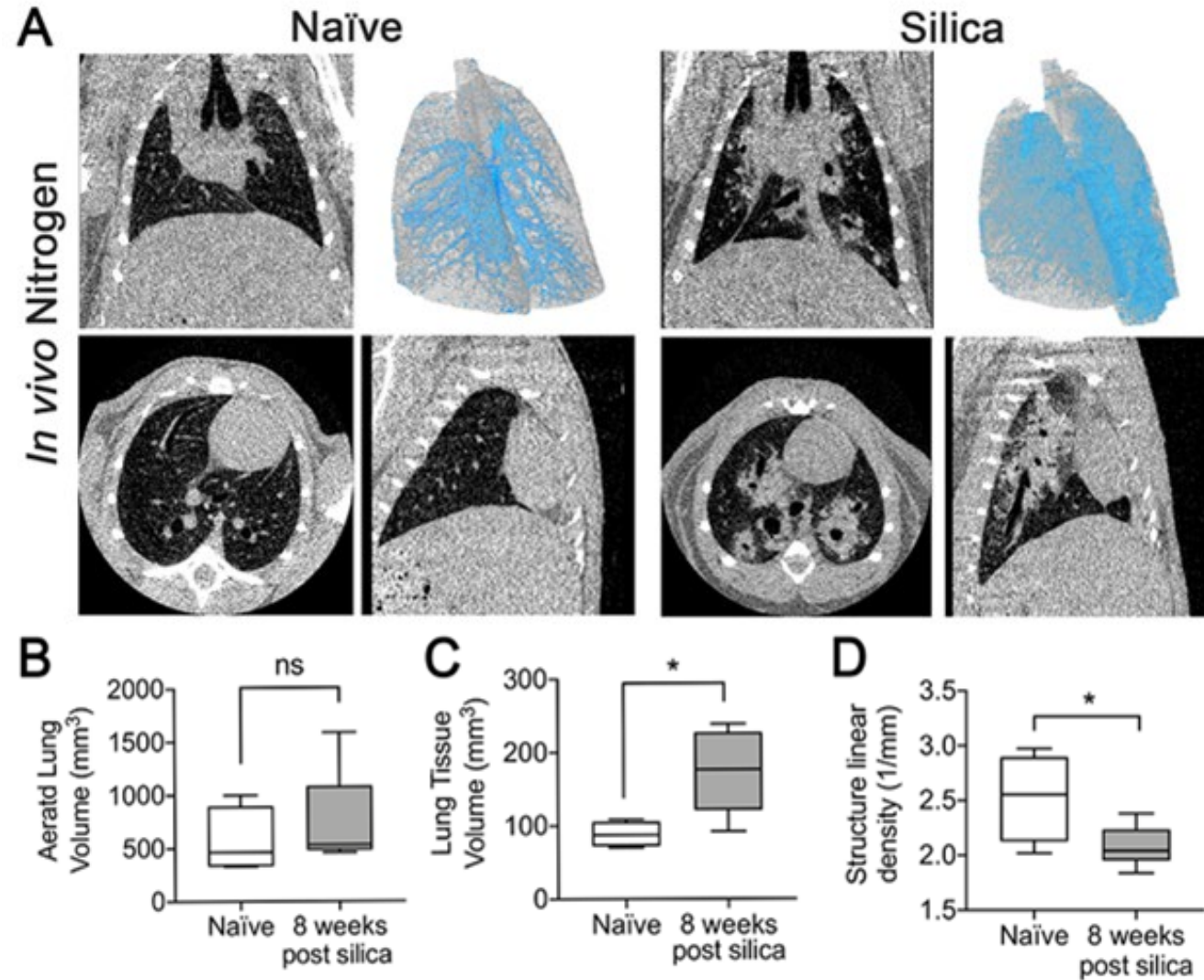
- Simplified Model
- Development of Silicotic Nodules with Collagen Deposition
 - Heterogenous
- Progressive, Non-Resolving

Histological Features of Silica Exposure-Induced Pulmonary Fibrosis

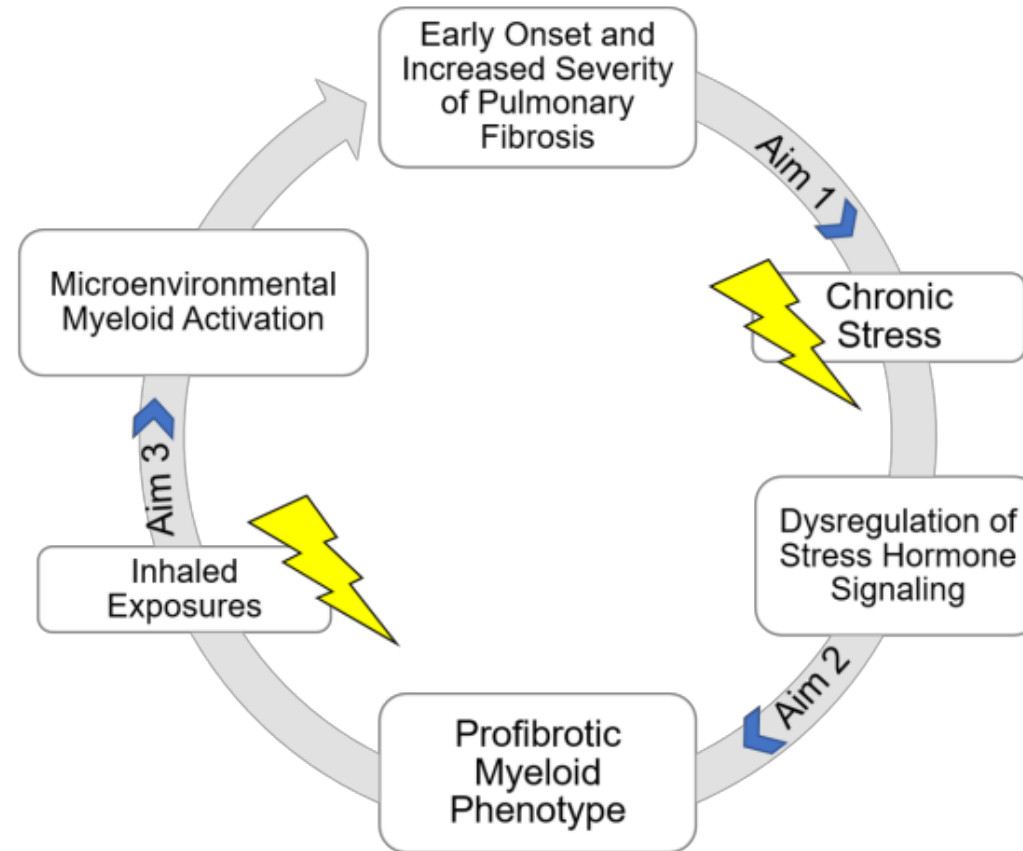


- Increased collagen deposition 4-8 weeks post-instillation
- Development of fibrotic nodules
- Neutrophilic infiltrate

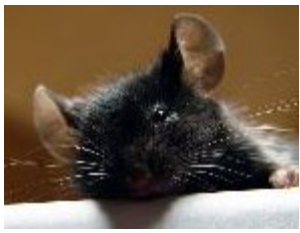
Radiographic Features of Silica Exposure-Induced Pulmonary Fibrosis



Two-Hit Hypothesis for Pulmonary Fibrosis



- ❖ Hypothesis - Chronic stress is associated with early onset & increased incidence of respiratory disease
 - ❖ How does stress impact patient experience and mechanisms of pulmonary fibrosis?



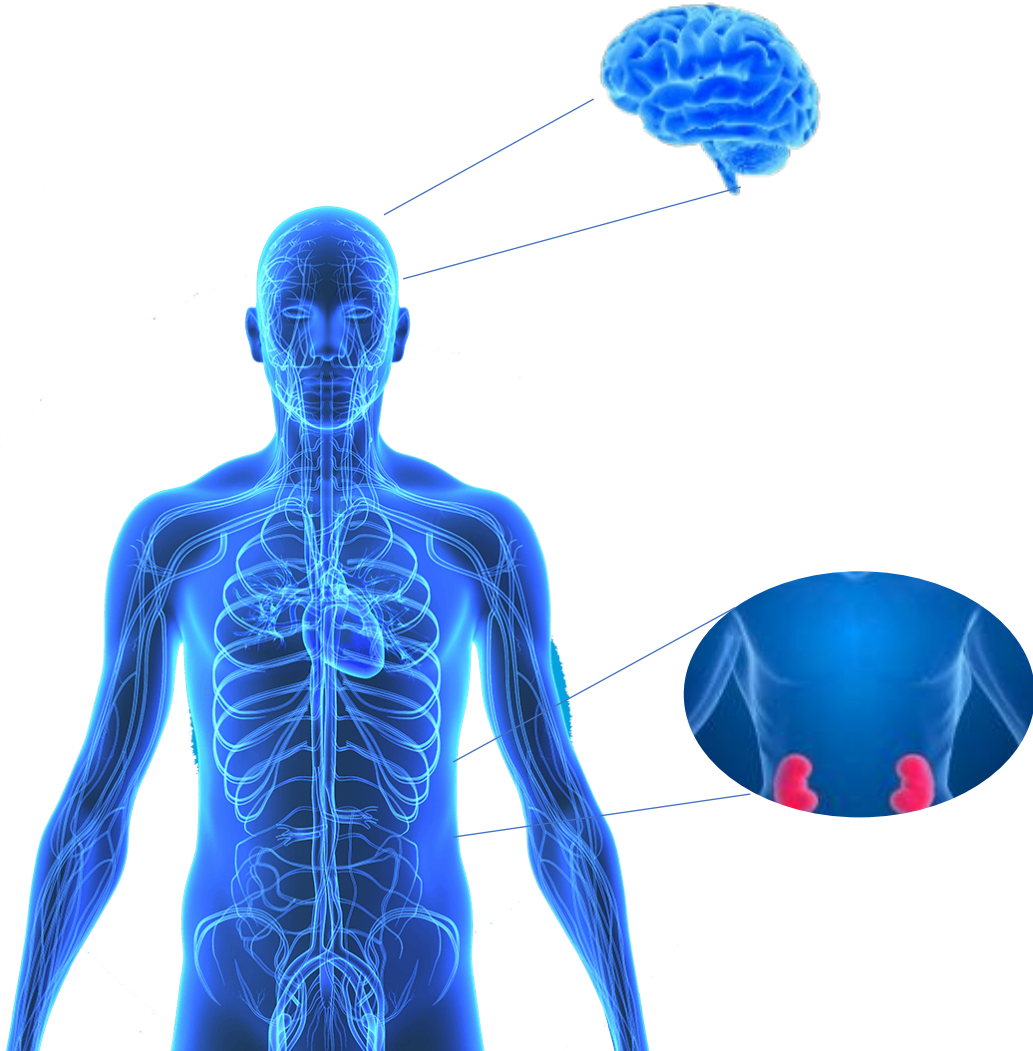
Modeling Human Stress in Animals

Multiple models:

- Chronic Unpredictable Stress (CUS) - Mice are exposed to a variety of mild stressors daily
- Repeated stress – Forced Swim
- PTSD-like models – Combining stress with a “cue”



Stress Pathways



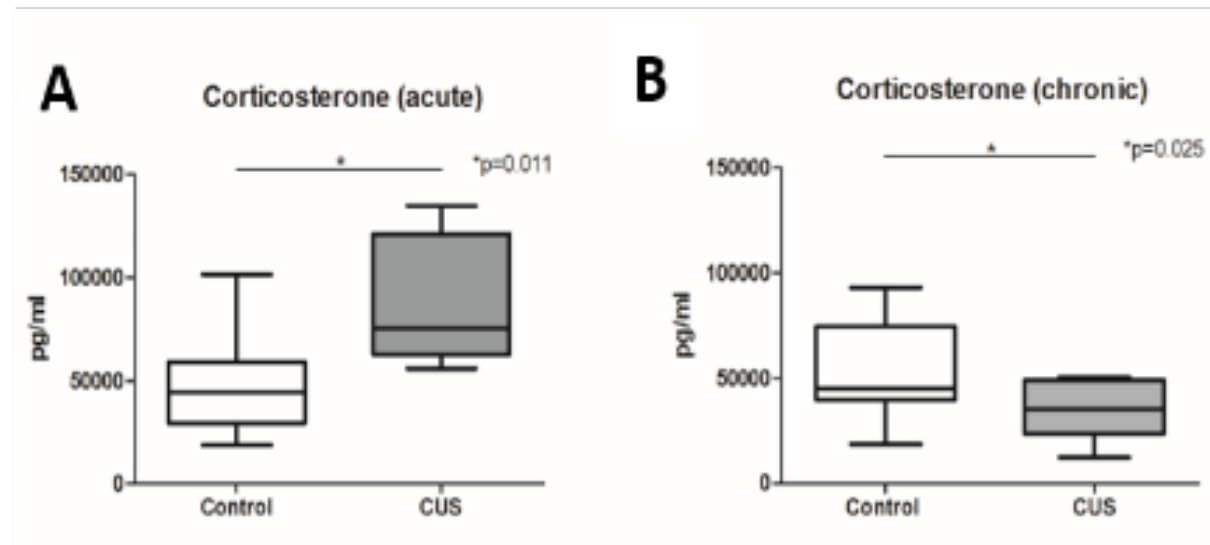
The Hypothalamic Pituitary Adrenal Axis (HPA)

- **Glucocorticoids - Cortisol (Corticosterone)**
- **Dysregulation occurs in many who experience chronic stress**

β -adrenergic system

- Catecholamines
- Epinephrine, Norepinephrine
- Fight or flight

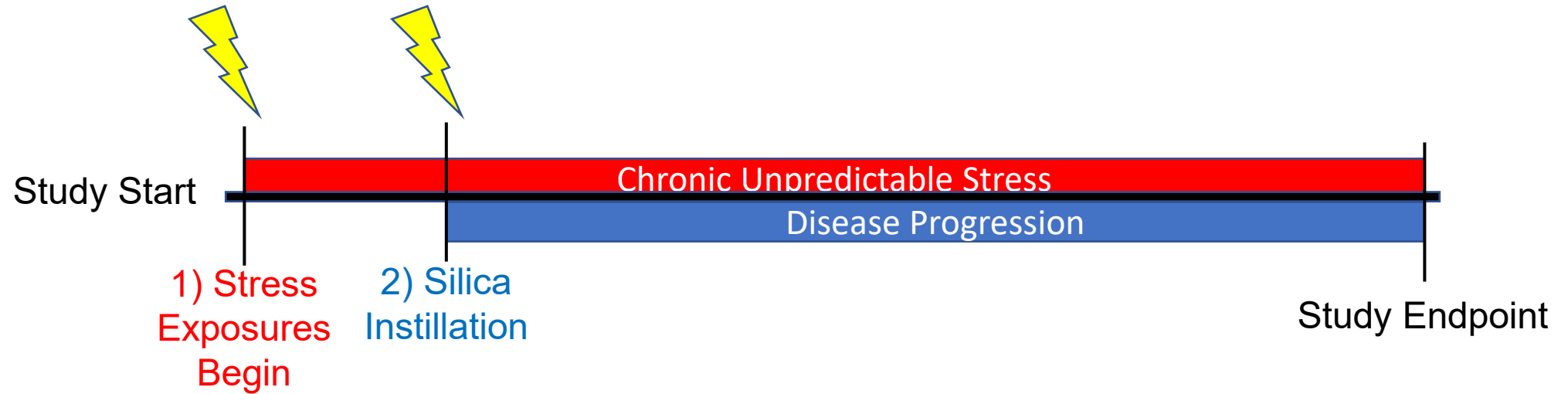
Stress Signaling Pathways are Dysregulated in Mice Exposed to Chronic Unpredictable Stress



McDonald et. al. Frontiers of Psychiatry 2019

- ❖ Stress signaling through glucocorticoids is dysregulated as a result of 10 days of chronic unpredictable stress

Experimental Design



Four Cohorts: No Stress, Stress, Silica, Stress Silica

Behavioral Assessment – Open Field Test

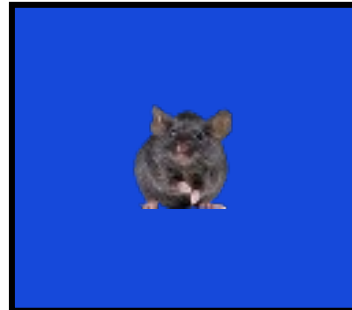
Anxiety

- Increased time in periphery
- Decreased time in center
- Decreased mobility

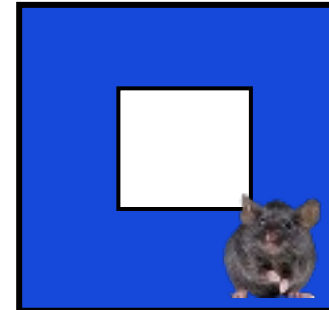
Open Field



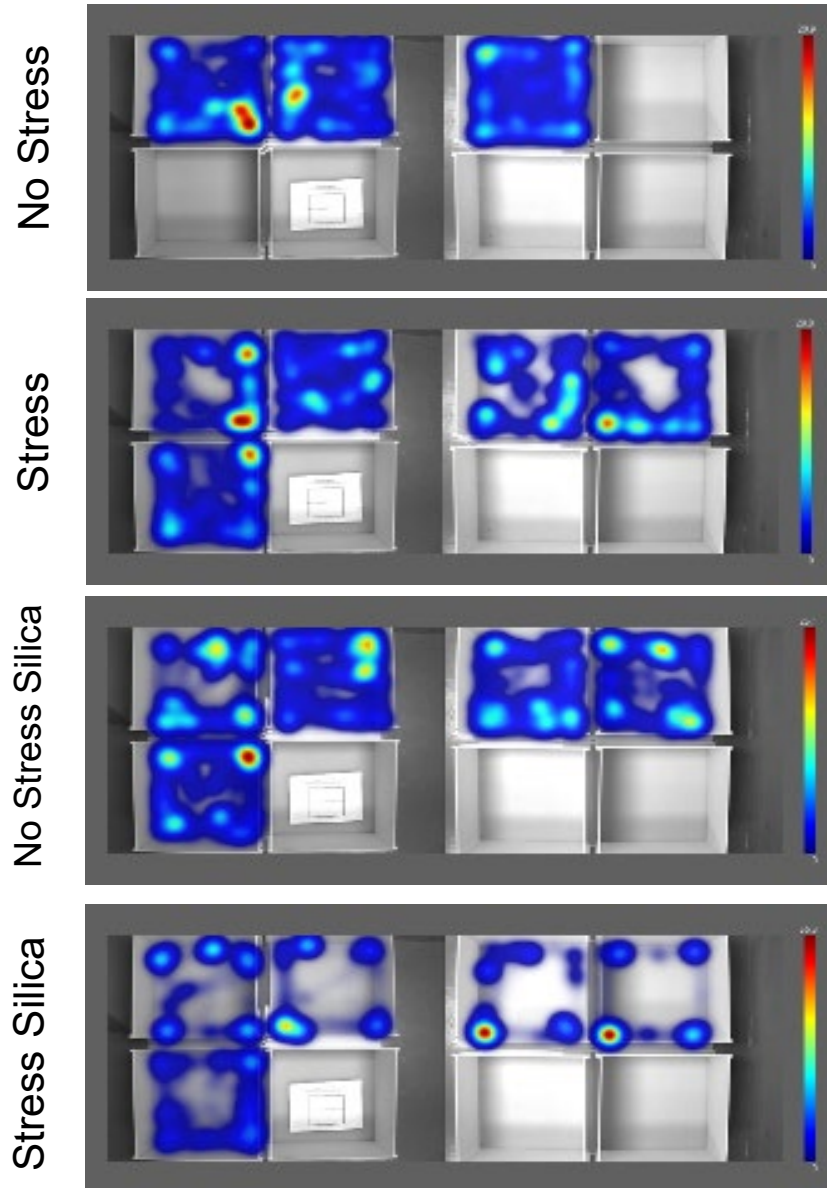
Normal Exploration



Anxious Behavior



Chronic Stress and Silica-induced Fibrosis Result in Anxious Behavior

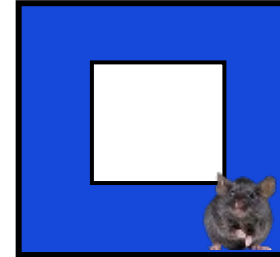


- Increased time in periphery of the open field
- Decreased time in center
- Decreased mobility
- ❖ Combined stress and silica exposure increase anxious behavior

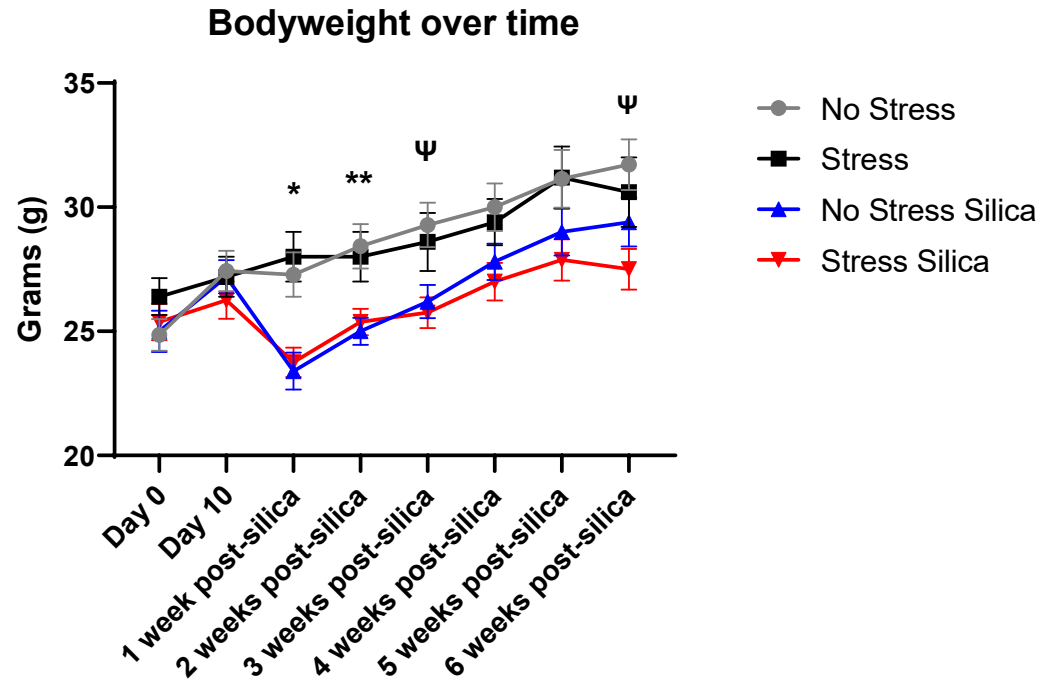
Normal Exploration



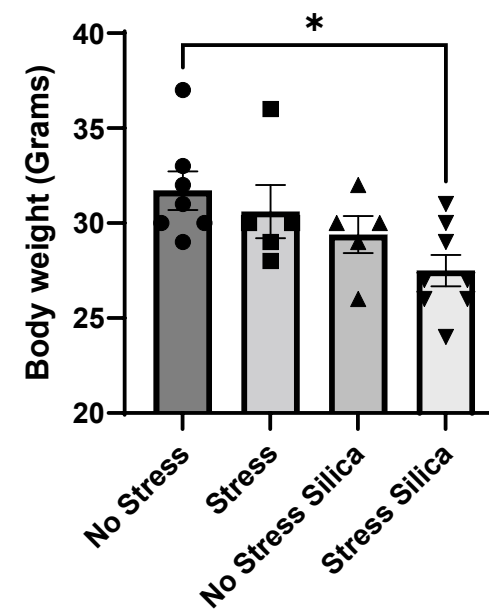
Anxious Behavior



Chronic stress leads to decreased bodyweight and slower recovery following silica-instillation



Bodyweight at Endpoint (6 wks)

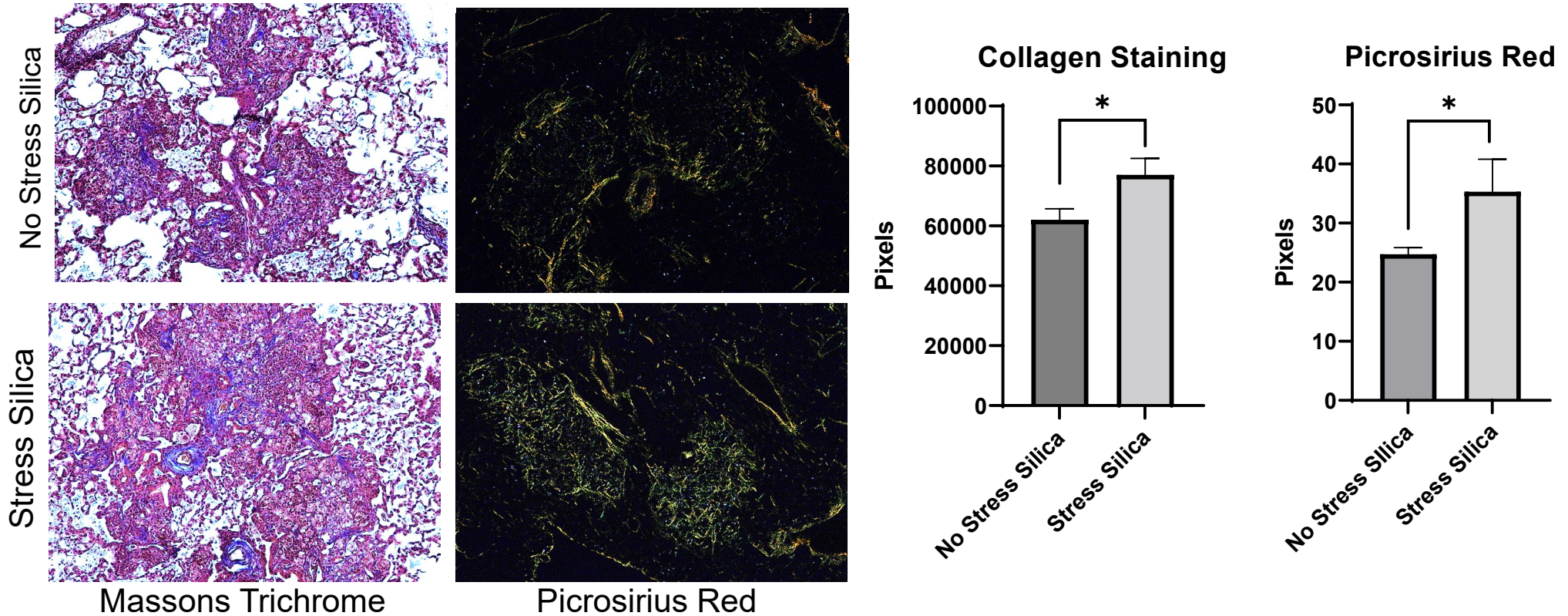


- Decreased bodyweight is associated with poor prognosis
- Lower bodyweight is independently associated with reduced survival in patients with pulmonary fibrosis

• *Respiration* 2018;96:338–347 DOI: 10.1159/000490355
 • *Jouneau et al. Respiratory Research* (2020) 21:312
 • *Kulkarni PIOs* (2019) <https://doi.org/10.1371/journal.pone.0221905>

❖ Chronic stress may significantly impact patient outcome

Chronic Stress Increases Collagen Deposition in Silica-induced Pulmonary Fibrosis

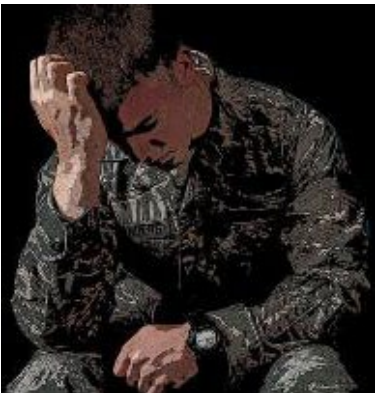


❖ Chronic Psychological Stress Exacerbates Silica Exposure-Induced Pulmonary Fibrosis

Summary

Chronically stressed mice and mice with silica-induced pulmonary fibrosis exhibit:

- Anxiety and increased stress response
- Dysregulation of glucocorticoid signaling
- Decreased bodyweight
- Slower recovery following silica exposure
- Increased collagen deposition in fibrotic lungs (fibrotic response)



- ❖ In our animal studies, chronic stress results in physiological effects known to contribute to worse prognosis and decreased survival in patients

Future Directions Toward Achieving Positive Real-World Impact



- ❖ Elucidate mechanisms by which stress impacts pulmonary pathologies
 - Glucocorticoids (HPA axis)
 - β -adrenergic signaling
 - Brain-Body Feedback Loop

- ❖ Identify potential therapeutics for pulmonary fibrosis resulting from toxic exposures
 - Increase understanding of mechanisms driving pulmonary disease
 - Clarify guidance for use of corticosteroids toward personalized medicine

- ❖ Identify patients for early monitoring and intervention
 - Mental health screening for those identified as having experienced a toxic exposure

- ❖ Improve awareness of the risks of mental health impact on lung disease

THANK YOU!



- RMR VA and PACT Act Symposium Organizers for the invitation and opportunity to share my research
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