World Trade Center (WTC) Health Program

World Trade Center (WTC) Health Program

Research Meeting 2023 SUMMER

Since 2001 the WTC Health Program has funded research of the 9/11-exposed population. This research fortifies our understanding of 9/11 health effects. Research also provides a pathway to improved healthcare for people afflicted from 9/11 exposure. To read more about the history of WTC Health Program research, visit the Research section of our online museum exhibition.

- About Research
- Blogs
- Publications
- Compendium Archive

Updates

NIOSH Science Blog: The Availability and Validity of Information on Children Exposed to the 9/11/2001 Disaster

NIOSH Science Blog: The Changes to Scientific Peer Review as a Result of the Pandemic

WTCHP Research Grant Project Details and Data Center Outputs

This interactive PowerBI guide can be clicked to filter on our Project grants and contracts to learn more about the project outputs, research topics, the populations investigated, funding awarded, and the principal investigators and their institutions. New projects are awarded every June. **How to use this report:** Click on an element in the report to filter all of the data. For instance, click on the Responders Population segment of the Population pie chart to view the projects, principal investigators and institutions associated with Responders. Hold the <CNTRL> key while clicking Responders and Adult Mental Health to filter on both variables to only view the data on Responder mental health projects. Double-click the Responders segment to undo the filter and see the complete dataset again. **Updated December 9, 2022.**

PI Last Name

ZEIG-OWENS
ZAMMIT
WOLD
WISNIVESKY
WEISENBACH
WEIDEN
WEBBER
WASZCZUK/KOTOV
VERMA
VANGERWIN
TRASANDE

Project Number

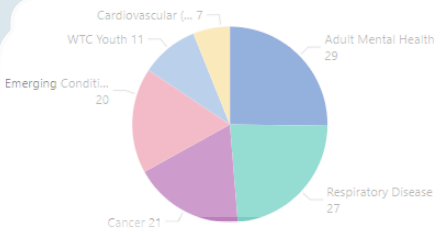
Project Number	Funder
74705	NIA
74706	NIA
74707	NIA
74708	NIA
10394	WTCHP
10395	WTCHP
10396	WTCHP
10399	WTCHP
10401	WTCHP
10401-05	WTCHP
10401-09	WTCHP

Institution Name

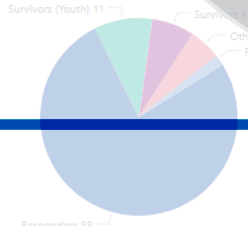
ALBERT EINSTEIN COLLEGE OF MEDICINE
CITY UNIVERSITY of NEW YORK QUEENS (CUNY-Queens)
COLUMBIA UNIVERSITY HEALTH SCIENCES
FEINSTEIN INSTITUTE FOR MEDICAL RESEARCH
FORDHAM UNIVERSITY
HENRY M. JACKSON FDN FOR THE ADV MIL/MED
NEW YORK STATE PSYCHIATRIC INSTITUTE
NEW YORK UNIVERSITY SCHOOL OF MEDICINE

Number of Projects Selected

Number of Projects by Topic



Number of Projects by Cohort Population



Number of Publications in this Filter Selection

214

The citations link to external sites if link is available

Publication
Aldrich, T. K., Weakley, ... Dhar, S., Hall, C. B., Crosie, T., Banauch, G. I., Weiden, M. D., Izbicki, G., Cohen, H. W., Gupta, A., King, C., Christodoulou, V., Webber, M. P., Zeig-Owens, R., Moir, W., Nolan, A., Kelly, K. J., & Prezant, D. J. (2016). Bronchial reactivity and lung function after World Trade Center exposure. Chest, 150(6), 1333-1340. https://doi.org/10.1016/j.chest.2016.07.005
Ayappa, I., Chen, Y., Bagchi, N., Sanders, H., Black, K., Twumasi, A., Rapoport, M. D., Lu, S.-E., & Sunderram, J. (2019). The association between health conditions in World Trade Center responders and sleep-related quality of life and sleep complaints. Int J Environ Res Public Health, 16(7). https://doi.org/10.3390/ijerph16071229

148.2M

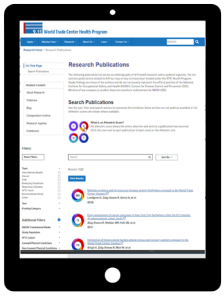
Total Awarded Budget (2011-2022)*

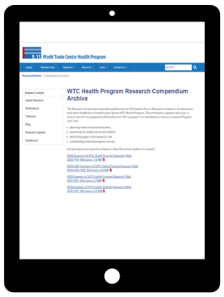
* The National Institute on Aging (NIA) awarded funding for four WTC research projects in 2021. These four awards are

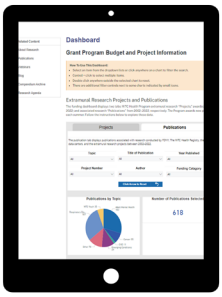
Number of Projects Awarded by Fiscal Year. (The budget filter reflects the total project funds distributed to date for all projects awarded in a given fiscal year.)

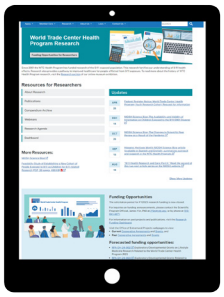
9.11
WTC Health Program

World Trade Center (WTC) Health Program









www.cdc.gov/wtc/research

WTC Health Program

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Association of Lung Function Decline with All-Cause and Cancer-Cause Mortality after World Trade Center Dust Exposure | *David Goldfarb, PhD, MPH* 161

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On overview of cancers in Survivors in the WTC EHC with a focus on breast cancer | *Joan Reibman, MD | Professor of Medicine and Environmental Medicine, NYU Langone Medical Center Medical Director, H+H WTC Environmental Health Center* 231

Cognitive Function among WTC-Exposed Community Members with Mental Health Symptoms | *Rebecca Rosen, Ph.D. Director of Mental Health | WTC EHC Clinical Center of Excellence H+H: Bellevue, Gouverneur, Elmhurst | Clinical Associate Professor of Psychiatry | Grossman School of Medicine | June 28, 2023* 263

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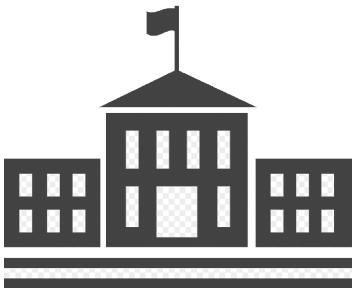
RUTGERS
Robert Wood Johnson Medical School

Pathogenesis and Consequences of **OSA** in **WTC** Responders

Jag Sunderram, ***MD***
Professor of Medicine
Interim Chief
Division of Pulmonary and Critical Care Medicine

Rutgers, The State University of New Jersey



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RUTGERS
Robert Wood Johnson
Medical School

Pathogenesis and Consequences of **OSA** in **WTC** Responders

Jag Sunderram, ***MD***
Professor of Medicine
Interim Chief
Division of Pulmonary and Critical Care Medicine

Rutgers, The State University of New Jersey

WTC Dust and Health Consequences

- **Large dust cloud of particles consist of a mixture of highly alkaline crushed concrete, gypsum and synthetic fibers.**
- **Upper and lower airway injury.**

Lioy PJ et.al., Environ Health Perspect, 2002

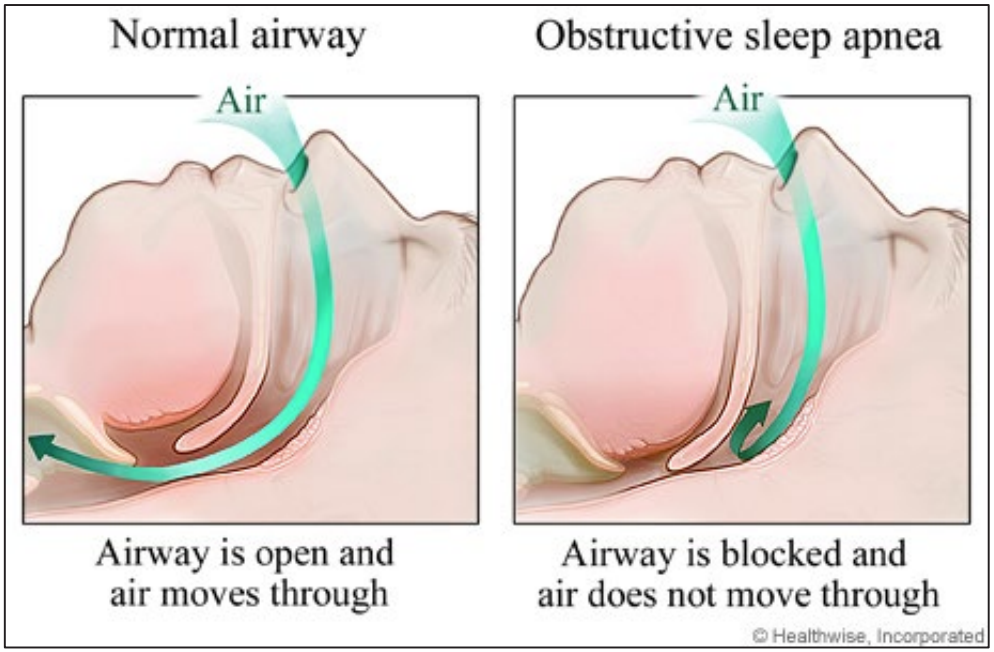
Clinical Manifestation

- **Upper Airway involvement**
  - Chronic Rhinosinusitis
  - Obstructive Sleep Apnea
  - **GERD**
- **Lower Respiratory Involvement**
  - Chronic Cough-Asthma
  - Sarcoid like granulomas
  - Constrictive bronchiolitis
  - Peribronchiolar emphysematous changes
- **Cognitive Issues**
  - Mild Cognitive Impairment
  - **PTSD**

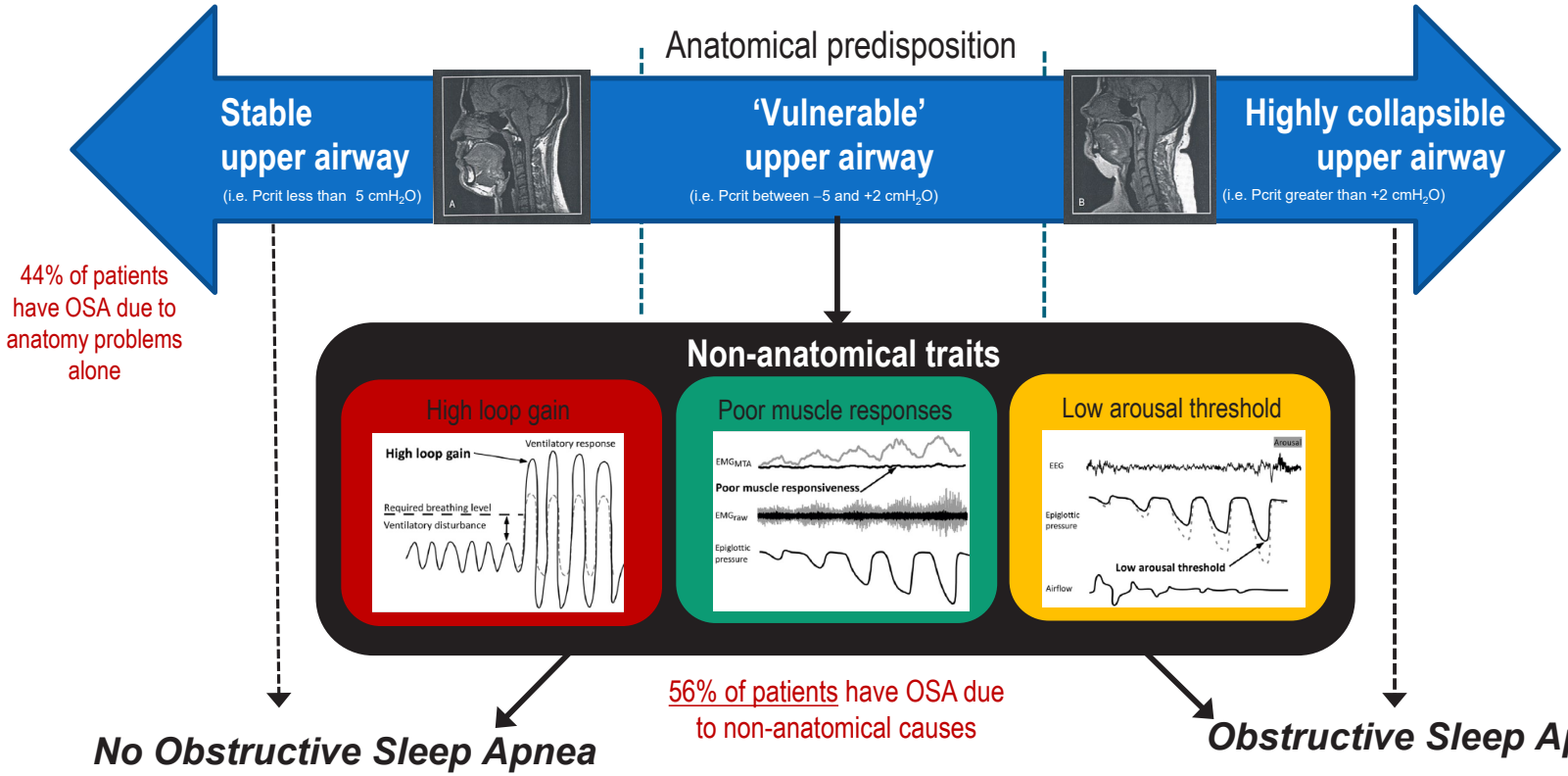
Guidotti, et.al., Am.J.Ind.Med. 2011

Obstructive Sleep Apnea

- Obstructive Sleep Apnea ***(OSA)*** is characterized by repeated closure of the upper airway during sleep.
- Anatomical, mechanical and sleep factors lead to airway obstruction in **OSA.**



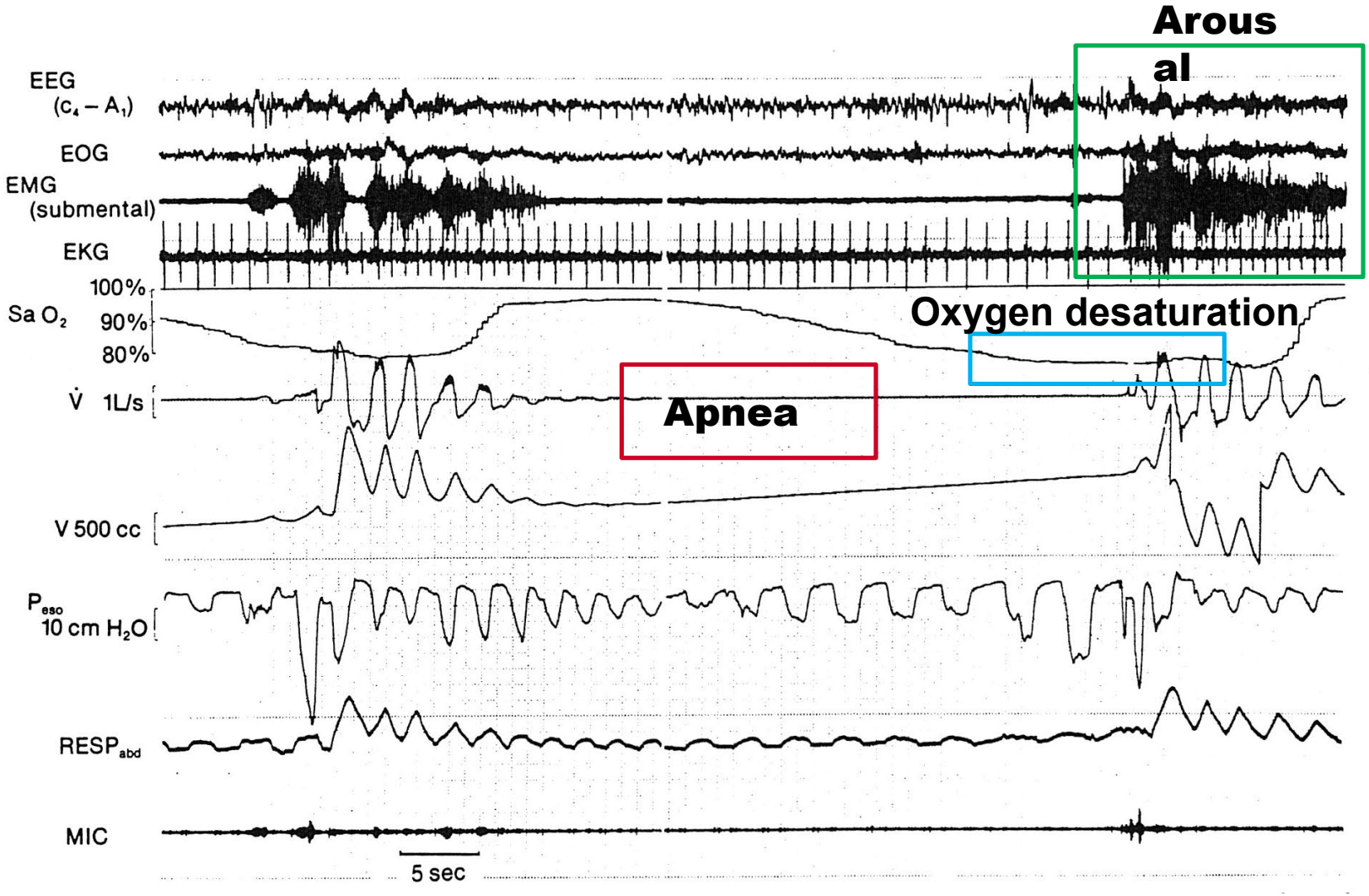
Understand the mechanisms causing OSA in an individual



Schwab. Clinics in Chest Medicine, 1998
Owens et al. SLEEP, 2015
Carberry et al. Chest, 2017
Eckert et al, ARJCCM, 2013

Patients do not all get OSA for the same reason

Pathophysiological consequences of OSA



RUTGERS

Cardiometabolic Consequences of Chronic Intermittent Hypoxia (CIH)

- **Hypertension**
- **CAD**
- **CHF**
- **Atrial Fibrillation**
- **Stroke**
- **Diabetes**
- **Metabolic Syndrome**

Neurocognitive Consequences of Sleep Fragmentation

- **Excessive daytime sleepiness**
- **Reduced Attention**
- **Increased MVAs**
- **Depression**
- **Impaired quality of life**
- **Cognitive Impairment**

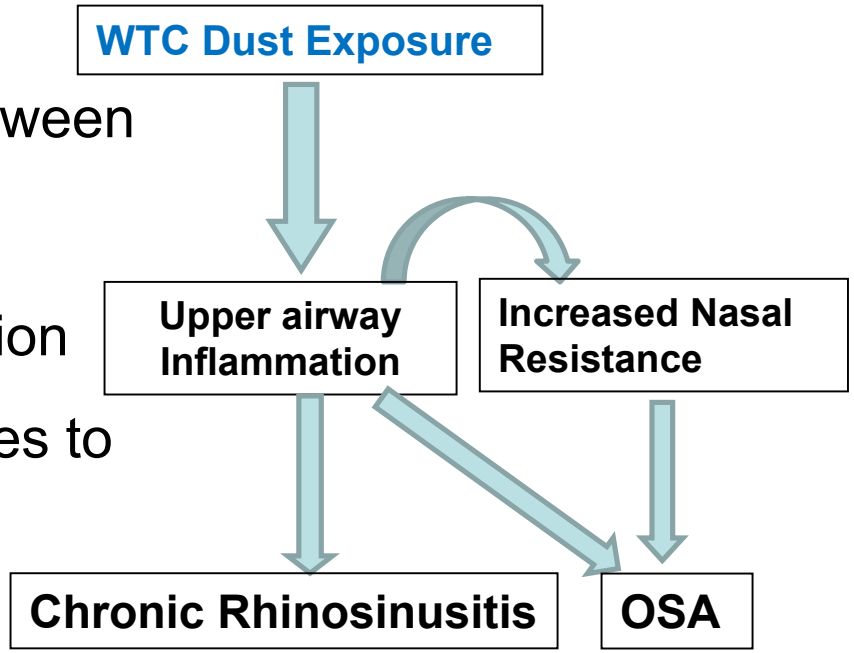
Diagnosis and Classification of severity of **OSA**

- **Diagnosis is based on number of Apnea+Hypopnea**
  - **AHI** *(Apneas+ Hypopneas/total sleep time in hours)*

- **Severity classification**
  - **Mild: AHI** of **5-14.9** events per hour of sleep
  - **Moderate: AHI: 15-29.9** events per hour of sleep
  - **Severe: AHI: >30** events per hour of sleep of sleep

WTC SNORE STUDY

- Examine the relationship between nasal pathology and **OSA**.
- Hypothesis: nasal inflammation leads to **CRS** and predisposes to **OSA** either directly or
- mediated by an increase in nasal resistance in this population.



U01OH010415 CDC/NIOSH

WTCSNORE Cohort

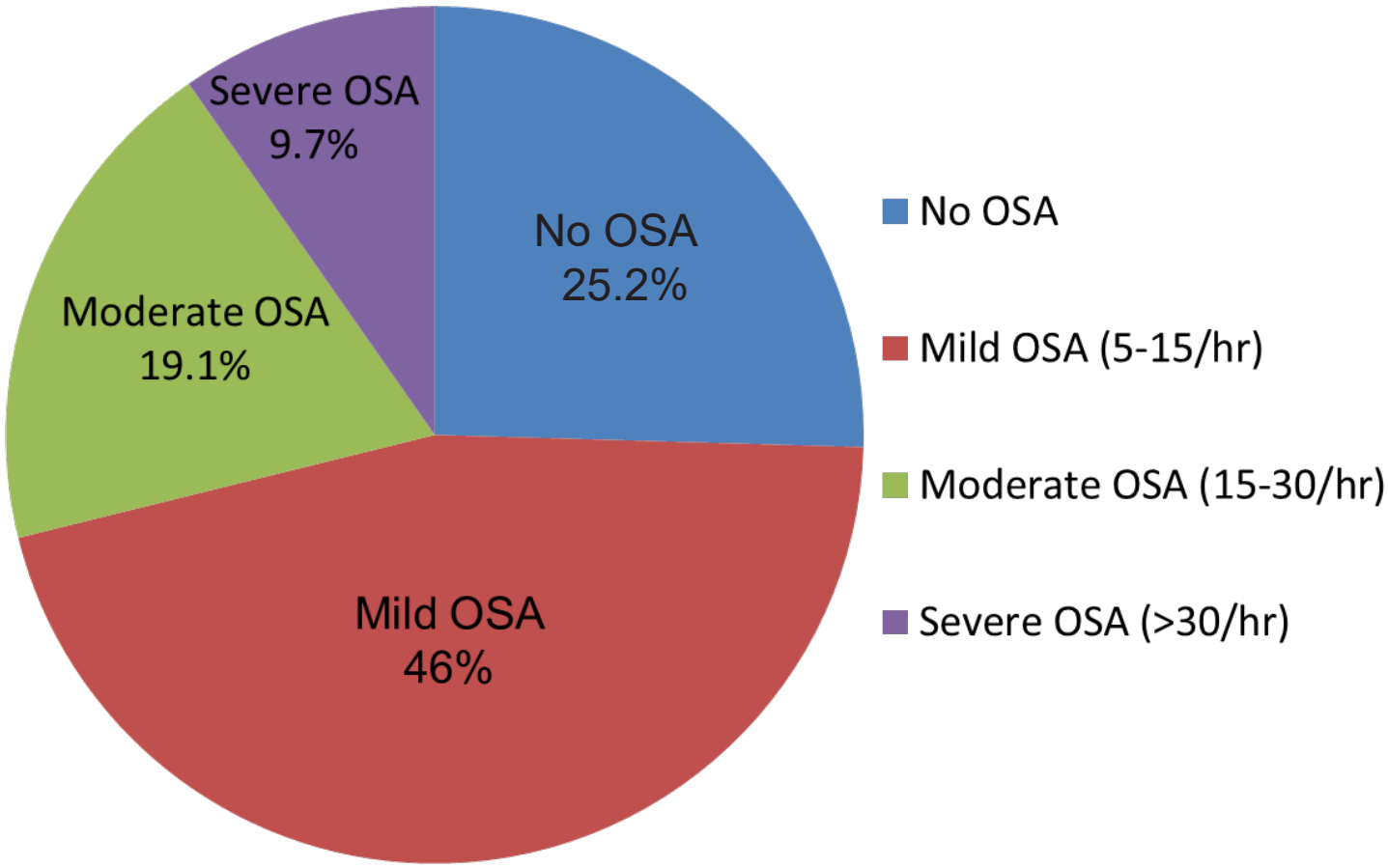
- Recruited subjects from WTCHP at Rutgers, NYU and ISMMS
- Inclusion:
  - No snoring or OSA prior to 9/11/2001
  - Not currently on OSA treatment
  - Efforts to recruit current non-snorers

U01OH010415 CDC/NIOSH

Demographics of the study participants

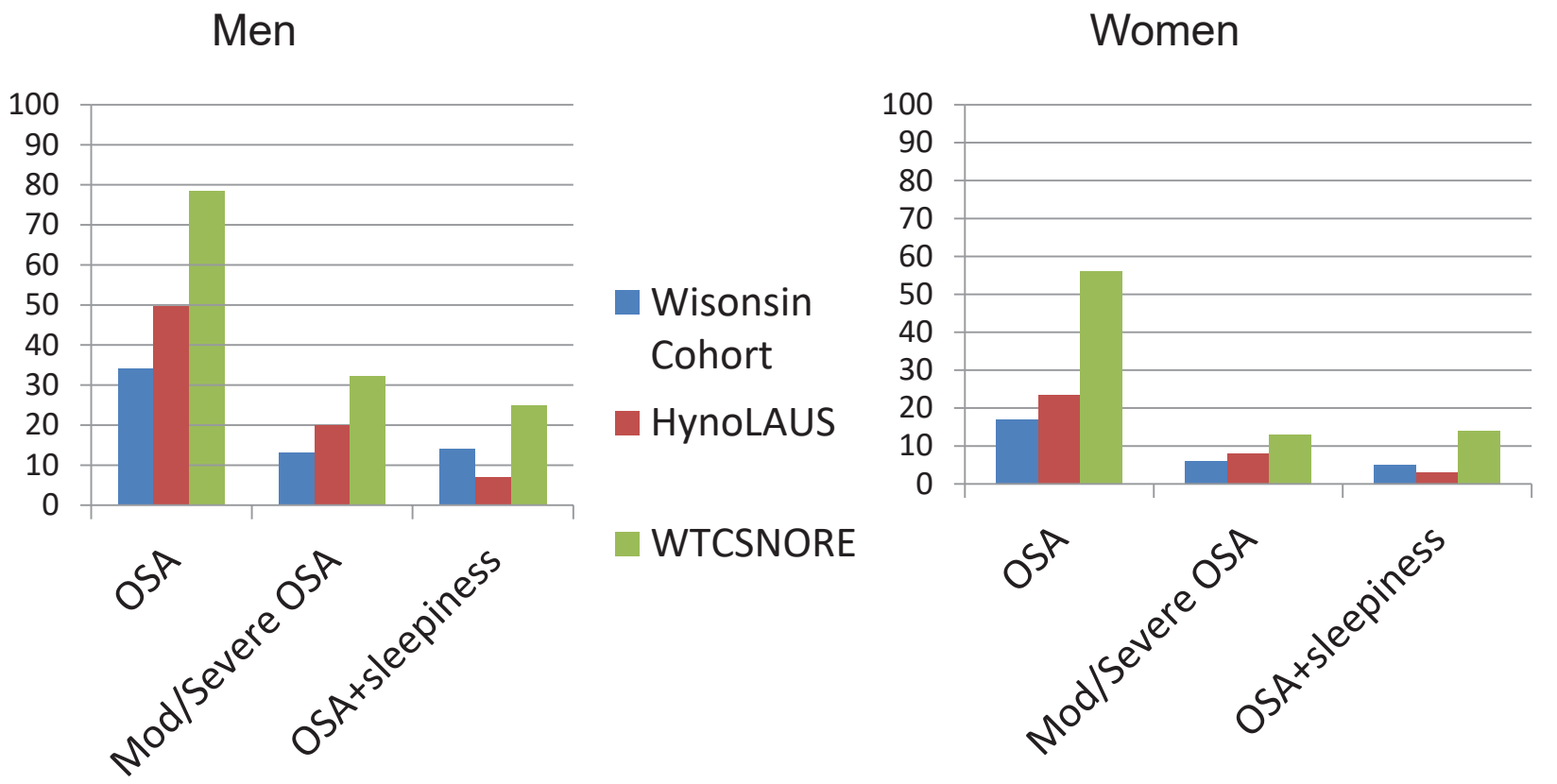
Variable	*N* of Valid Data	Summary
Age (years, Mean ± SD)	626	52.8 ± 8.6
BMI (kg/m^{2,} Mean ± SD)	626	29.9 ± 5.5
Female (%)	626	109 (17.3%)
Sleep Duration (h, Mean ± SD)	588	6.4 ± 1.3
≥7 h (%)		42.6%
6–6.99 h (%)		30.9%
<6 h (%)		26.5%
Snoring (Yes, %)	626	312 (49.8%)
Quality of Life (FOSQ) (Mean ± SD)	566	17.4 ± 2.6
Good, ≥17 (%)		62.0%
Poor, <17 (%)		38.0%
Sleepiness (ESS, Mean ± SD)	620	8.3 ± 4.8
Sleepy, >10 (%)		31.3%
Not Sleepy, ≤10 (%)		**68.7%**
Poor Sleep Quality (Yes, %)	**623**	**441(70.8%)**
Sleep Onset Insomnia (Yes, %)	**609**	**296 (48.6%)**
Sleep Maintenance Insomnia (Yes, %)	**622**	**116 (18.7%)**

Prevalence of OSA in the WTC Responder population is 75%



Sunderram et al, 2019. Chest

OSA Prevalence : Comparison to other cohorts



Sunderram et al, 2019. Chest

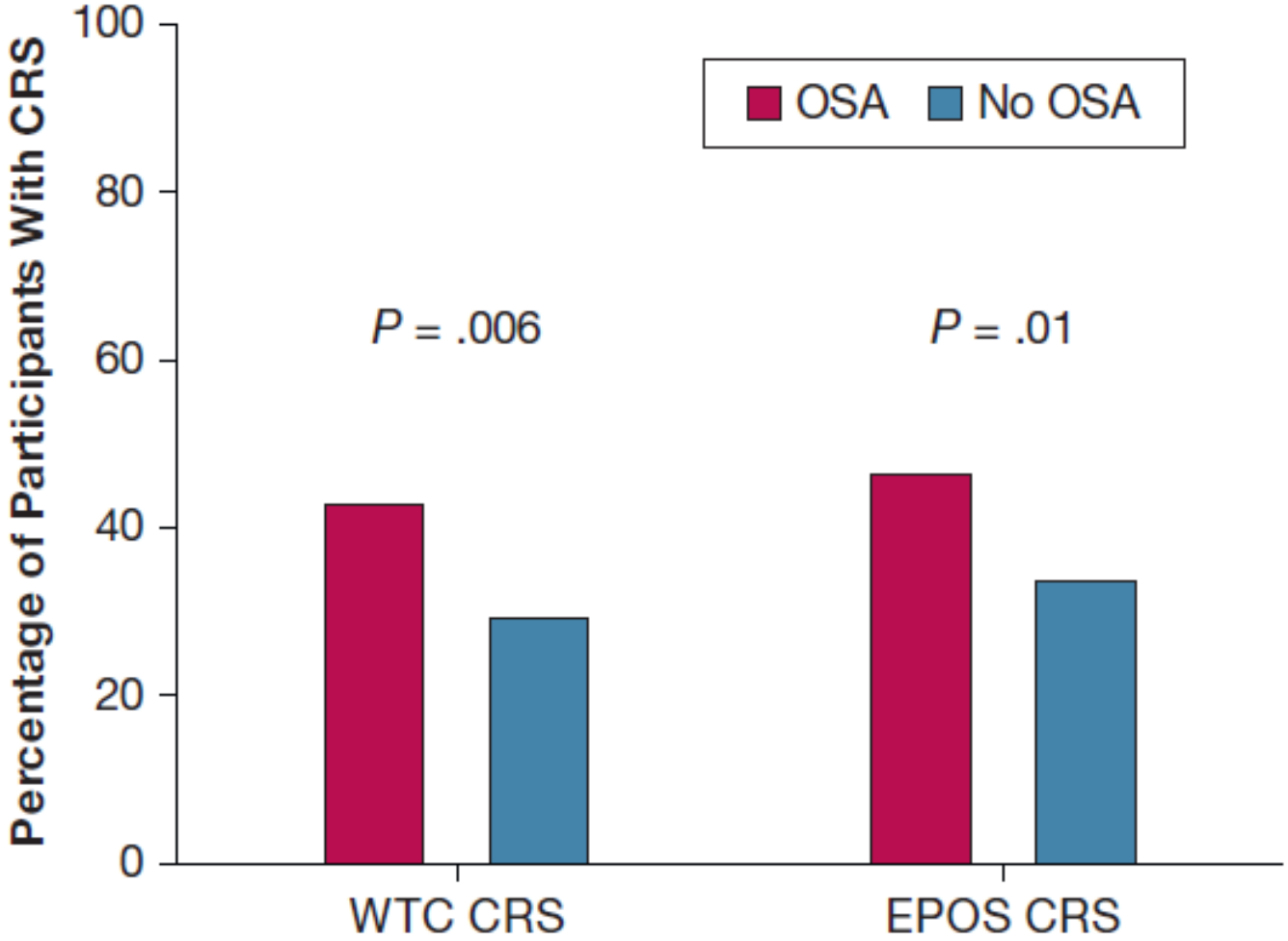
CRS is a risk factor for OSA

TABLE. 6] Unadjusted and Adjusted OR (95% CI) for OSA in Subjects with New-Onset or Worsening CRS using the WTC and the EPOS Definition for CRS

Nasal Symptom Score	Unadjusted OR (95% CI)	Adjusted for Age, Sex, and BMI (Model 1)	Adjusted for Age, Sex, BMI, and GERD (Model 2)	Adjusted for Age, Sex, BMI, GERD, and Regular Alcohol Use (Model 3)
No CRS	1.0	1.0	1.0	1.0
WTC CRS	1.8 (1.18-2.73)	1.69 (1.08-2.65)	1.76 (1.09-2.85)	1.76 (1.08-2.88)
P value	.006	.02	.02	.02
EPOS CRS	1.69 (1.12-2.53)	1.56 (1.01-2.4)	1.59(1-2.5)	1.52 (0.95-2.4)
P value	.01	< .05	.05	.08

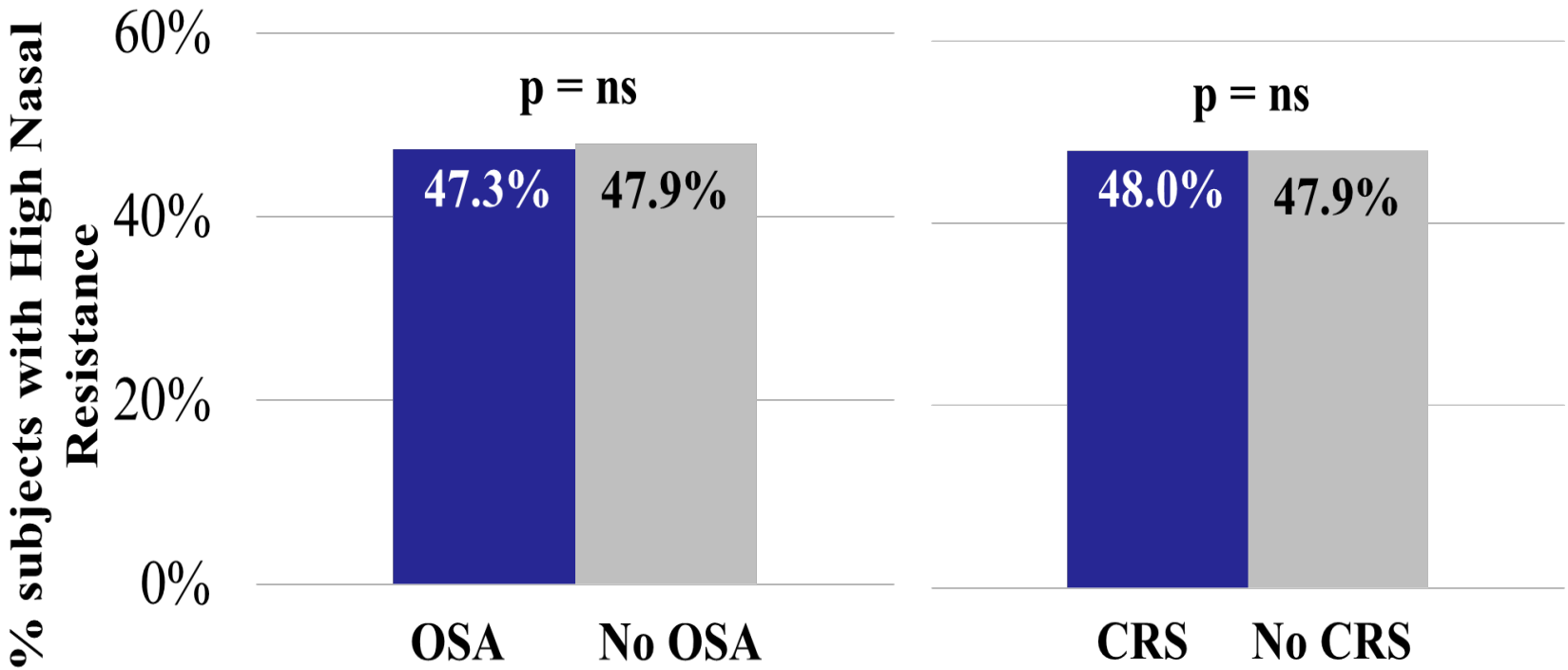
Sunderram et al, 2019. Chest

OSA and CRS



Sunderram et al, 2019. Chest

OSA and CRS not related to an increase in nasal resistance



Sunderram et al, 2019. Chest

Relationship of nasal inflammation to CRS and OSA

Inflammation Markers	CRS+ vs CRS-			OSA+ vs OSA-		
MODEL 1: Unadjusted	OR	95% CI	p-value	OR	95%CI	p-value
IL8	1.34	(1.14, 1.59)	0.001	1.24	(1.03, 1.49)	0.025
ECP	1.17	(1.06, 1.29)	0.002	1.12	(1.01, 1.25)	0.030
Neutrophils	1.14	(1.01, 1.28)	0.035	1.07	(0.94 ,1.22)	ns
IL6 Quartiles						
Q1	1	-	-	1	-	-
Q2	1.08	(0.64, 1.85)	ns	1.36	(0.77, 2.42)	ns
Q3	0.94	(0.55,1.61)	ns	1.59	(0.88, 2.87)	ns
Q4	2.00	(1.17, 3.41)	0.011	2.08	(1.12, 3.86)	0.021

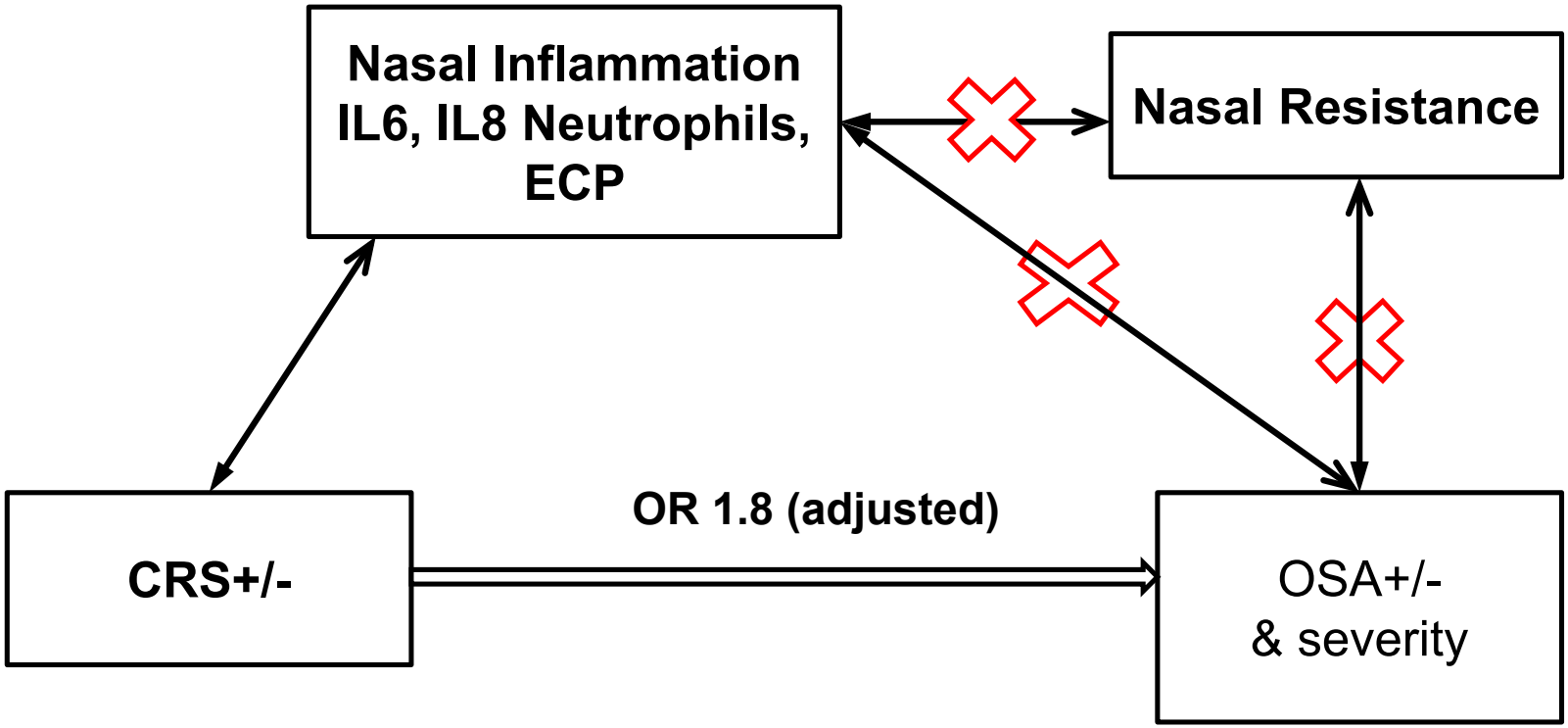
AJRCCM in review

Relationship of nasal inflammation to CRS and OSA

	CRS+ vs CRS-			OSA+ vs OSA-		
	OR	95% CI	p-value	OR	95%CI	p-value
	1.33	(1.12, 1.58)	0.001	1.09	(0.89, 1.34	
ECP	1.16	(1.05, 1.28)	0.003	1.08	(0.97, 1.22)	
	1.13	(1.00, 1.27)	0.052	1.04	(0.90,1.19)	
IL6 Quartiles						
	1	-	-	1	-	
Q2	1.03	(0.59, 1.77)	ns	0.98	(0.52, 1.83)	
	0.87	(0.50, 1.51)	ns	1.34	(0.70, 2.56)	
Q4	1.90	(1.10, 3.25)	0.021	1.68	(0.87, 3.27)	

AJRCCM in review

Nasal Inflammation is associated with CRS but not OSA



AJRCCM in review

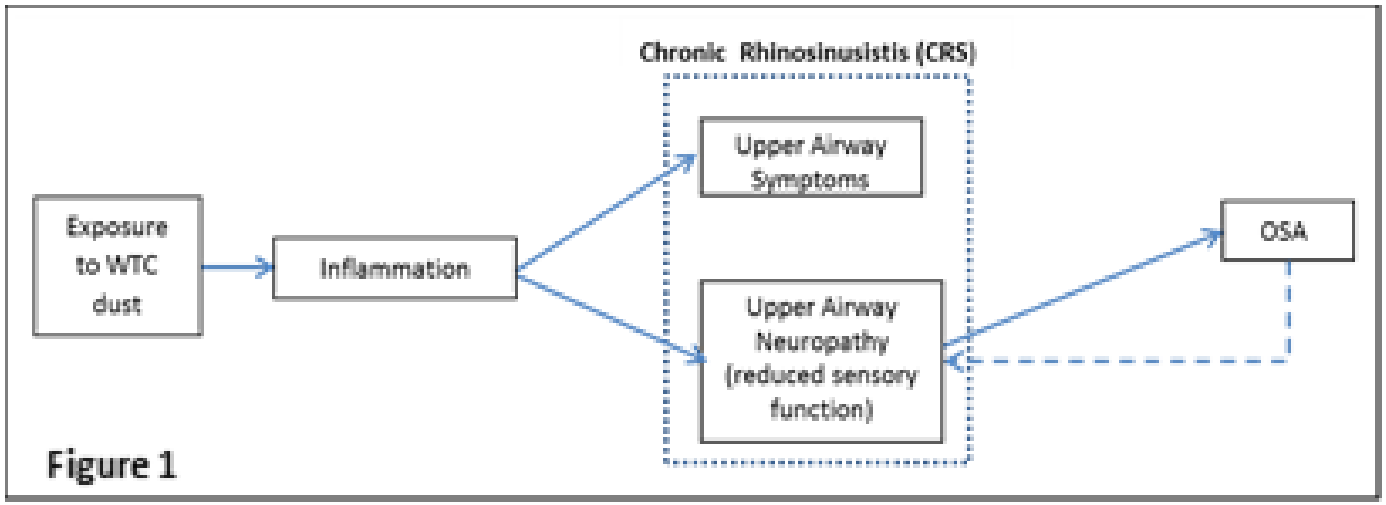
Conclusions

- Consistent with previous data, we found a high proportion of OSA and chronic rhinosinusitis in **WTC** responders.
- Chronic rhinosinusitis is an independent risk factor for **OSA**.
- However, an increase in awake nasal resistance did not explain this relationship.
- Nasal inflammation is associated with **CRS** but not with **OSA**.

What is the mechanism of increased risk of OSA with CRS?

- An impaired afferent limb of upper airway reflexes impairs the ability to perceive and/or process upper airway loading and contributes to failure of upper airway stiffening

- Subjects with both CRS and OSA will have decreased sensation in the upper airway compared to control subjects with neither CRS nor OSA.



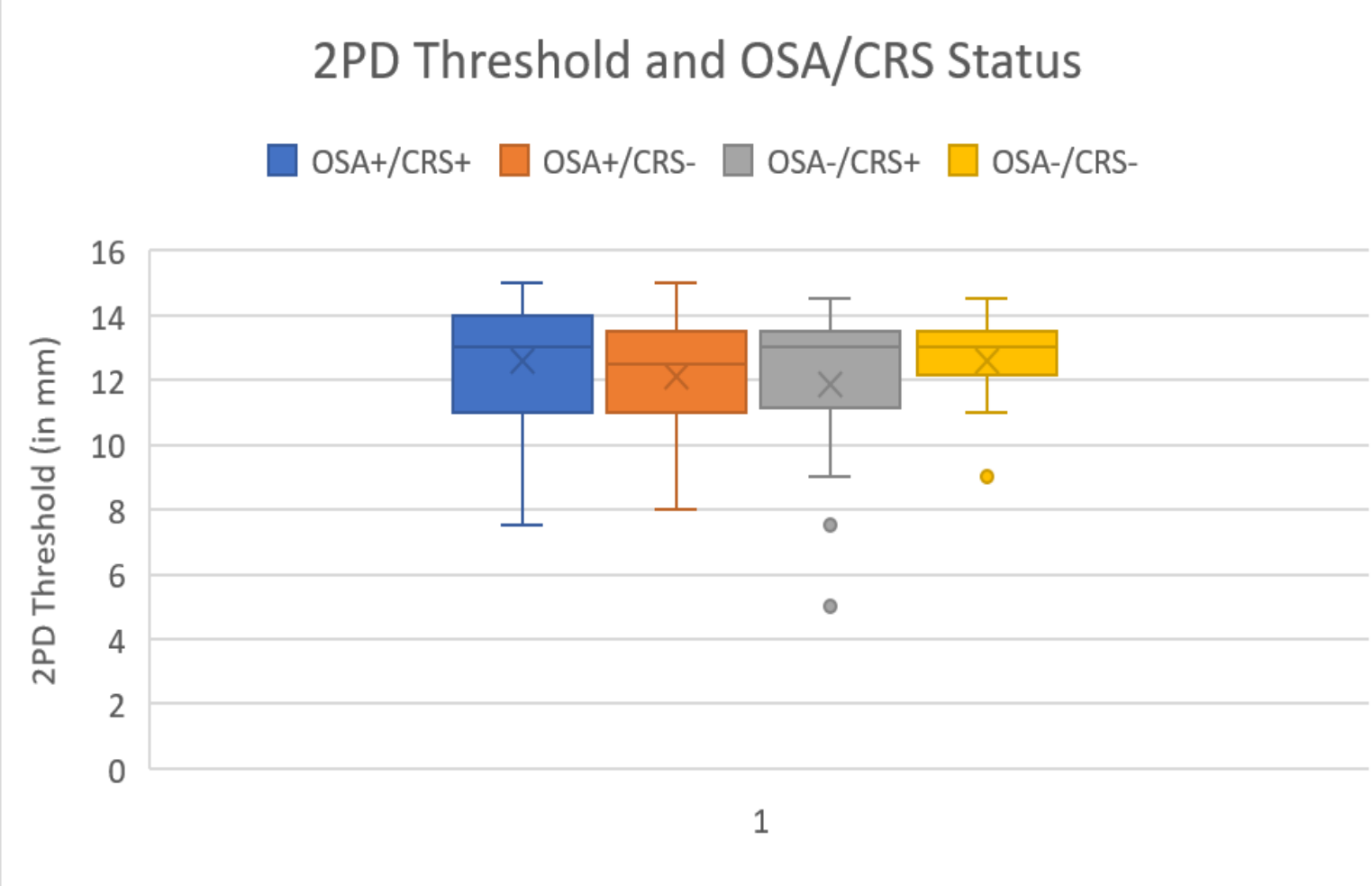
Grant Info: U01OH011481 CDC/NIOSH

Methods

- Upper Airway sensory testing
  - vibration sensitivity threshold
  - 2-point discrimination
- **OSA** diagnosis by in laboratory or home sleep test
- **CRS** status: questionnaire
- **4** groups of **50** subjects with and without **OSA** and with and without **CRS**

U01OH011481 CDC/NIOSH

No difference in 2PD and OSA/CRS status



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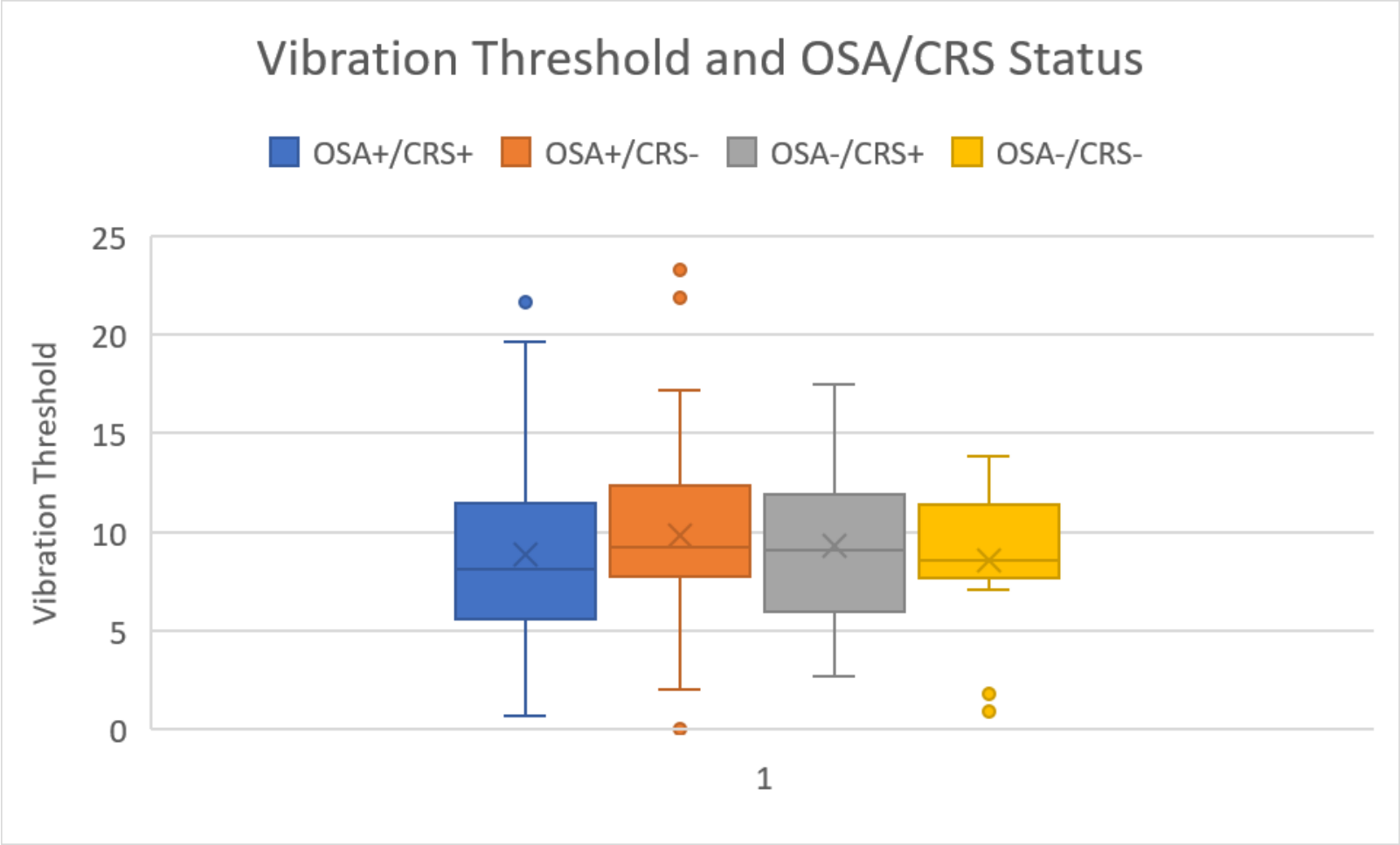
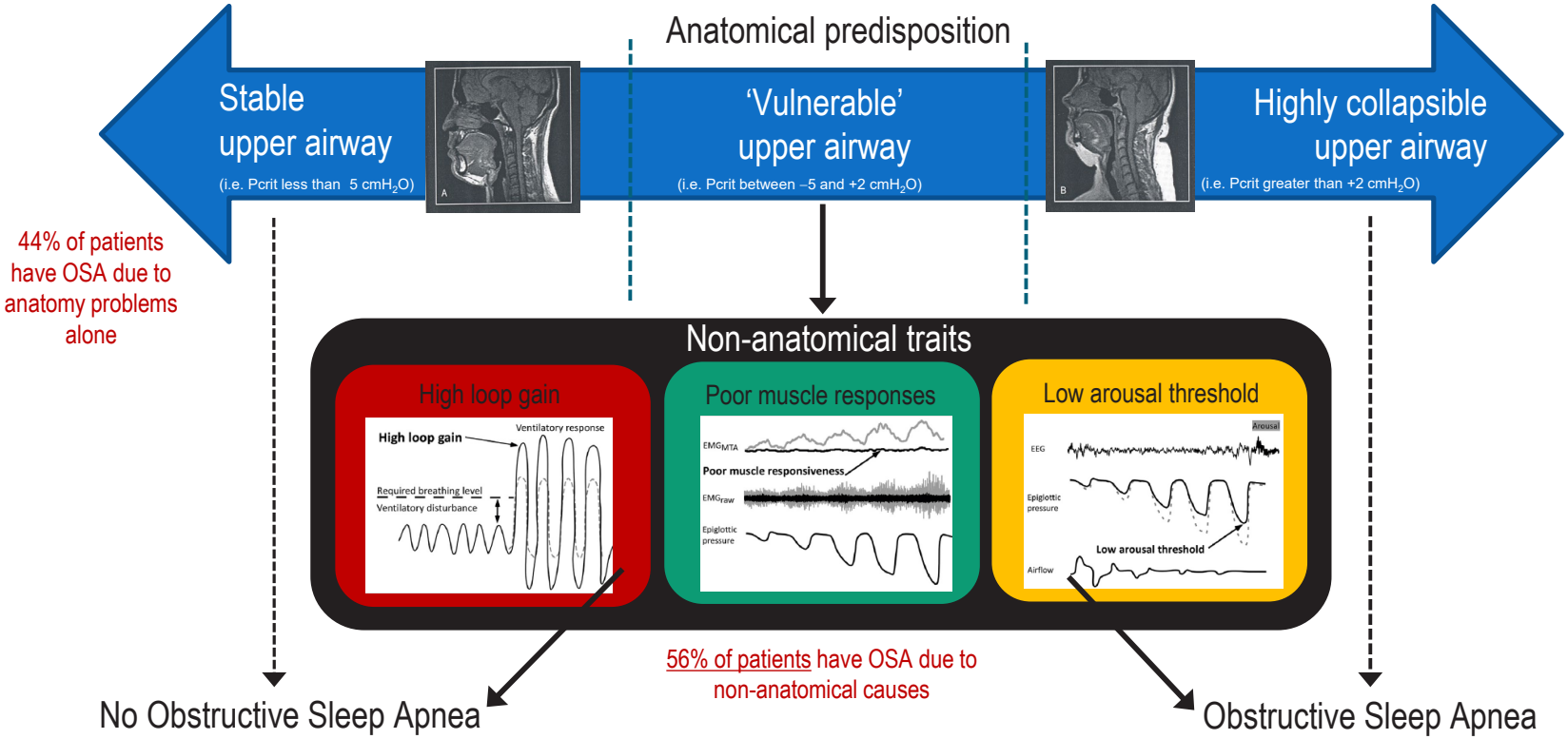
No difference in vibration threshold in OSA/CRS status



U01OH011481 CDC/NIOSH

Understand the mechanisms causing OSA in an individual



Schwab. Clinics in Chest Medicine, 1998
Owens et al. SLEEP, 2015
Carberry et al. Chest, 2017
Eckert et al, ARJCCM, 2013

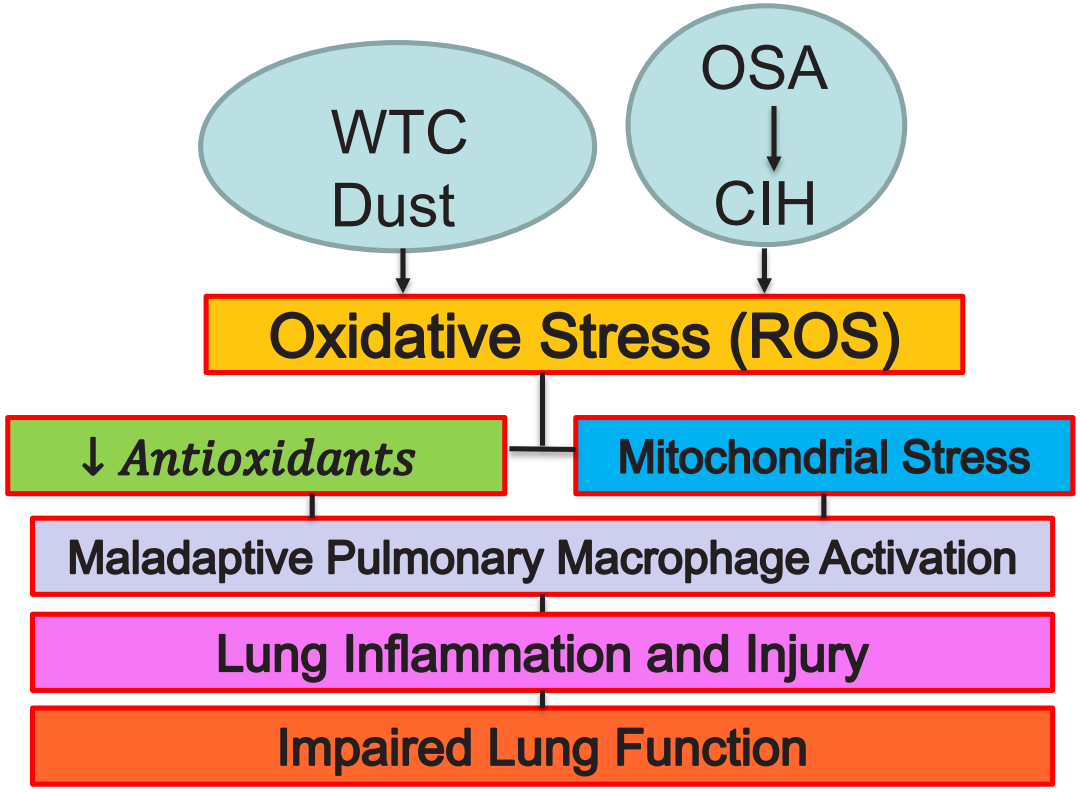
OSA Endotypes and CRS

- Examine the relationship of the mechanistic OSA endotypes to CRS in WTC responders.
- Test if upper airway muscle compensation is lower in subjects with CRS diagnosed with OSA compared to those without CRS.
- Examine differences in OSA endotypes in WTC responders and matched patients from a sleep clinic population without exposure to WTC dust.

U01OH011481 CDC/NIOSH

Consequences of OSA

- Does the double hit of WTC Dust and chronic intermittent hypoxia (CIH) from OSA result in lung injury ?



U01 OH012072-CDC/NIOSH

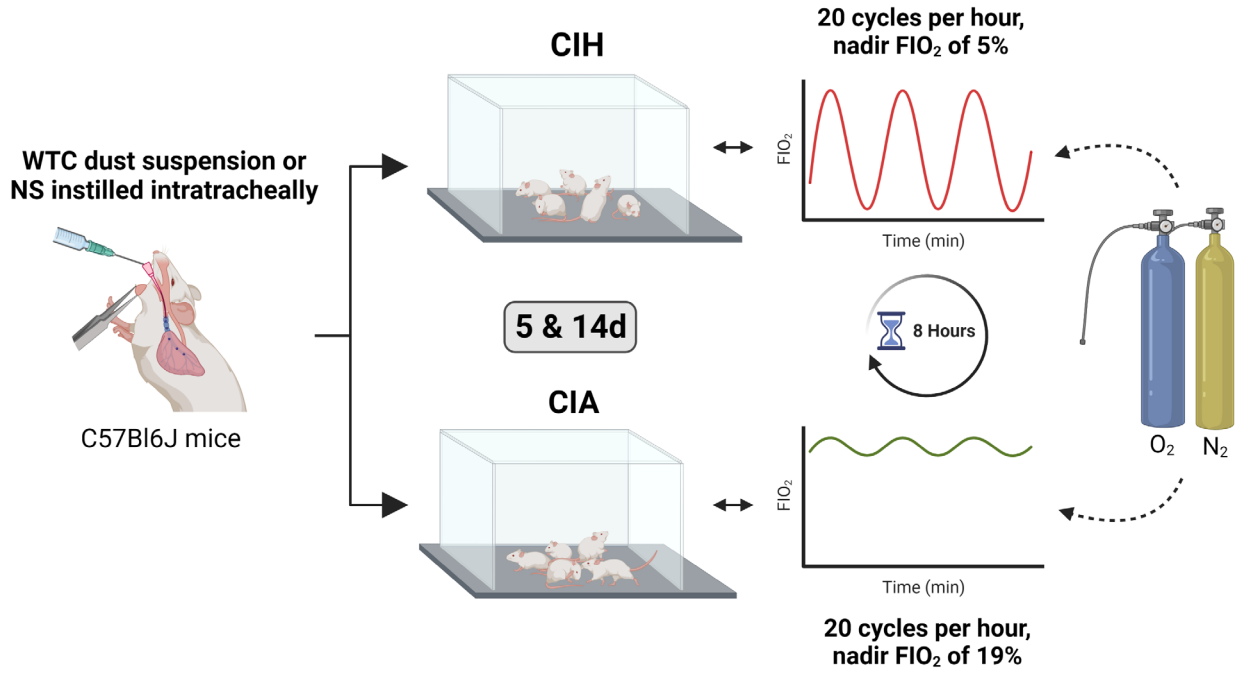
Hypothesis

- CIH will exacerbate WTC dust induced lung oxidative stress, and inflammation with resultant lung remodeling and aberrations in lung function over the time course of CIH exposure.

- To test this hypothesis, C57Bl6J mice were exposed to 5 and 14 days of chronic intermittent hypoxia (CIH) or chronic intermittent air (CIA) after being instilled with WTC dust or control.

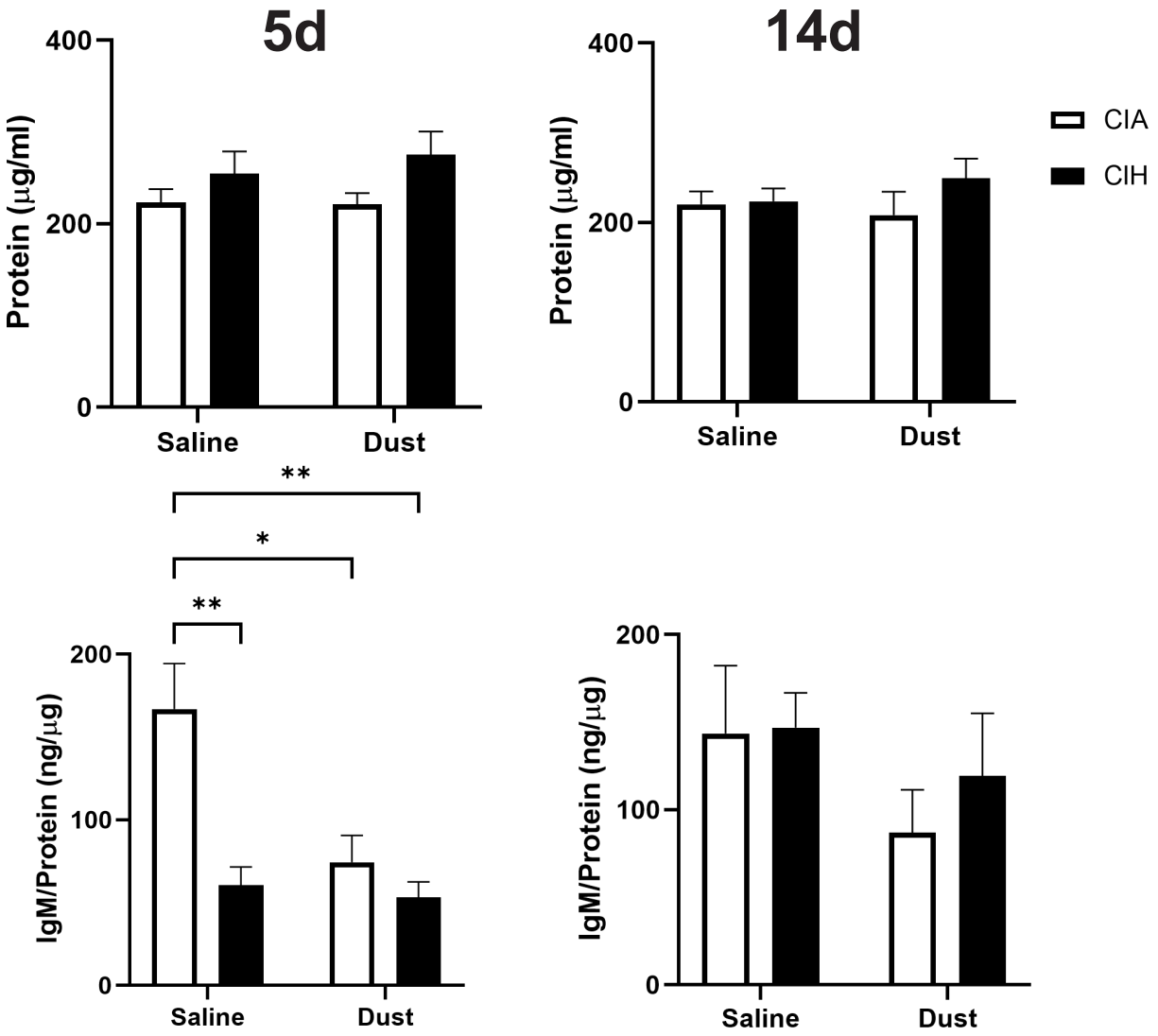
U01 OH012072-CDC/NIOSH

Methods

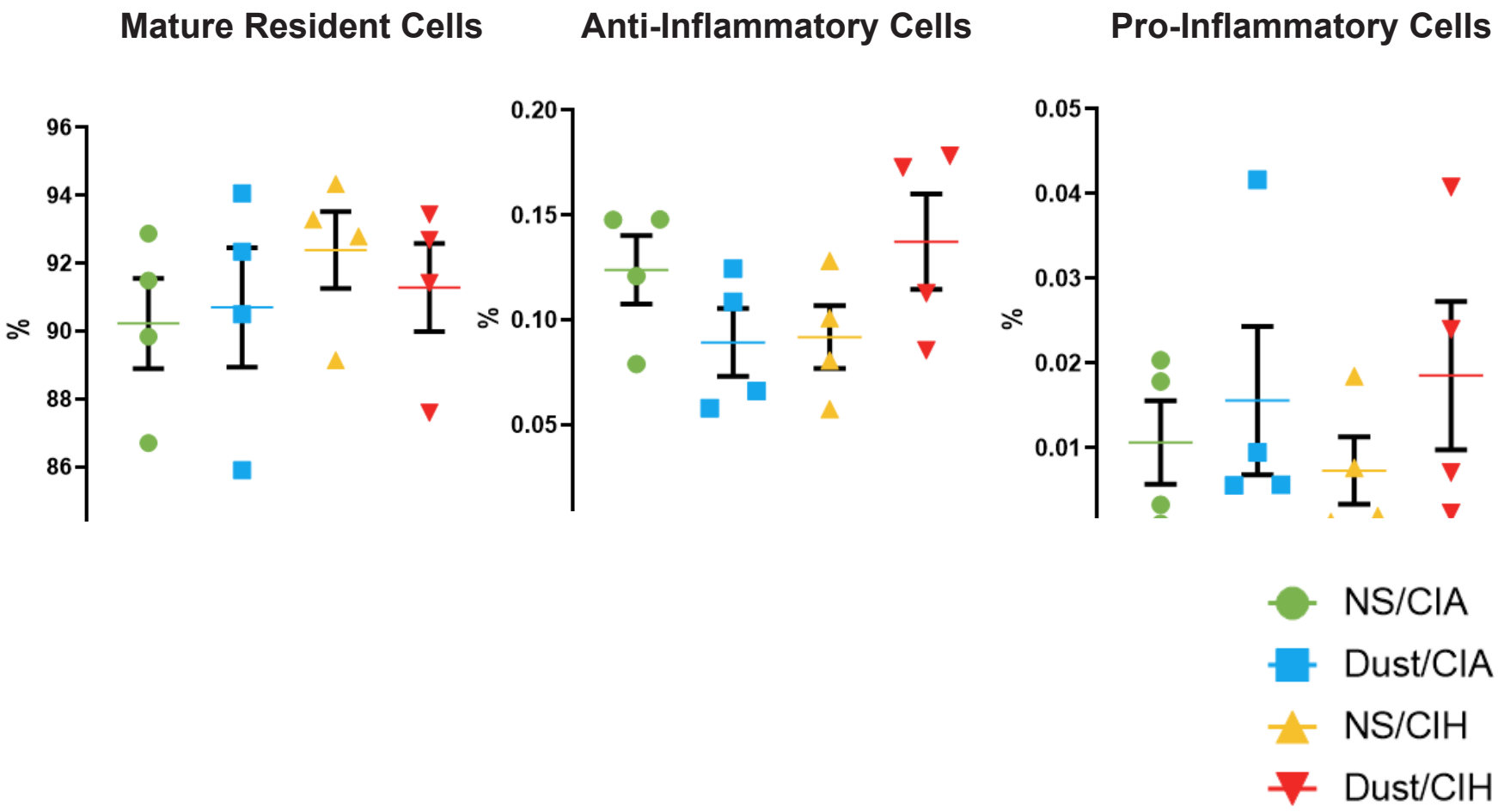


- BAL for protein, IgM, cell count and flow cytometry
- Histology
- Pulmonary mechanics: Flexivent
- Immunohistochemistry: Hemoxygenase-1 (HO-1) and proliferating cell nuclear antigen (PCNA)

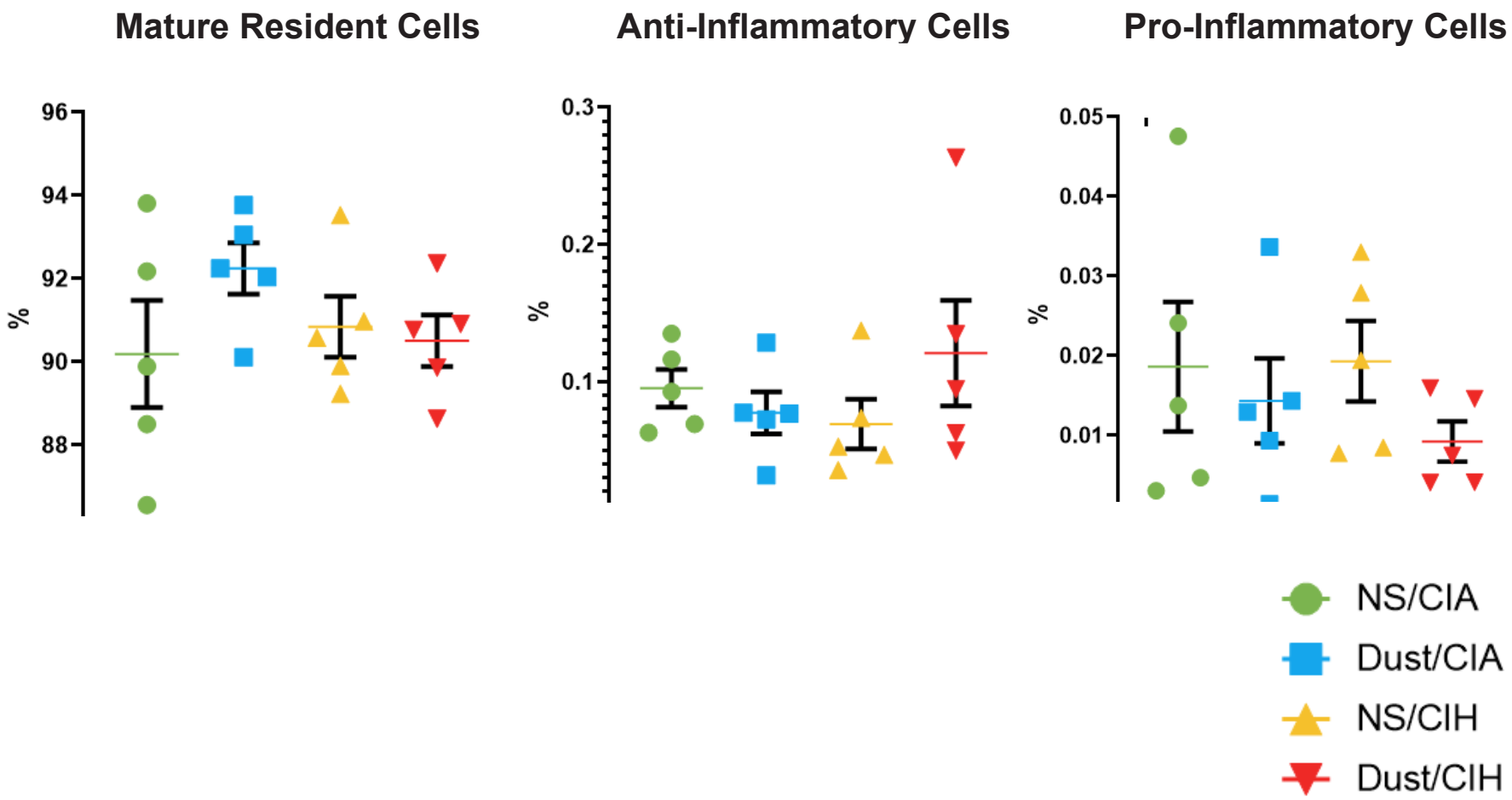
Bronchioalveolar Fluid Protein and IgM Levels



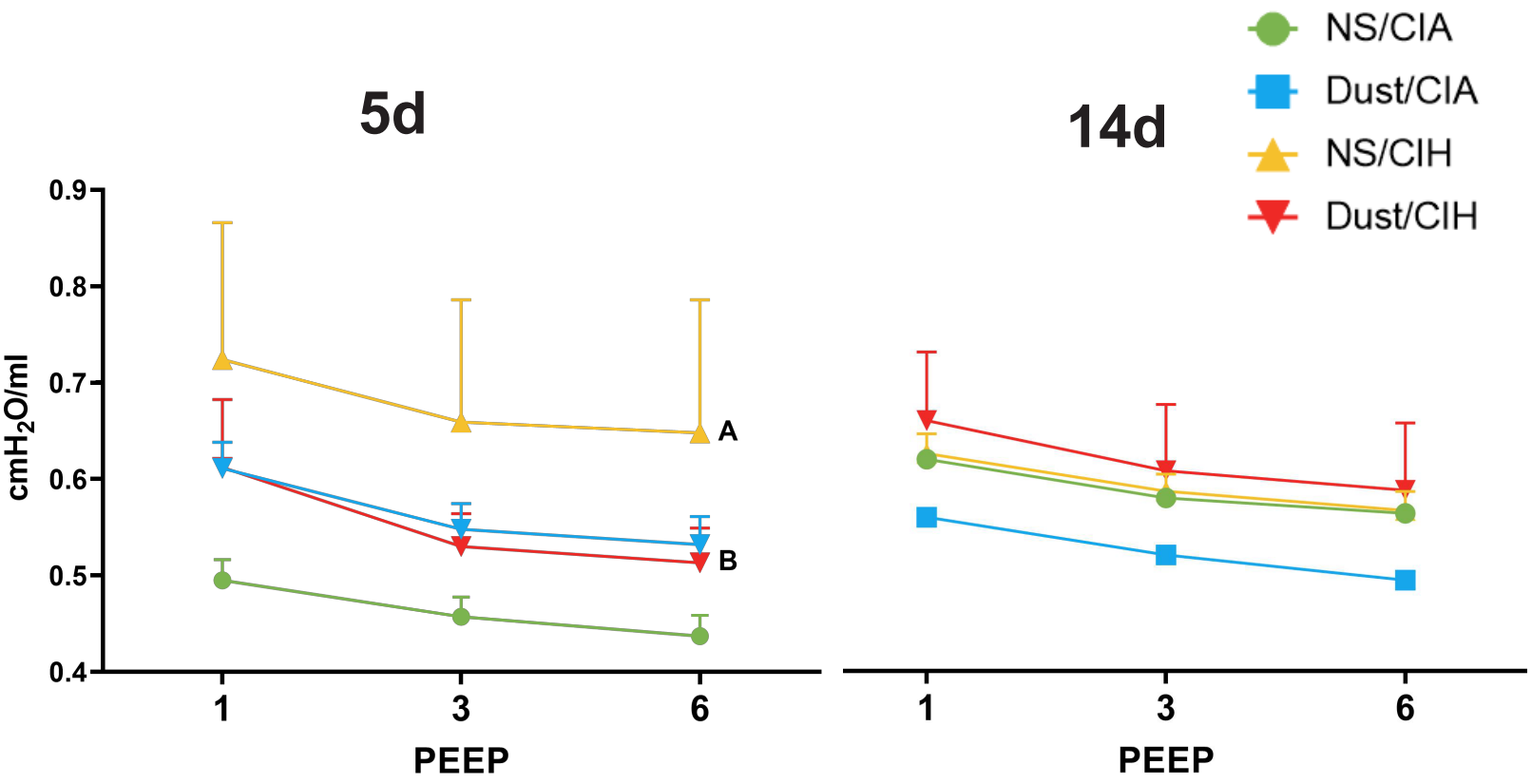
Bronchioalveolar fluid Flow Cytometry (5d)



Bronchioalveolar fluid Flow Cytometry (14d)

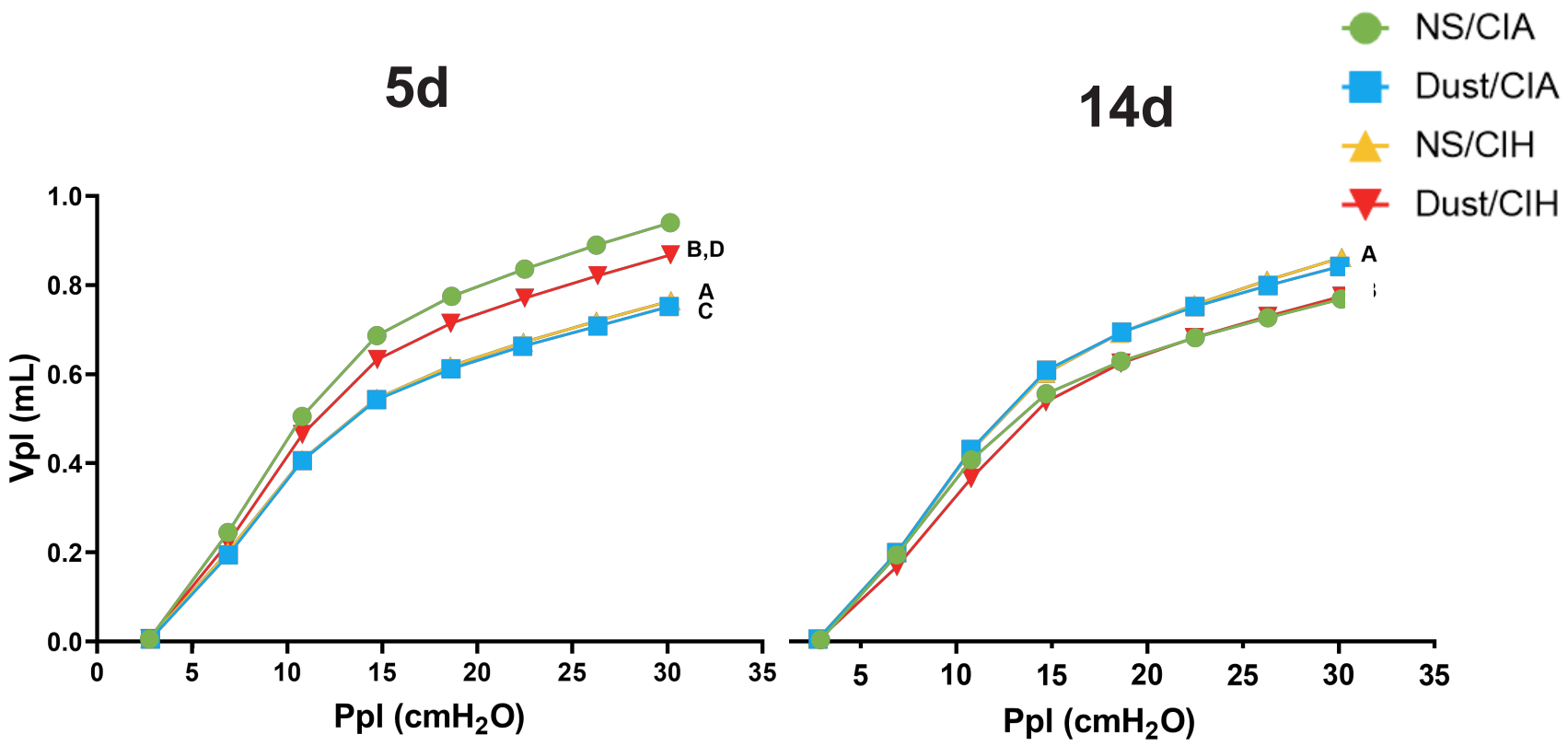


Pulmonary Resistance



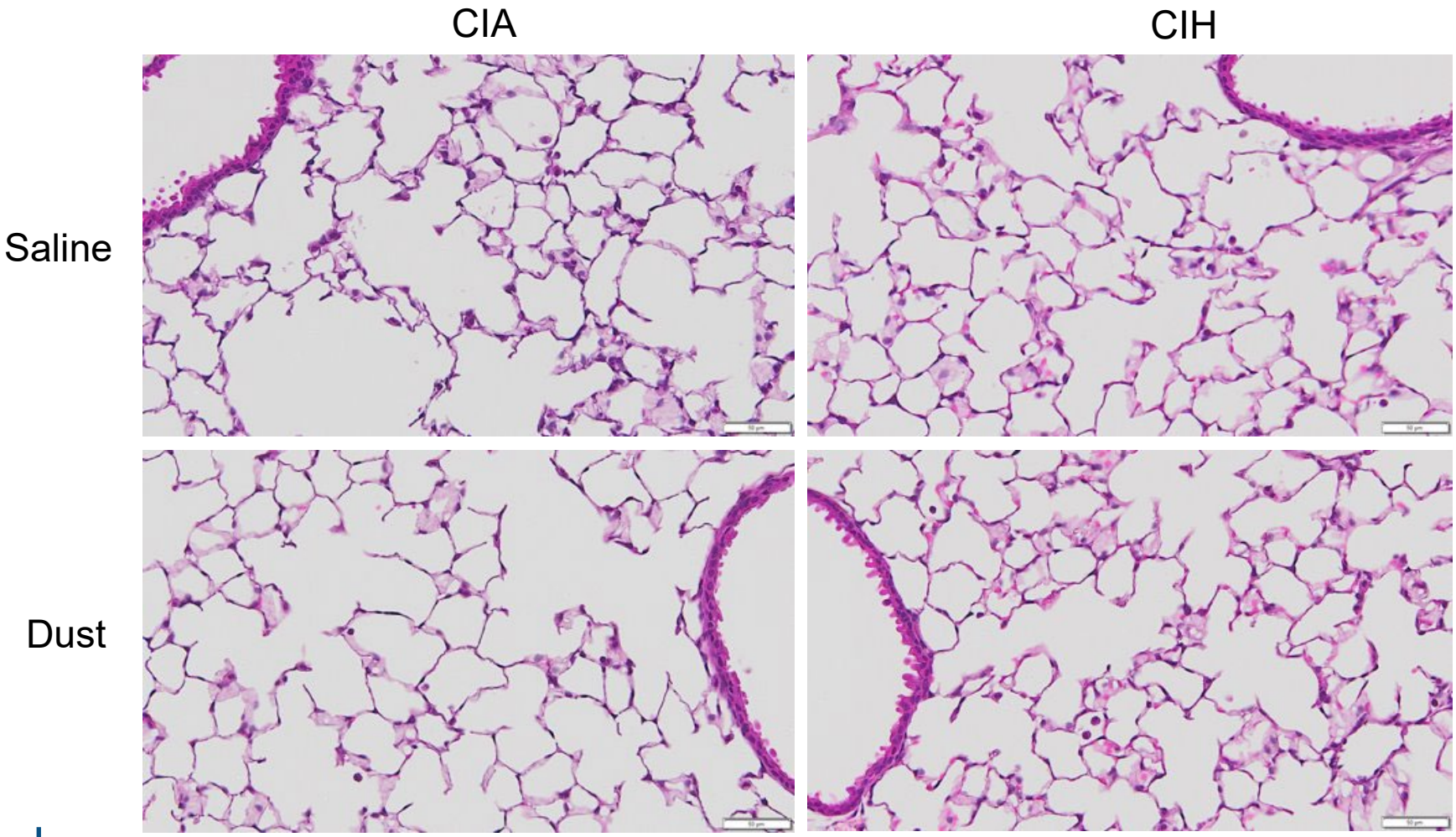
A. NS/CIH vs NS/CIA
B. Dust CIH vs NS/CIA

Pulmonary Compliance at low PEEP (PEEP3)

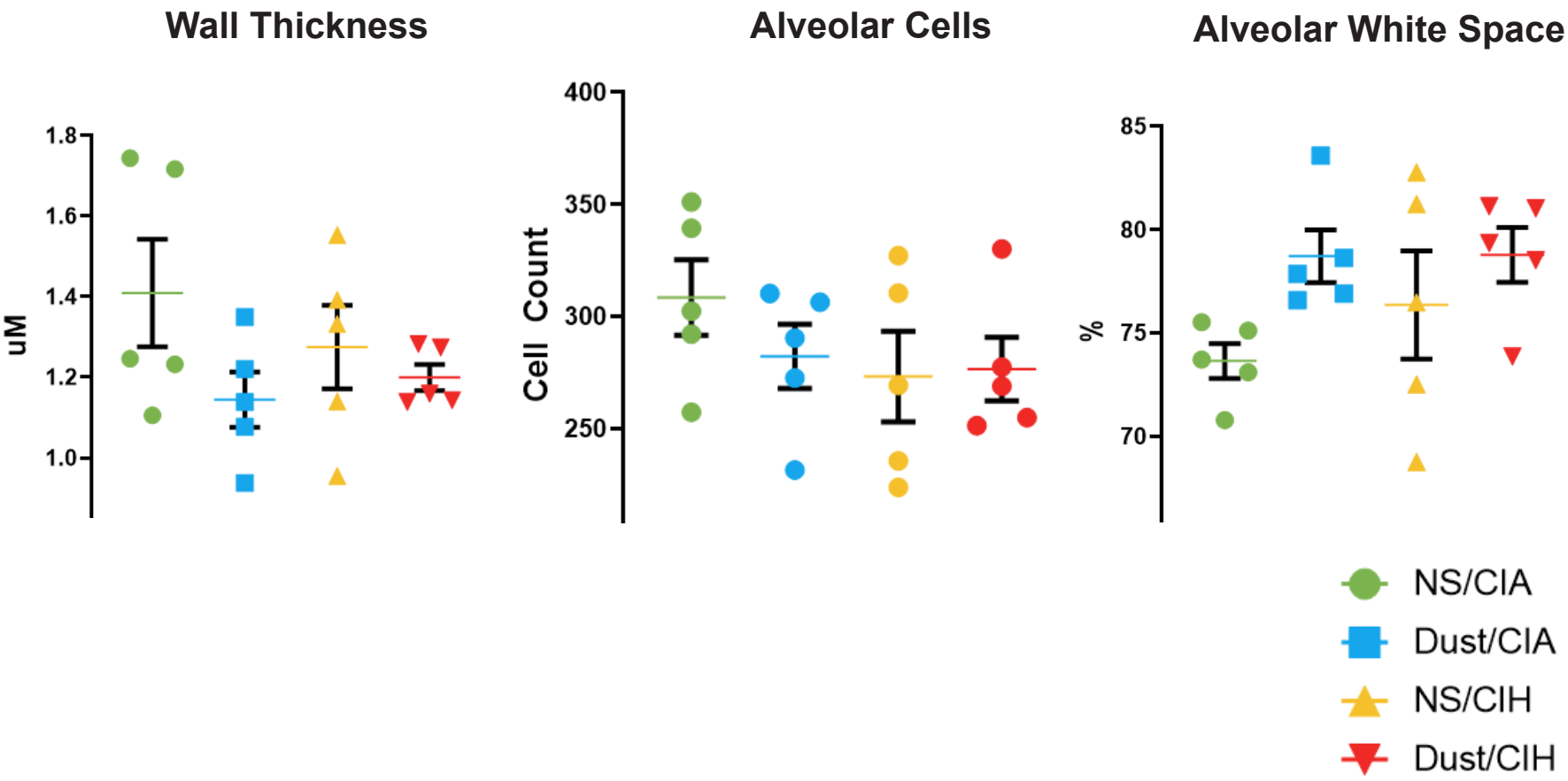


A. NS/CIA vs NS/CIH
B. NS/CIA vs Dust/CIH
C. NS/CIA vs Dust/CIA
D. NS/CIH vs Dust/CIH

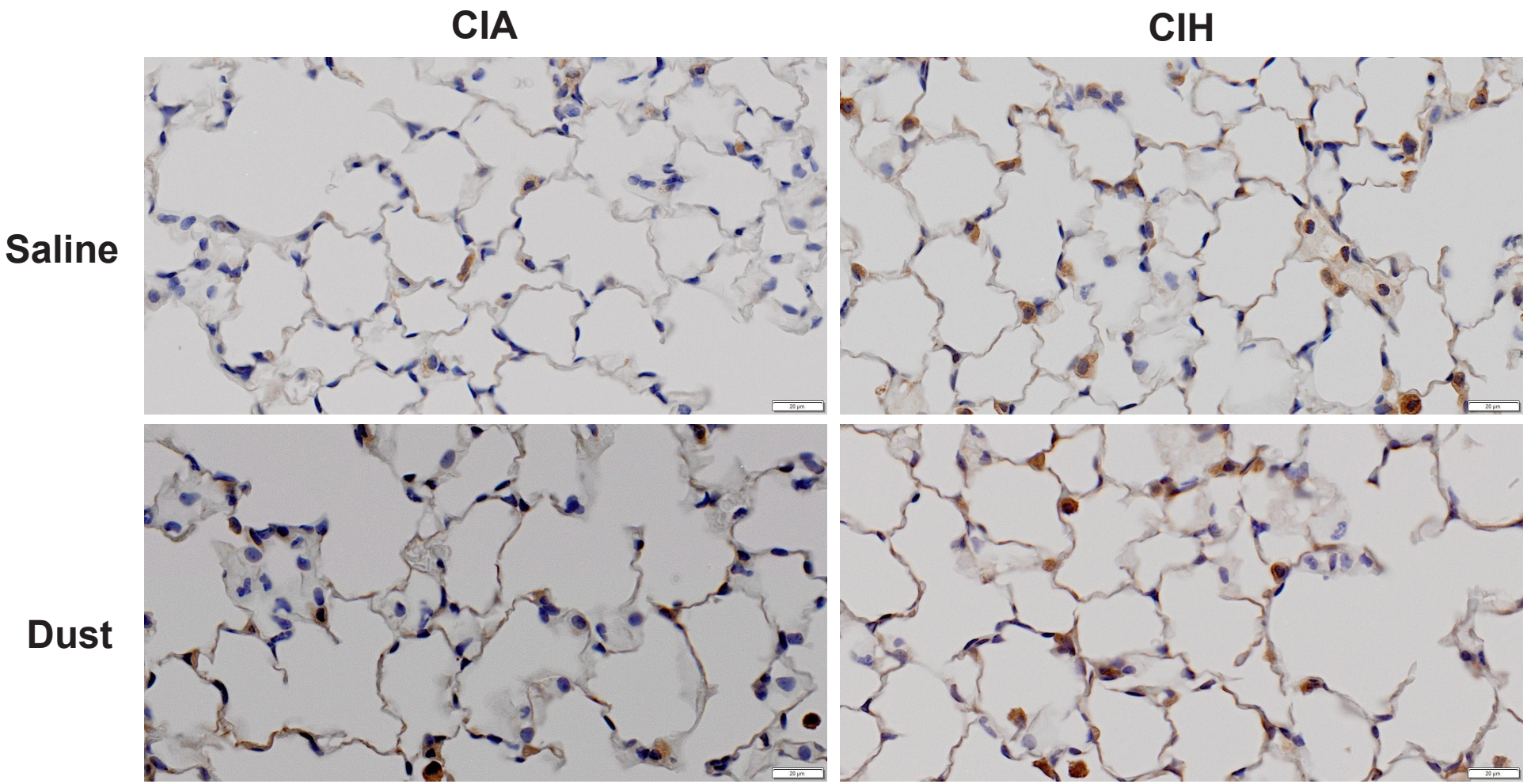
Histological Changes Following 14d of CIH



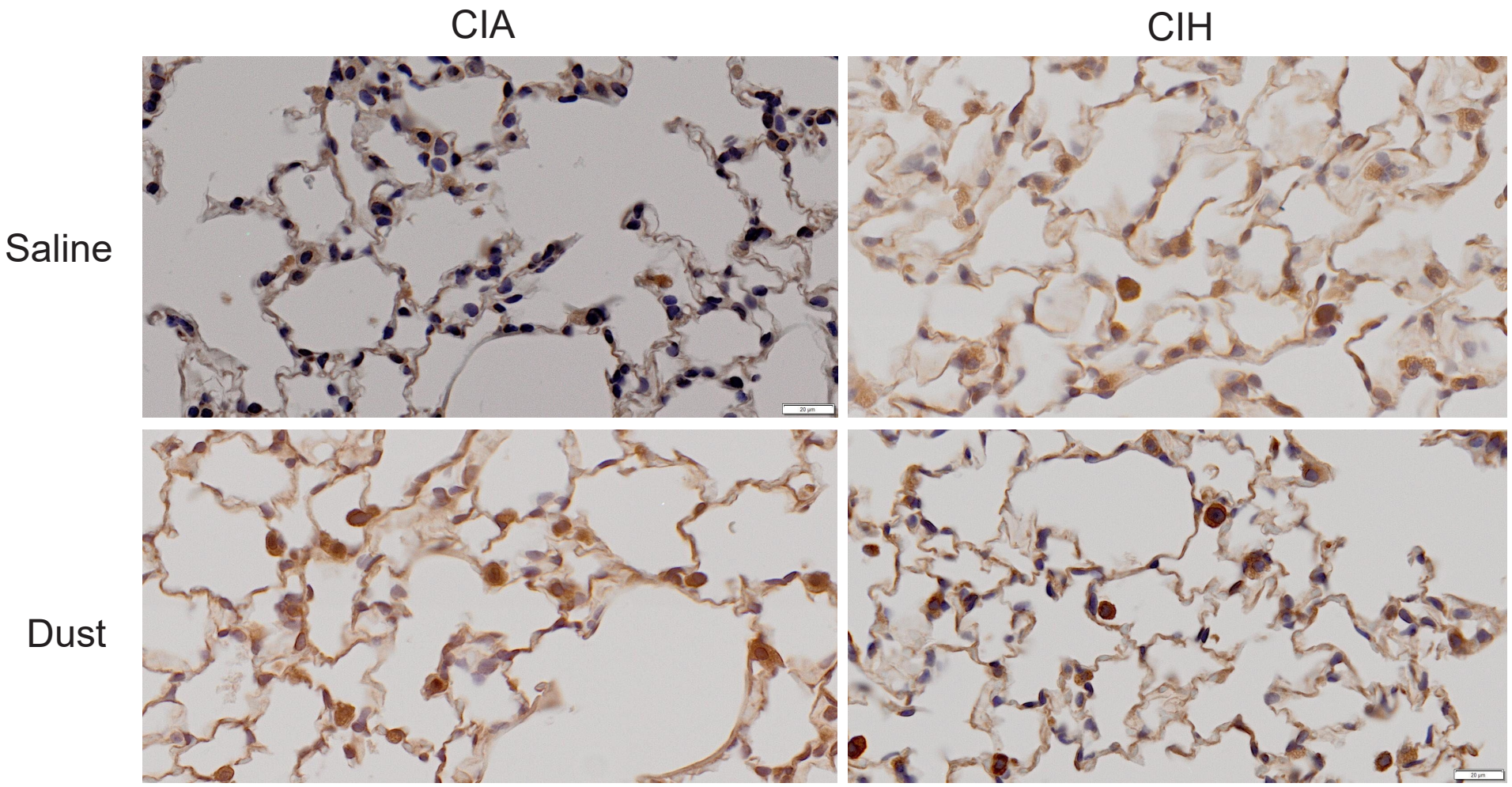
Quantitative Changes in Histology Following 14d of CIH



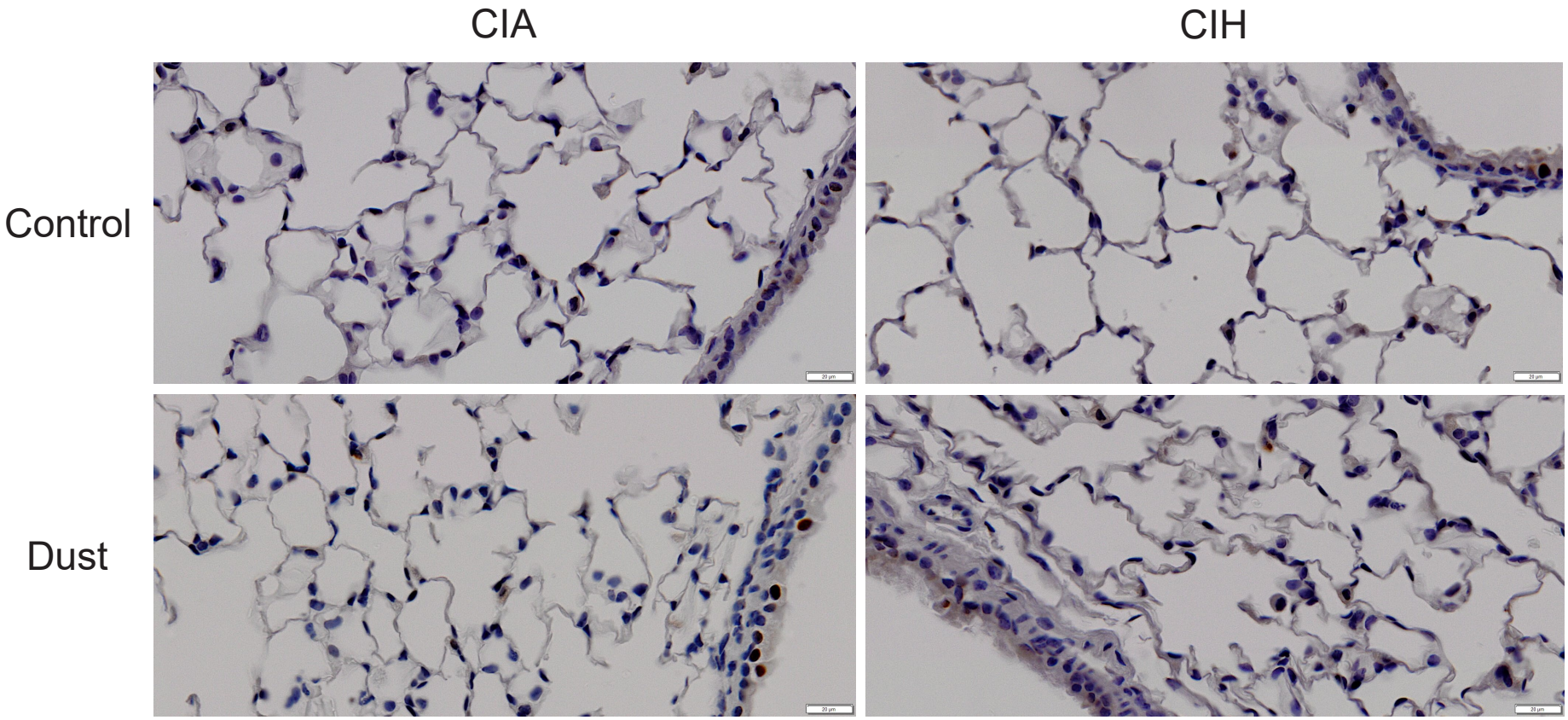
HO-1 Immunohistochemistry: 5d of CIH Exposure



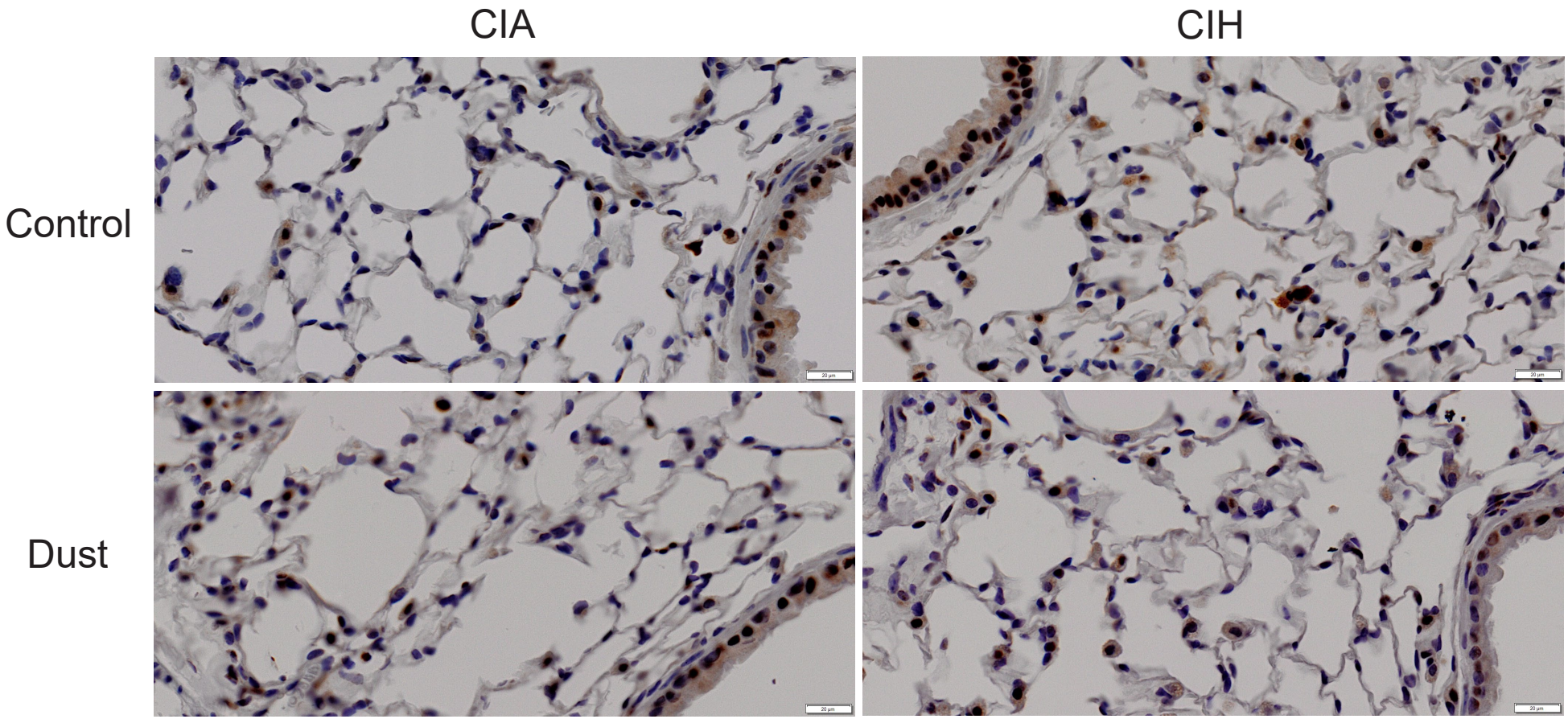
HO-1 Immunohistochemistry: 14d of CIH Exposure



PCNA Immunohistochemistry: 5d of CIH Exposure



PCNA Immunohistochemistry: 14d of CIH Exposure



Conclusion

- In our model of dust instillation and following **5** days of **CIH** exposure there is evidence of increase levels of **BAL** protein but with a concomitant reduction in **BAL IGM** suggesting an absence of a loss of alveolar epithelial barrier dysfunction.
- **5** Days of **CIH** exposure leads to increased oxidative stress that results in a loss of surfactant function and impaired pulmonary mechanics.
- However, the injury level is insufficient to produce significant epithelial proliferation although there is evidence of **type 2 pneumocyte dysfunction**.
- No significant increases in pro or anti-inflammatory cells were observed following either **5** or **14** days of **CIH** exposure.
- There is evidence of persistent oxidative stress by day **14** and changes in pulmonary mechanics and lung structure suggesting an **emphysematous phenotype**.

Future Direction

- Does continued oxidative stress from prolonged period of **CIH** exposure to lead to activation of factors that may result in fibrosis or worse emphysema?
- Metabolomic analysis will help determine biomarkers of future changes in lung structure and function.
- Consider single cell data points as there may be significant changes in small population of cells that significantly alter the disease process.

RUTGERS

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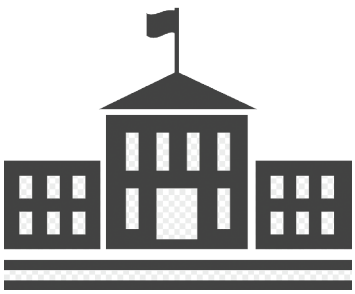
Icahn School of Medicine at Mount Sinai

Impact of Sleep and Sleep Disorders on Memory and Cognition- Implications for the WTC responder population

Andrew W. Varga, ***MD***, ***PhD***

Mount Sinai Integrative Sleep Center
Friedman Brain Institute



Disclaimer: Funding for this conference was made possible *(in part)* by the **Centers for Disease Control and Prevention**. The views expressed in written conference materials or publications and by speakers and moderators do not necessarily reflect the official policies of the **Department of Health and Human Services**, nor does the mention of trade names, commercial practices, or organizations imply endorsement by the **U.S. Government**.

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Andrew W. Varga, ***MD***, ***PhD***

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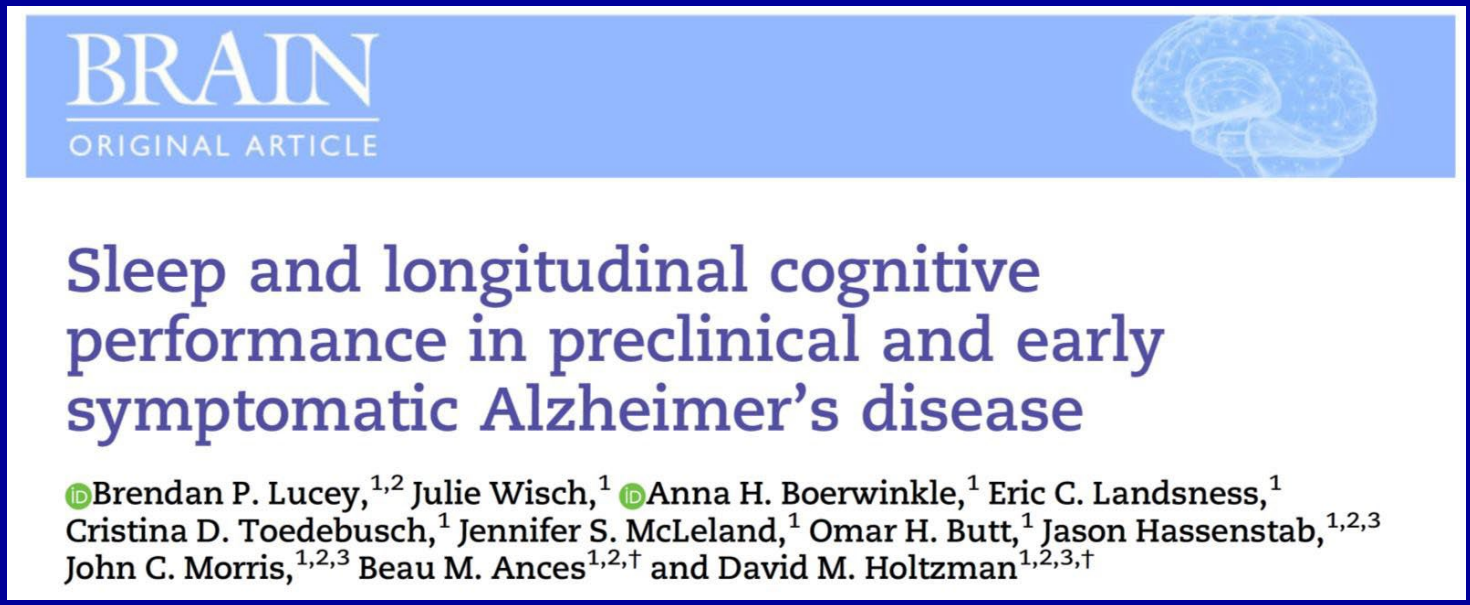
- **Disclosures:**
  - Merck: consultant, grant support (MISP)
  - Eisai: consultant
  - Jazz: consultant
  - None relevant to the current presentation

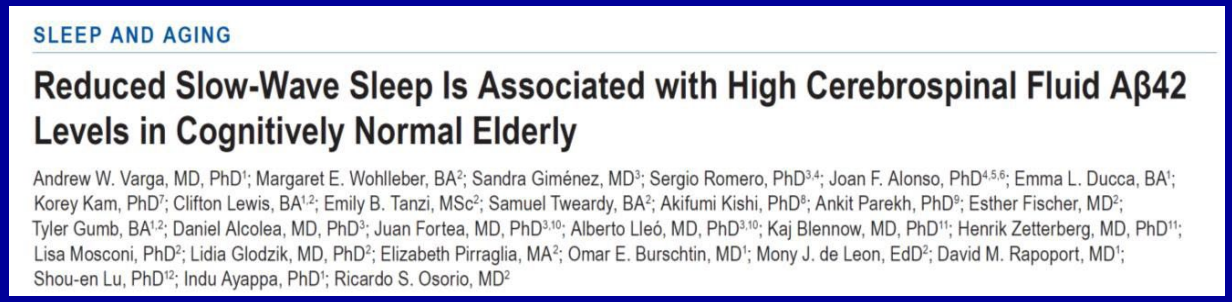
- **Disclosures:**
  - This presentation focuses on OSA in memory and AD risk
  - Sleep duration is important



  - Too little or too much sleep predicts poorer cognition longitudinally

• Disclosures:

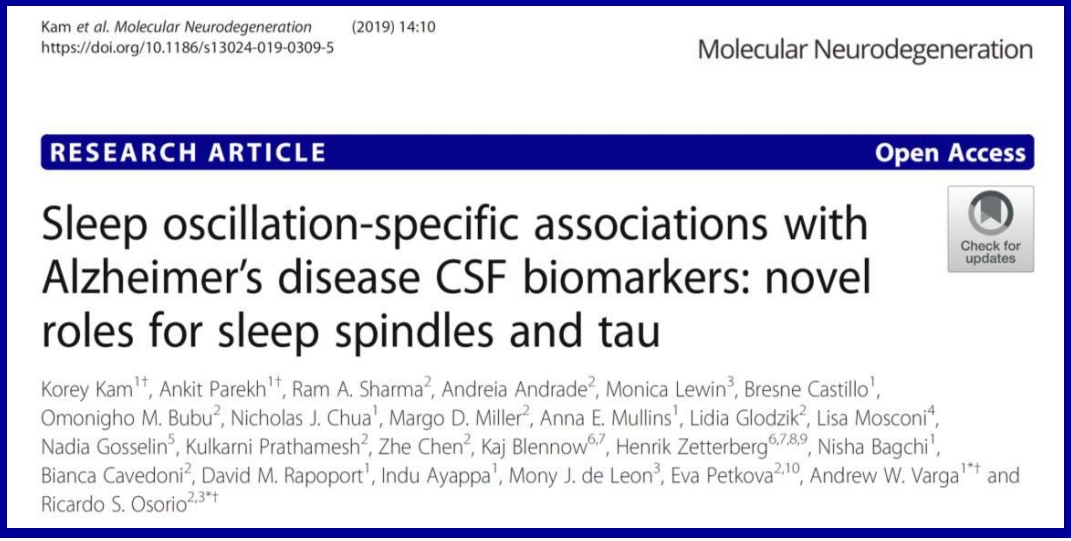
- This presentation focuses on OSA in memory and AD risk
- Sleep architecture is important



SLEEP AND AGING

Reduced Slow-Wave Sleep Is Associated with High Cerebrospinal Fluid Aβ42 Levels in Cognitively Normal Elderly

Andrew W. Varga, MD, PhD[1]; Margaret E. Wohlleber, BA[2]; Sandra Giménez, MD[3]; Sergio Romero, PhD[3,4]; Joan F. Alonso, PhD[4,5,6]; Emma L. Ducca, BA[1]; Korey Kam, PhD[7]; Clifton Lewis, BA[1,2]; Emily B. Tanzi, MSc[2]; Samuel Tweardy, BA[2]; Akifumi Kishi, PhD[8]; Ankit Parekh, PhD[9]; Esther Fischer, MD[2]; Tyler Gumb, BA[1,2]; Daniel Alcolea, MD, PhD[3]; Juan Fortea, MD, PhD[3,10]; Alberto Lleó, MD, PhD[3,10]; Kaj Blennow, MD, PhD[11]; Henrik Zetterberg, MD, PhD[11]; Lisa Mosconi, PhD[2]; Lidia Glodzik, MD, PhD[2]; Elizabeth Pirraglia, MA[2]; Omar E. Burschtin, MD[1]; Mony J. de Leon, EdD[2]; David M. Rapoport, MD[1]; Shou-en Lu, PhD[12]; Indu Ayappa, PhD[1]; Ricardo S. Osorio, MD[2]



Kam *et al. Molecular Neurodegeneration* (2019) 14:10
https://doi.org/10.1186/s13024-019-0309-5

Molecular Neurodegeneration

RESEARCH ARTICLE Open Access

Sleep oscillation-specific associations with Alzheimer's disease CSF biomarkers: novel roles for sleep spindles and tau

Korey Kam[1†], Ankit Parekh[1†], Ram A. Sharma[2], Andreia Andrade[2], Monica Lewin[3], Bresne Castillo[1], Omonigho M. Bubu[2], Nicholas J. Chua[1], Margo D. Miller[2], Anna E. Mullins[1], Lidia Glodzik[2], Lisa Mosconi[4], Nadia Gosselin[5], Kulkarni Prathamesh[2], Zhe Chen[2], Kaj Blennow[6,7], Henrik Zetterberg[6,7,8,9], Nisha Bagchi[1], Bianca Cavedoni[2], David M. Rapoport[1], Indu Ayappa[1], Mony J. de Leon[3], Eva Petkova[2,10], Andrew W. Varga[1*†] and Ricardo S. Osorio[2,3*†]

Your patients with Alzheimer's dementia (AD) can feel like they are trapped in a maze...

Hypothesis

- Induction of **OSA** exclusively in **REM** sleep will negatively affect spatial navigational memory consolidation that occurs across sleep

Subjects

- Subjects with severe **OSA** recruited ***(AHI4% > 30 /hr)*** who are highly compliant with therapeutic **CPAP**
- **18** subjects recruited ***(14 men, 4 women)***
- Average age is **53.6 +/- 10.5** years ***(range 31 to 70 years)***

Methods

- Subjects explore one of two **3D** computer-generated spatial mazes and then complete **3** timed trials before and after sleep, capped at **10** minutes/trial.

First Person View of Maze

Birds Eye View of Maze

Methods

- Metrics of performance include completion time ***(CT),*** total distance traveled (DT), and distance spent backtracking ***(BT)***
- Performance across sleep is defined as:

  (Average $\mathbf{CT}_{\text{pre-sleep}}$ – Average $\mathbf{CT}_{\text{post-sleep}}$) / Average $\mathbf{CT}_{\text{pre-sleep}}$

- Subjects perform maze trials across **2** nights:

  -Therapeutic CPAP throughout

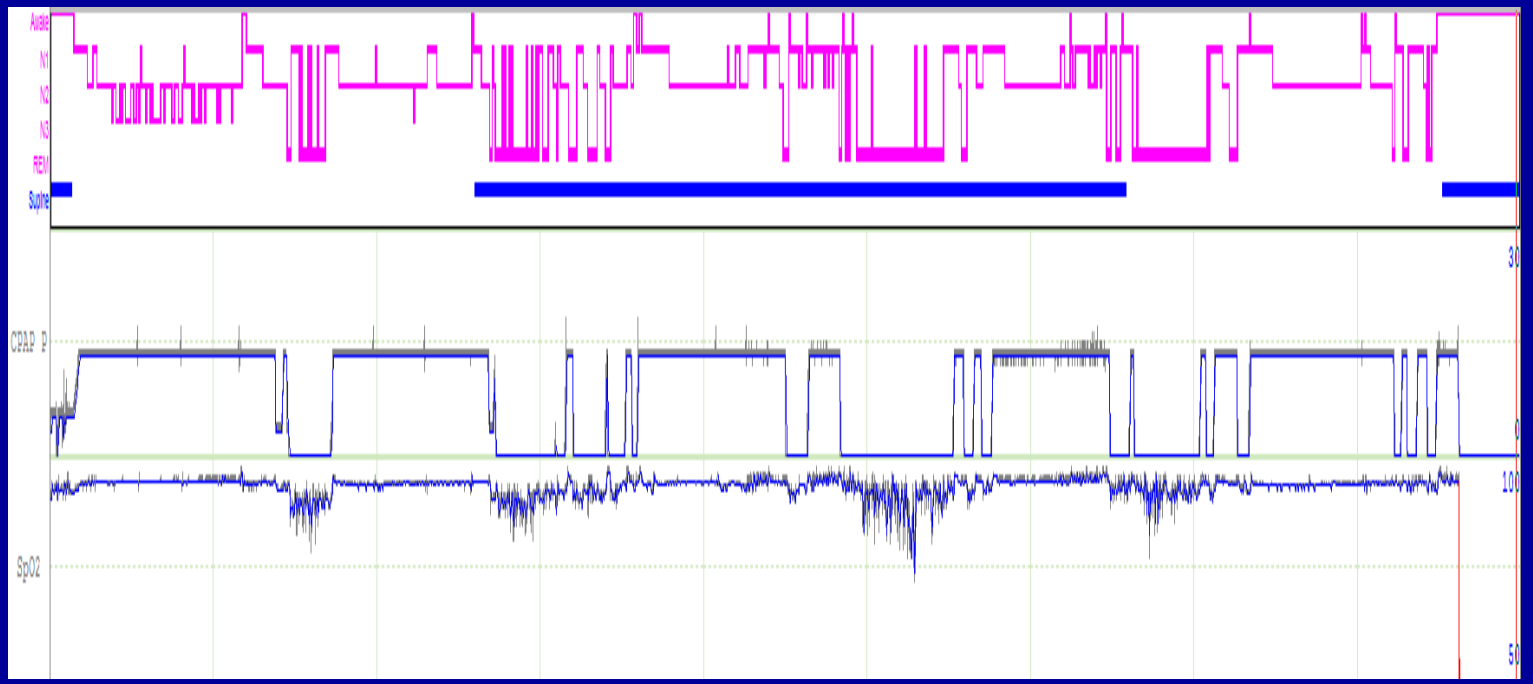
  - **CPAP** dropped to **4** cm or **0** cm in **REM**, returned to therapeutic **CPAP** in all **NREM** stages

OSA Induced by **CPAP** Withdrawal in **REM**

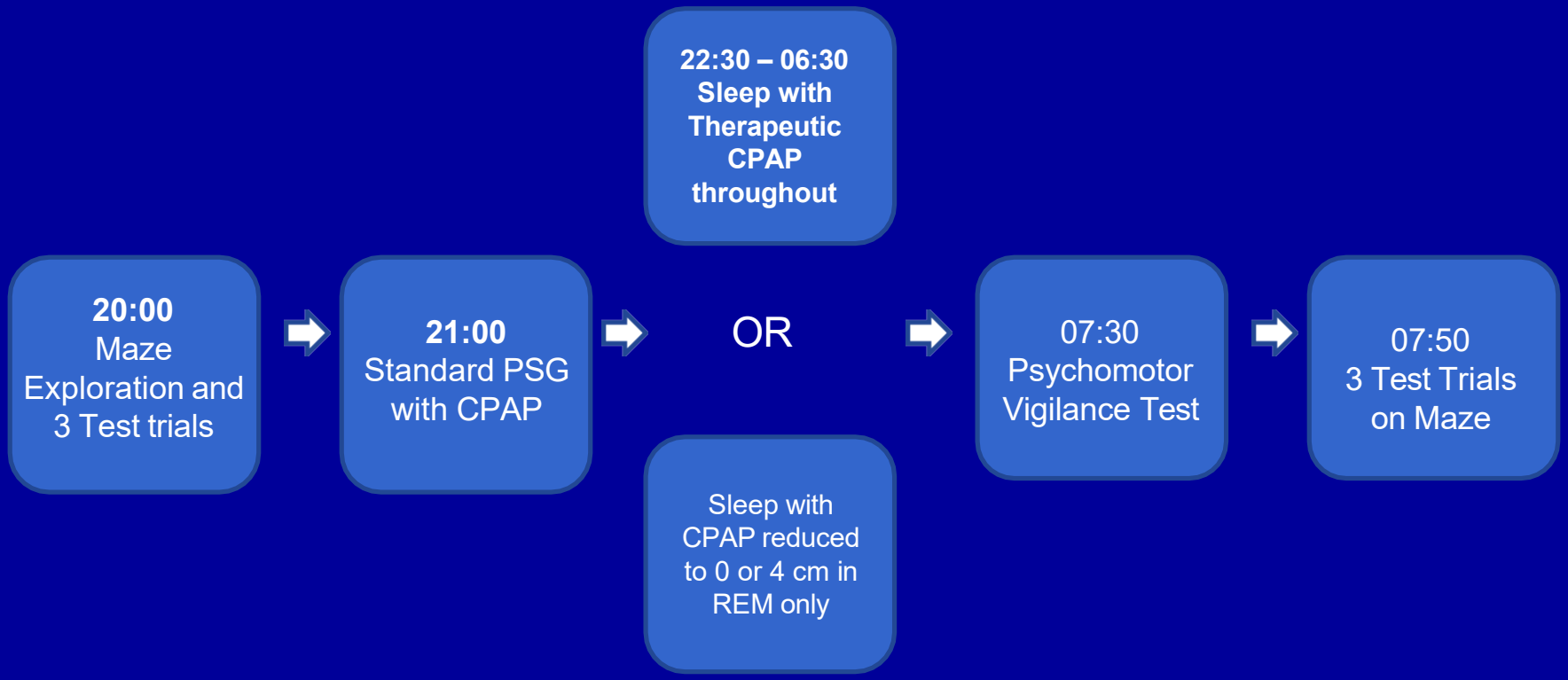
Hypnogram

CPAP

O_2 Sat



Experimental Timeline



- Subjects counterbalanced for maze encountered and condition encountered first
- Conditions separated by **~2 weeks**

Sleep Measures

Sleep Measure	Normal Sleep on CPAP	REM Disrupted	
Total Sleep Time	**366.4 min +/- 76**	**380.0 min +/- 68**	
Sleep Efficiency	81.4% +/- 14	82.6% +/- 9	
% NREM 1	23.1% +/- 10	29.5% +/- 11	**
% NREM 2	39.7% +/- 8	42.4% +/- 7	*
% NREM 3	16.7% +/- 10	16.6% +/- 11	
NREM AHI4%	0.65 /hr ***(median)***	3.9 /hr ***(median)***	*
NREM AHI-all	5.7 /hr ***(median)***	12.4 /hr ***(median)***	*

* = p < 0.05, ** = p < 0.001

Sleep Measures

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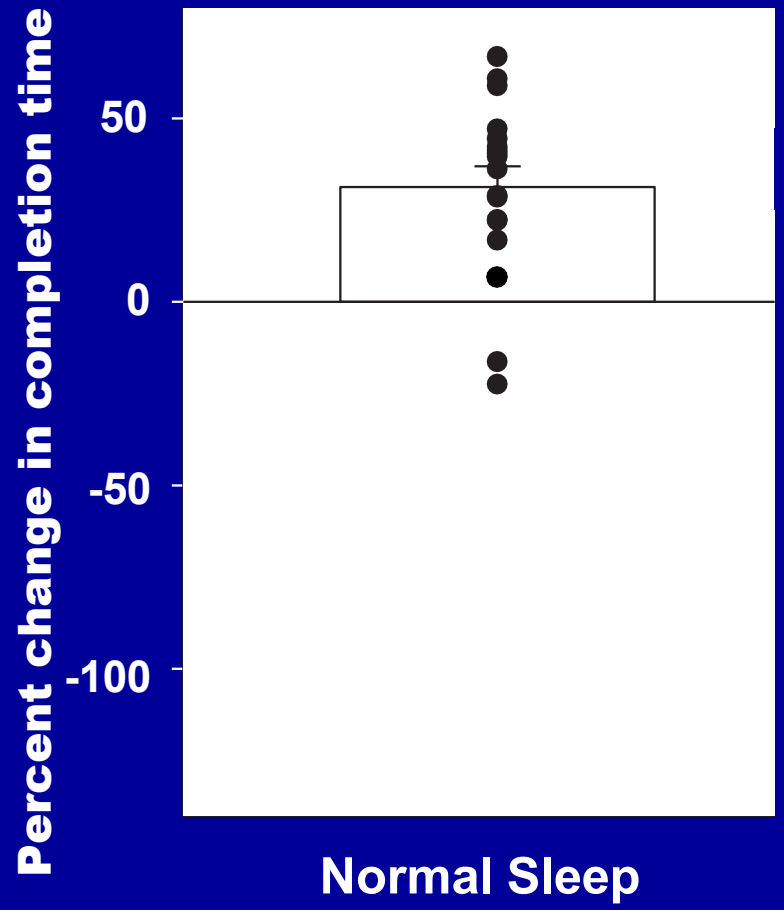
% NREM 2	39.7% +/- 8	42.4% +/- 7	*
% NREM 3	16.7% +/- 10	16.6% +/- 11	
NREM AHI4%	0.65 /hr (median)	3.9 /hr (median)	*
NREM AHI-all	5.7 /hr (median)	12.4 /hr (median)	*
% REM Sleep	20.5% +/- 5	11.5% +/- 6	**
REM AHI4%	1.2 /hr +/- 1.5	29.9 /hr +/- 18	**
REM AHI-all	9.3 /hr +/- 4	46.1 /hr +/- 15	**
# Arousals in REM	8.0 (median)	19.0 (median)	**

* = $p < 0.05$, ** = $p < 0.001$

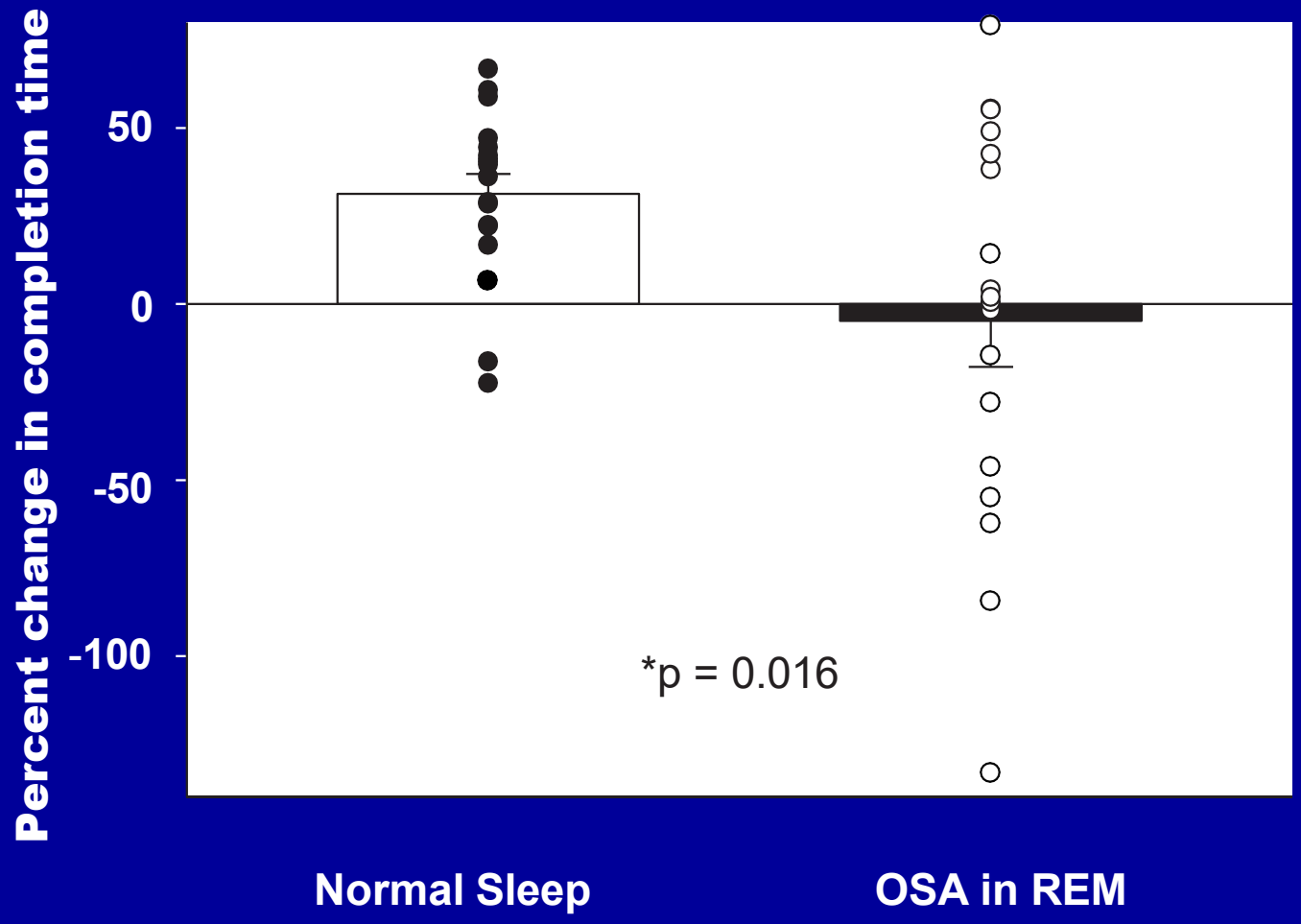
Normal Sleep Helps Consolidate Spatial Memory



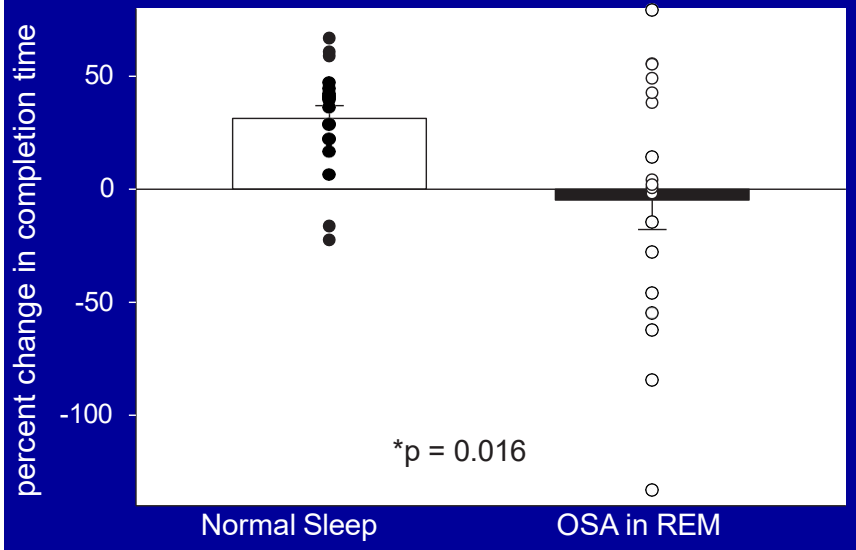
31.3%
Improvement
across sleep

OSA in REM
Varga, et al, *J. Neurosci*. 2014

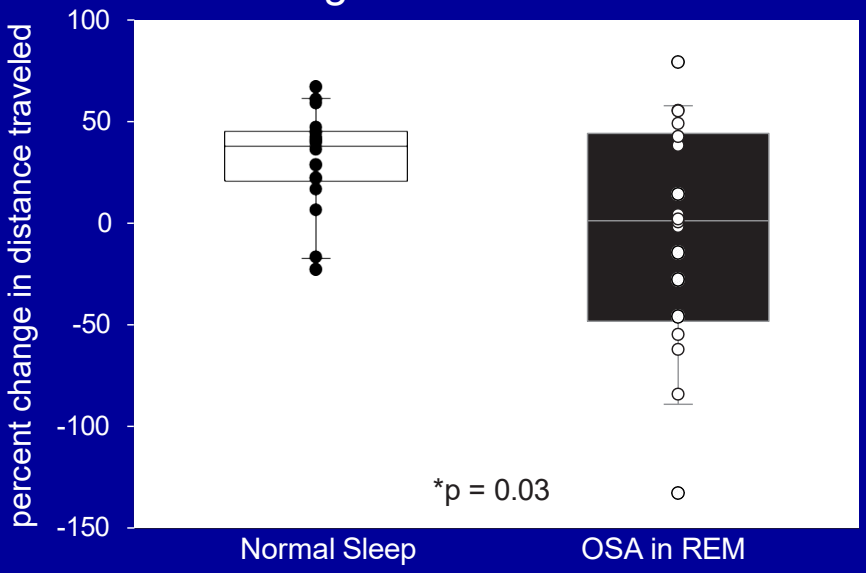
REM OSA Results in Worsened Maze Performance



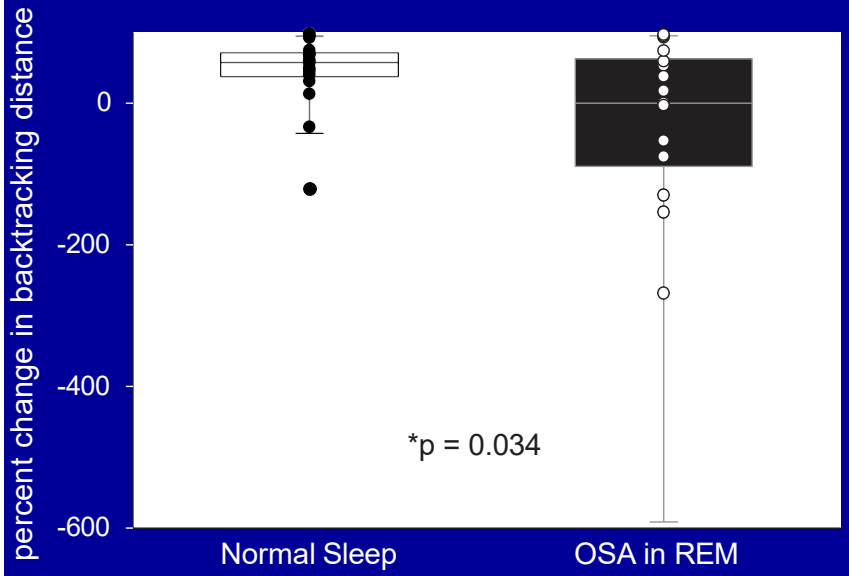
% Change in Maze Completion Time



% Change in Distance Traveled

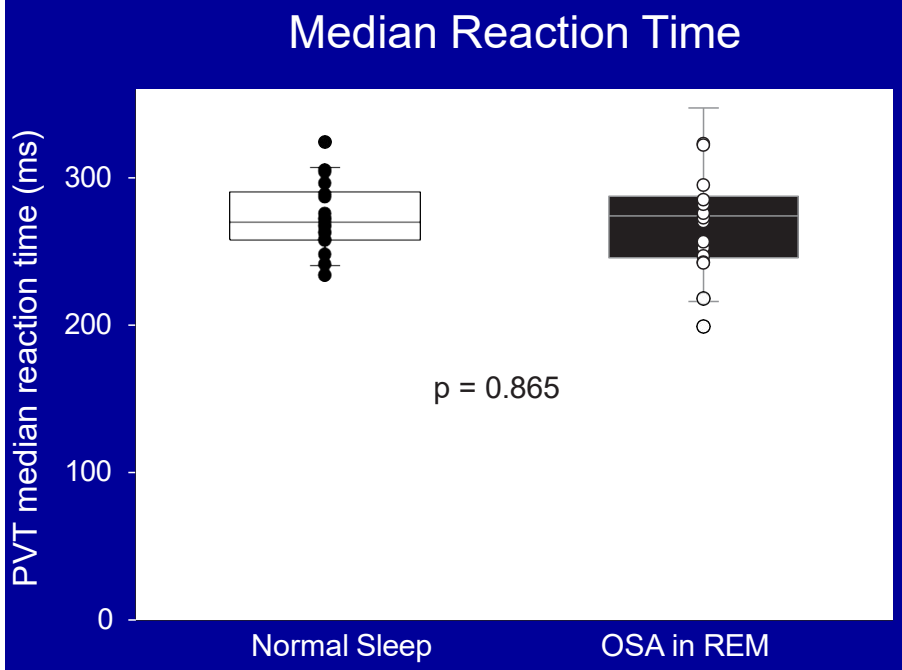


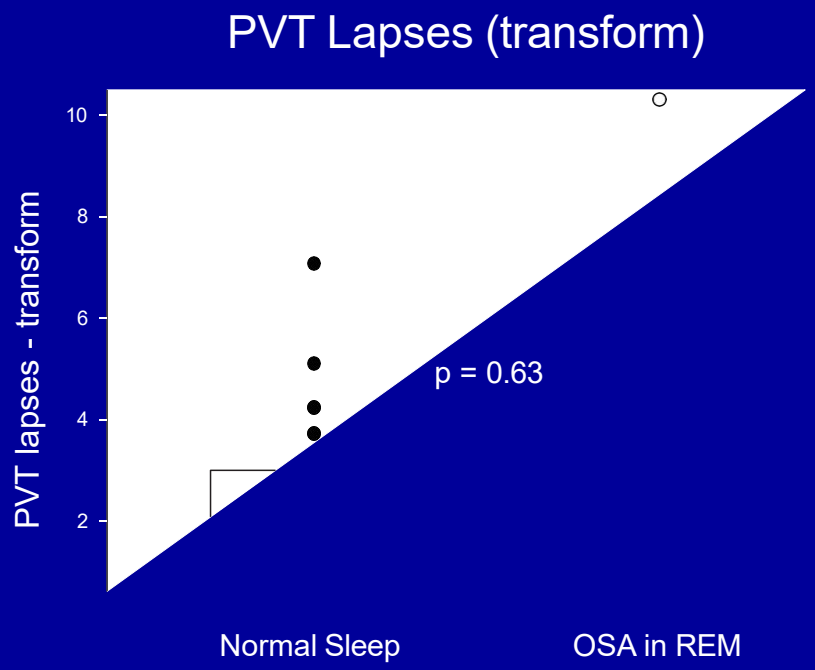
% Change in Distance Spent Backtracking



Varga, et al, *J. Neurosci*. 2014

No Difference in PVT Reaction Time or Lapses





Varga, et al, *J. Neurosci*. 2014

- **OSA** can negatively impact prospective memory acutely
- **OSA** may also have a chronic effect on modulating Alzheimer's disease risk

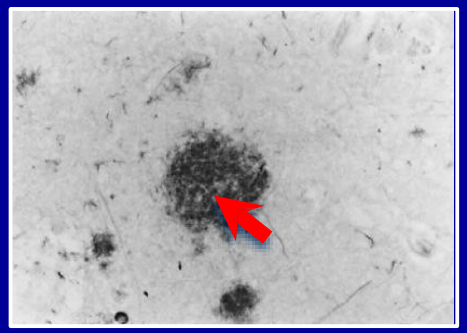
Alzheimer's Disease

Clinically characterized by progressive loss of memory and executive dysfunction

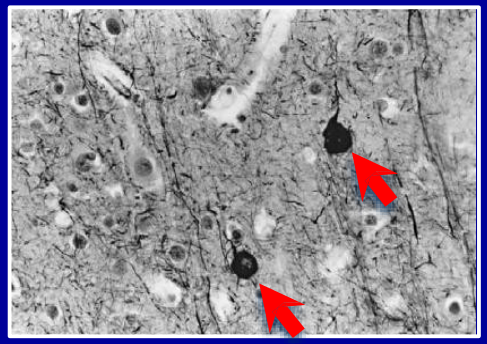
- Deterioration in ability to form new memories prospectively (affected earlier)
- Deterioration of remote, established memories

Neuropathologic/Biomarker Hallmarks

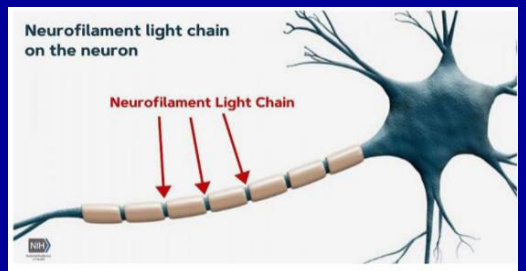
Neuritic plaques - βAmyloid



Neurofibrillary tangles - tau



Neurofilament Light (NfL)



Neurofilament Light Chain on the Neuron Credit: Pashtun Shahim, M.D., Ph.D *NIH Clinical Center*

JAMA Neurology | Original Investigation

Longitudinal Associations of Blood Phosphorylated Tau181 and Neurofilament Light Chain With Neurodegeneration in Alzheimer Disease

Alexis Moscoso, PhD; Michel J. Grothe, PhD; Nicholas J. Ashton, PhD; Thomas K. Karikari, PhD; Juan Lantero Rodríguez, MSc; Anniina Snellman, PhD; Marc Suárez-Calvet, MD, PhD; Kaj Blennow, MD, PhD; Henrik Zetterberg, MD, PhD; Michael Schöll, PhD; for the Alzheimer's Disease Neuroimaging Initiative

Sleep, ***A***ging, and ***R***isk for ***A***lzheimer's (***SARA***) Cohort of Cognitively Normal Elderly (CNE)

Ricardo Osorio, MD

PSG, brain imaging, Amyloid PET, blood/CSF evaluation,

Table 1: Baseline demographic characteristics of the subjects in CNE cohort

Characteristics	All	Normal	Mild OSA	Moderate-Severe OSA
No. of Participants (%)	208 (100)	97 (46.63)	76 (36.53)	35 (16.82)
Female sex, number (%)	129 (62)	67 (69.1)	44 (57.9)	18 (51.4)
BMI (Kg/m2), median (IQ range)	25.79 (22.7,29.87)	24.61 (22.32,28.17)	26.89 (23.32,29.9)	29.76 (23.49,33.51)
Age, years, mean ±	68.46 ± 7.38	67.56 ± 7.32	68.60 ± 7.19	70.68 ± 7.69
ESS, median (IQ range)	5 (3,8)	4 (3,7)	6 (3.5,8.5)	6 (4,9)
TST,hours, median (IQ range)	7 (6.5, 8)	7.48 (6.75,8)	7.00 (6.5,8)	7.50 (6.5,8)

Sleep, ***A***ging, and ***R***isk for ***A***lzheimer's (***SARA***) Cohort of Cognitively Normal Elderly (CNE)

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BMI (Kg/m2), median (IQ range)	25.79 (22.7,29.87)	24.61 (22.32,28.17)	26.89 (23.32,29.9)	29.76 (23.49,33.51)
Age, years, mean ±	68.46 ± 7.38	67.56 ± 7.32	68.60 ± 7.19	70.68 ± 7.69
ESS, median (IQ range)	5 (3,8)	4 (3,7)	6 (3.5,8.5)	6 (4,9)
TST,hours, median (IQ range)	7 (6.5, 8)	7.48 (6.75,8)	7.00 (6.5,8)	7.50 (6.5,8)

Sleep, ***A***ging, and ***R***isk for ***A***lzheimer's (***SARA***) Cohort of Cognitively Normal Elderly (CNE)

Ricardo Osorio, MD

PSG, brain imaging, Amyloid PET, blood/CSF evaluation

Table 1: Baseline demographic characteristics of the subjects in CNE cohort

Characteristics	All	Normal	Mild OSA	Moderate-Severe OSA
No. of Participants (%)	208 (100)	97 (46.63)	76 (36.53)	35 (16.82)
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Synergistic interaction between **OSA** and **HTN** on longitudinal amyloid load and cognition

98 subjects, age 69.6, 63% female, cognitively normal and community-dwelling

CSF Ab42 and Neurocognitive battery, 2.65 year average f/u interval

OSA+/HTN**+ [n=23]**
OSA+/HTN**- [n=24]**
OSA-/HTN**+ [n=20]**
OSA-/HTN- **[n=31]**

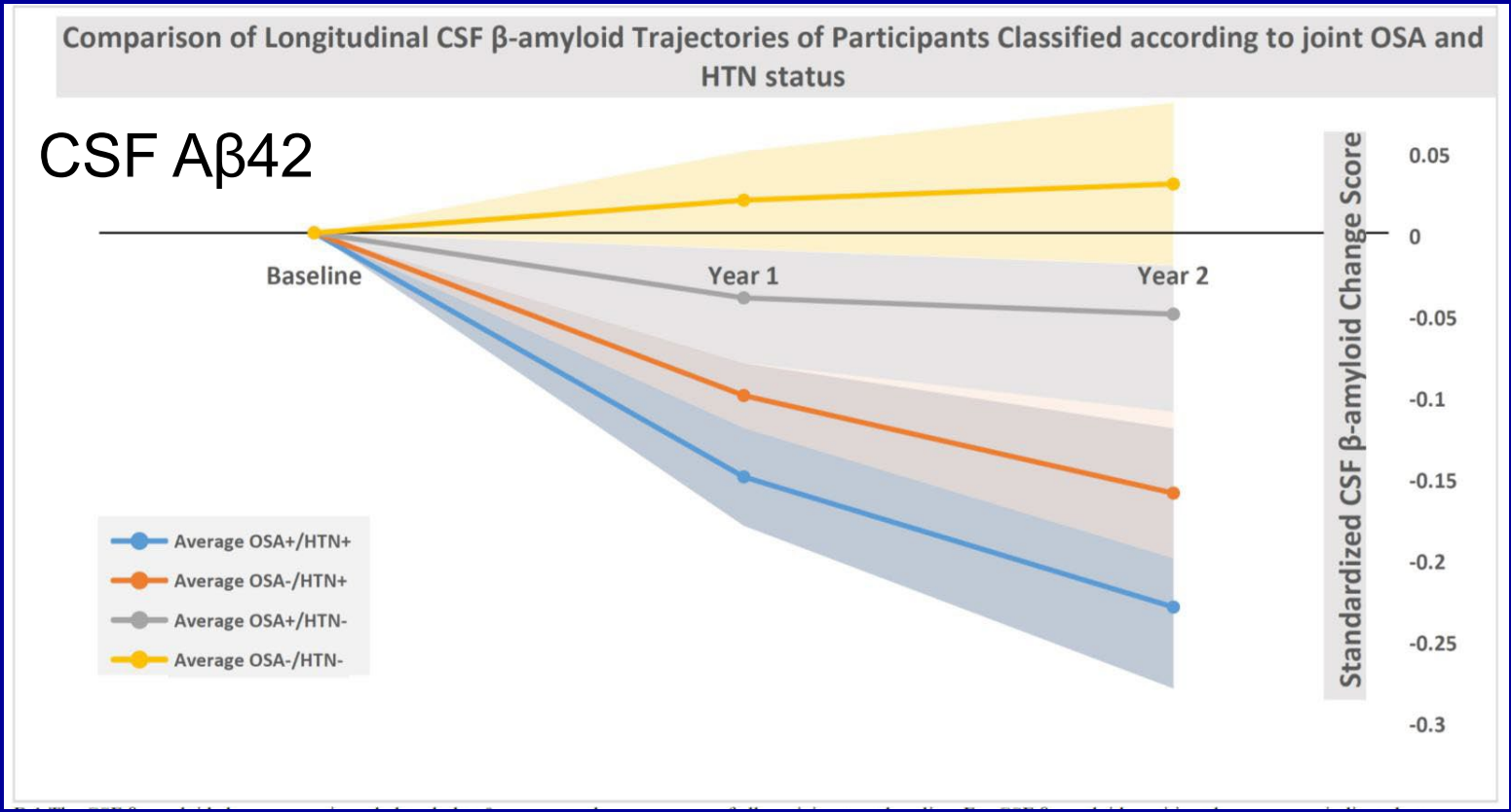
Michael Bubu, PhD

OSA = AHI4% **> 5**/hour

HTN = (**SBP** >140 mm **Hg** AND **DBP** > **90** mm **Hg**) OR
antihypertensive medication use OR
self-reports **HTN** diagnosis

All analyses controlled for age, sex, **BMI**, years of education, Apolipoprotein **E4**

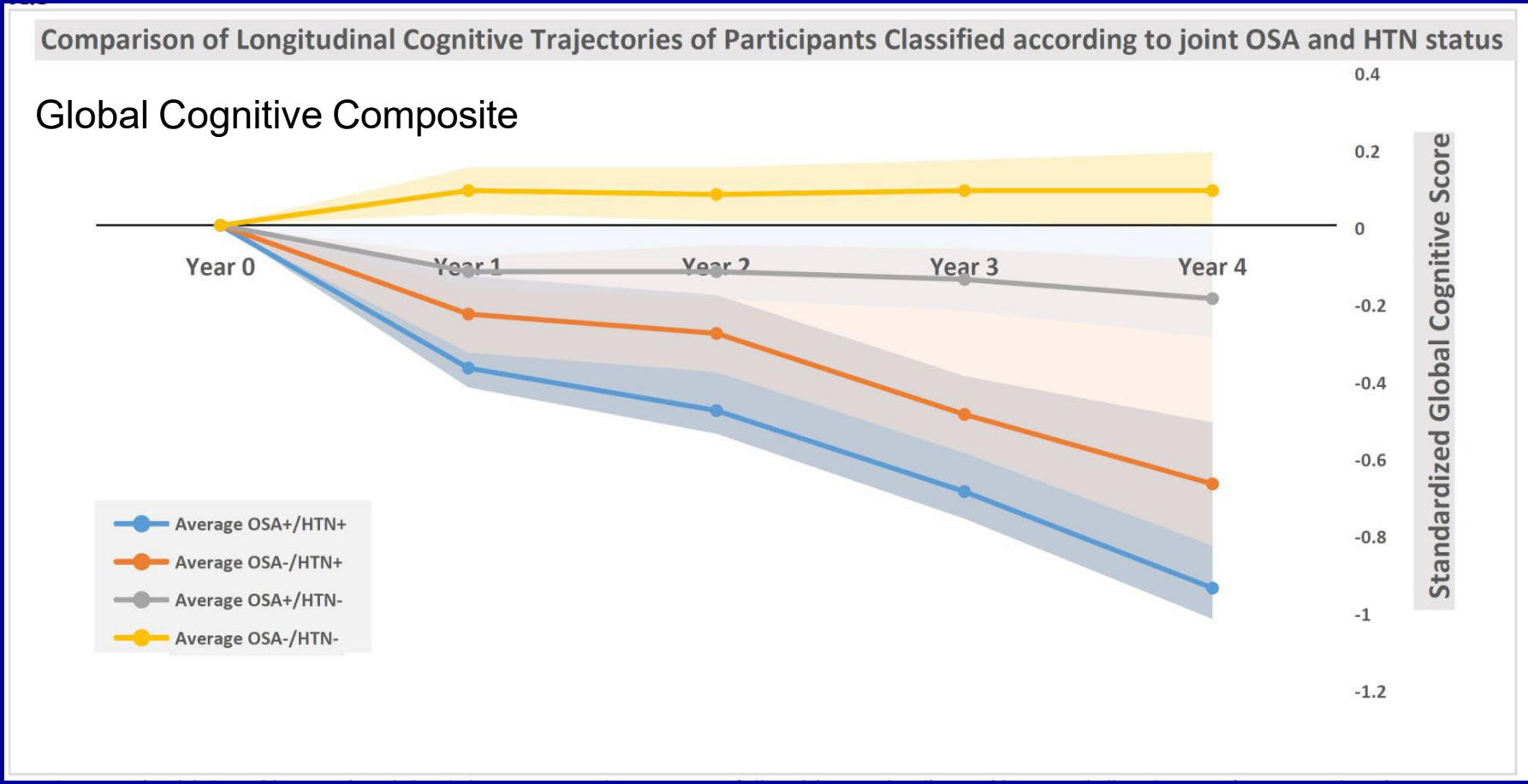
Synergistic interaction between OSA and HTN on longitudinal amyloid load and cognition



Outcome	Model Term	Standardized Estimate (95% CI)	P Value
Annual rate of change of CSF-Aβ42	OSA*time	-1.28 (-1.78 to -0.78)	<.01
	Hypertension*time	-2.82 (-3.29, -2.35)	<.01
	OSA*Hypertension*time	-3.11 (-3.71 to -2.51)	<.01

Bubu, et al. AJRCCM 2022

Synergistic interaction between OSA and HTN on longitudinal amyloid load and cognition



Bubu, et al, AJRCCM 2022

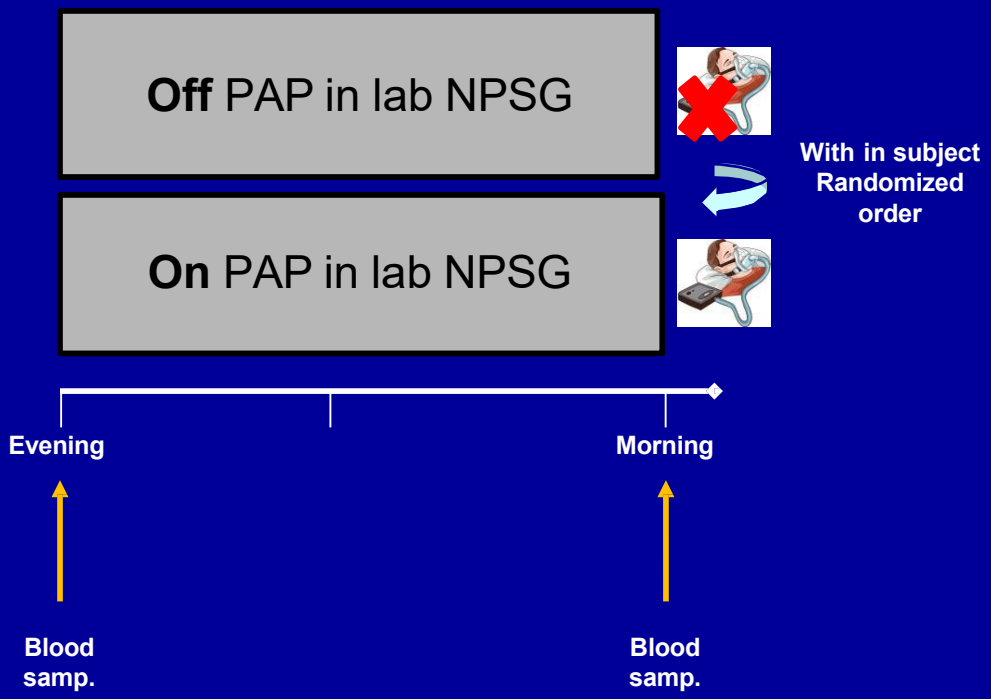
Synergistic interaction between OSA and HTN on longitudinal amyloid load and cognition

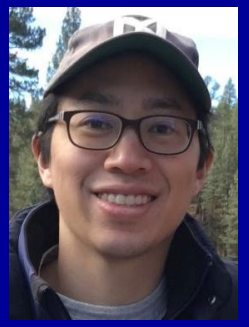
Annual decline in Executive Function (DSST, Trail Making A and B composite)	OSA*time	**-0.037 (-0.052 to -0.022)**	**0.01**
	Hypertension*time	**-0.058 (-0.092 to - 0.024)**	**<.01**
	OSA*Hypertension*time	**-0.048 (-0.063 to -0.033)**	**<.001**
Annual decline in Language(Verbal and Animal Fluency and BNT composite)	OSA*time	**-0.025 (-0.036 to -0.014)**	**0.03**
	Hypertension*time	**-0.034 (-.057 to -0.011)**	**0.04**
	OSA*Hypertension*time	**-0.054 (-0.094 to -0.013)**	**<.001**
Annual decline in Episodic Memory (Logic-1 and 2 composite)	OSA*time	-0.026 (-0.052 to 0.019)	0.43
	Hypertension*time	-0.019 (-0.038 to 0.008)	0.34
	OSA*Hypertension*time	-0.037 (-0.076 to 0.021)	0.33

Bubu, et al, AJRCCM 2022

SAAB3: **S**leep **A**pnea and **A**lzheimer disease **B**lood-**b**ased **B**iomarkers

30 subjects with severe **OSA**, adherent to **PAP**
2 PSG's: **1** on **PAP**, **1** OFF **PAP** (3rd night off)
Pre- and **Post**-sleep blood samples analyzed for **AD** biomarkers




Korey Kam, PhD


Jonathan Jun, MD

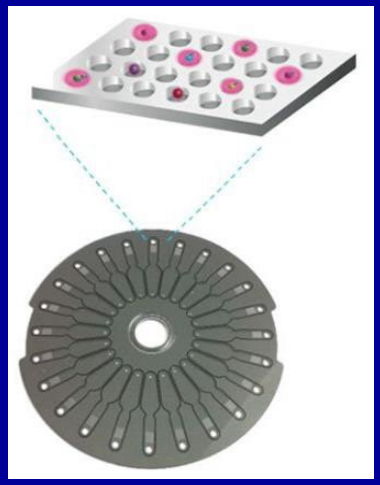
Kam, et al, AJRCCM 2022

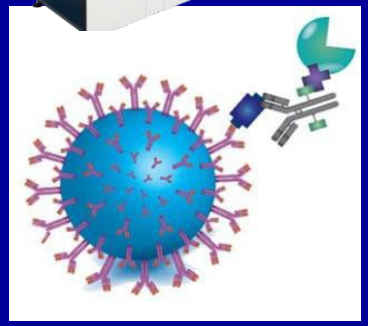
SAAB3: **S**leep **A**pnea and **A**lzheimer disease **B**lood-**b**ased **B**iomarkers

Korey Kam, PhD

Jonathan Jun, MD

30 subjects with severe OSA, adherent to **PAP 2**
PSG's: 1 on **PAP**, 1 OFF **PAP** (3rd night off)
Pre- and Post-sleep blood samples analyzed for **AD** biomarkers





Method*: SIMOA *(single molecule array)* assay of T-tau, Aβ42, Aβ40, NfL.

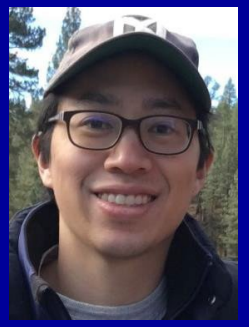
Samples run in duplicate

Samples with **CoV >20%**

were excluded:

25 subjects for **Aβ42**
27 subjects for **Aβ40**
13 subjects for **T-tau**
25 subjects for **NfL**

SAAB3: **S**leep **A**pnea and **A**lzheimer disease **B**lood-**b**ased **B**iomarkers



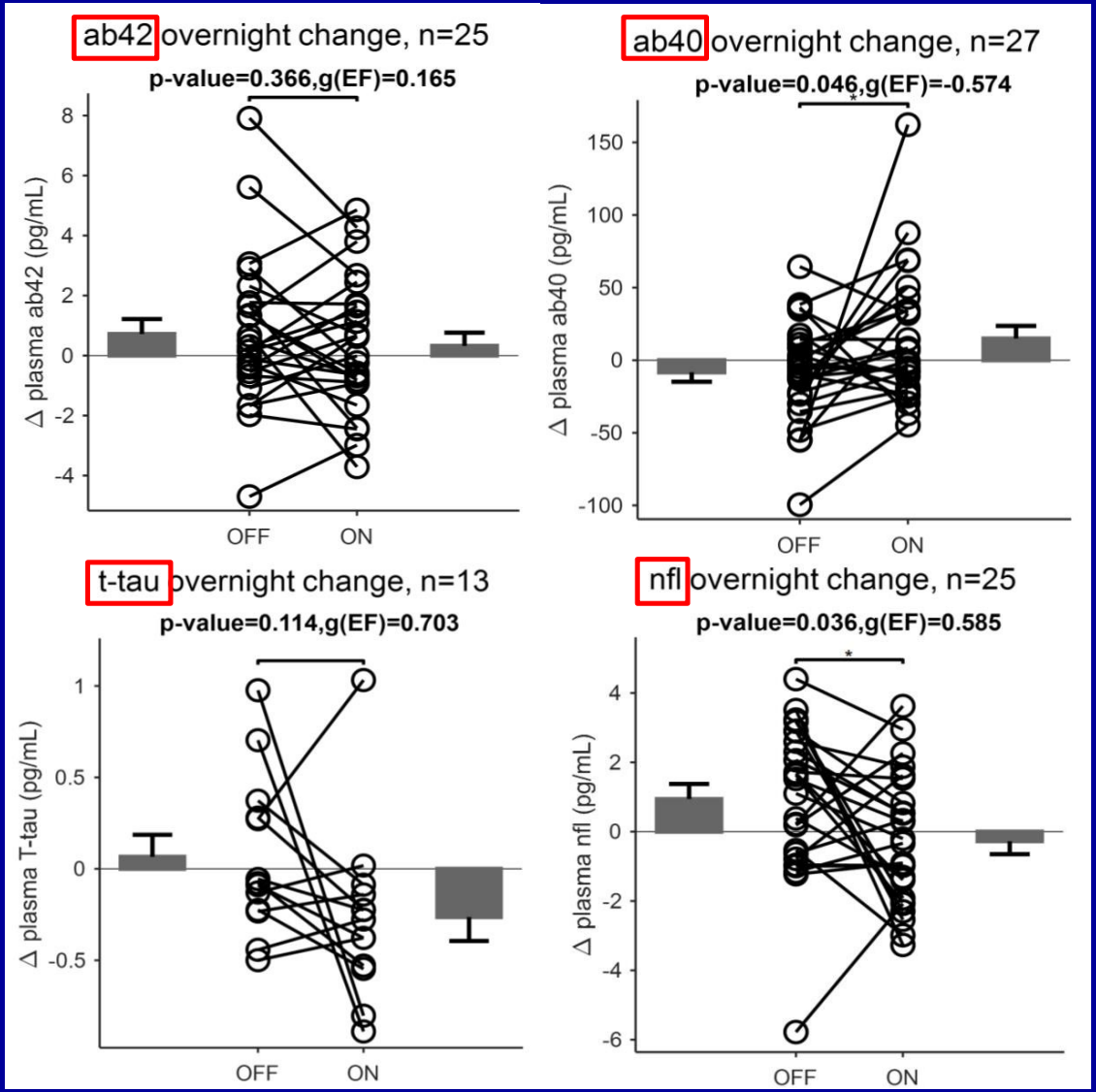
Korey Kam, PhD

Jonathan Jun, MD

Characteristic	n = 30 total	Expressed as mean (95% CI)
Age	51.5 (47.3-55.6)	
Sex, F, n (%)	8 (27%)	
BMI	35.4 (33.2-37.7)	

Polysomnographic measure	**OFF CPAP night**	**ON CPAP night**	**p-value**
TST, min	381 (365-398)	388 (372-404)	0.344
SE (%)	79 (76-82)	81 (78-84)	0.235
N3, (%)	6.1 (3.7-8.5)	15.1 (10.6-19.6)	**<0.001**
REM, (%)	11.8 (8.8-14.7)	20.6 (18.3-22.9)	**<0.001**
Arousal index, evt/hr	53 (44-62)	12 (9-14)	**<0.001**
Sleep-state transitions, total	194 (159-230)	121 (104-139)	**<0.001**
AHI4, evt/hr	63 (54-72)	3 (2-4)	**<0.001**
AHI3, evt/hr	74 (65-82)	7 (5-9)	**<0.001**
SpO2 <90%, min	20 (14-26)	1 (0-3)	**<0.001**
O2 min, %	77 (74-80)	88 (86-90)	**<0.001**
ODI4, evt/hr	58 (49-66)	3 (2-3)	**<0.001**

Kam, et al, AJRCCM 2022



No significant difference in evening levels of any biomarker between conditions

Kam, et al, AJRCCM 2022

Linear mixed effects modeling of overnight change in NfL

LME-Model 1: outcome overnight ΔNfL (pg/mL)			
Fixed effects	**β coefficient**	**95% CI**	**P**
SE, %	-0.025	(-0.097, 0.047)	0.491
Arousal Index, events/h	0.018	(-0.014, 0.051)	0.276
Sleep stage transitions, #	0.009	(0.002, 0.016)	0.012*
NREM 3, %	-0.020	(-0.083, 0.043)	0.521
REM, %	-0.075	(-0.158, 0.006)	0.069
AHI4%, events/h	0.022	(-0.010, 0.055)	0.179
O_2min, %	-0.054	(-0.141, 0.031)	0.209
T90, min	0.071	(0.016, 0.125)	0.011*
ODI4%, events/h	0.021	(-0.014, 0.057)	0.232

Kam, et al, AJRCCM 2022

Linear mixed effects modeling of overnight change in **Aβ40**

LME-Model 2: outcome overnight ΔAβ40 (pg/mL)			
Fixed effects	**β coefficient**	**95% CI**	**P**
SE, %	0.410	(-0.764, 1.585)	0.485
Arousal Index, events/h	0.303	(-0.25021, 0.856)	0.276
Sleep stage transitions, #	0.039	(-0.091, 0.170)	0.546
NREM 3, %	-0.560	(-1.759, 0.638)	0.352
REM, %	0.210	(-1.318, 1.739)	0.782
AHI4%, events/h	0.376	(-0.172, 0.926)	0.174
O_2min, %	-0.899	(-2.358, 0.559)	0.221
T90, min	-0.111	(-0.941, 0.719)	0.789
ODI4%, events/h	0.324	(-0.280, 0.929)	0.286

Kam, et al, AJRCCM 2022

Summary

Acute induction of **OSA** during **REM** sleep negatively impacts prospective spatial navigational memory, without change in psychomotor vigilance

OSA acts synergistically with **HTN** to cause greater longitudinal decreases in **CSF Aβ42** and longitudinal decreases in executive function and language domains

Acute induction of **OSA** via **PAP** withdrawal alters the overnight change in **Aβ40** and NfL measured in plasma

Overnight change in **NfL** is predicted by **T90** and sleep stage transitions

NIOSH U01 OH011852: Role of Sleep Apnea in Cognition and Alzheimer's Disease Biomarkers in WTC Responders


Indu Ayappa, PhD

- 64 WTC responders (60-75 yrs) with OSA (untreated for >5 years) and non-OSA subjects will complete baseline and 2-year followup visits
- In-lab PSG with pre- and post-sleep spatial navigation testing and blood draw
- Brain MRI and Tau PET imaging 18F-MK-6240, Full UDS-3 Neurocognitive Battery

- Aim 1: Determine whether OSA severity is correlated with (i) changes in plasma tau and (ii) with greater longitudinal intracerebral tau burden using Tau PET-MR imaging

- Aim 2: Test the hypothesis that OSA severity at baseline predicts longitudinal decline in spatial navigational memory

Thank you!

Mount Sinai Integrative Sleep Center:

David M. Rapoport, M.D.
Indu Ayappa, Ph.D.
Bresne Castillo, RPSGT
Haley Sanders, B.A.
Akosua Twumasi, B.A.
Omar Burschtin, M.D.
Zachary Roberts, RPSGT
Masrai Williams, MS-II
Korey Kam, Ph.D.
Ankit Parekh, Ph.D.
Anna Mullins, Ph.D.

NYU Center for Brain Health:

Ricardo Osorio, M.D.
Esther Fisher, M.D.
Ram Sharma, M.D.
Viachaslau Koushyk, M.D.
Akifumi Kishi, Ph.D.
Antonio Convit, M.D.

Johns Hopkins:

Jonathan Jun, M.D.

Rutgers:

Jag Sunderram, M.D.

Thank you!

Mount Sinai Integrative Sleep Center:

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Indu Ayappa, Ph.D.
Bresne Castillo, RPSGT
Ahmad Fakhoury, M.A.
Natasha Berryman, M.A.
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Anna Mullins, PhD


Michael Bubu, PhD


Masrai Williams, MD

Sponsored by:

- NIH – National Institute on Aging
- Alzheimer's Association
- American Sleep Medicine Foundation - Junior Faculty Awards
- American Thoracic Society Foundation
- Friedman Brain Institute

Sinai + NYU Sleep Research Team

Contact: andrew.varga@mssm.edu

Sleep Medicine Family!

Thank You

Contacts:

 Email: andrew.varga@mssm.edu

Mount Sinai Integrative Sleep Center

11 East 26th St., 13th Floor |  212-481-1818

Questions?

Outline

1. Evidence that **OSA** impacts memory
2. Evidence that **OSA** impacts **AD** biomarkers
3. Evidence that **OSA** treatment can impact both memory and **AD** biomarkers

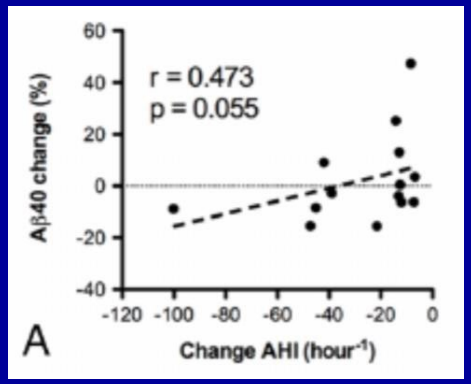
How does chronic OSA treatment impact AD fluid biomarkers?

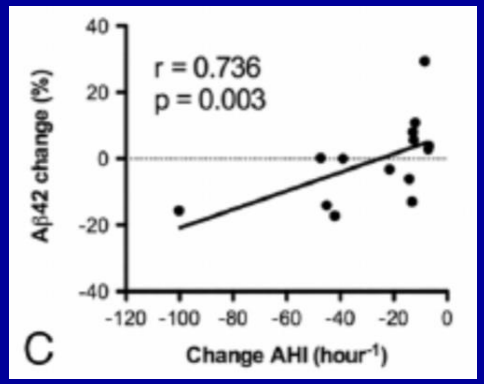
35 adults age **35**-65 (mean **57**) with **OSA** (AHI4% > 5/hour) prescribed **PAP** **CSF** collected pre-treatment and **1-4** months post-treatment

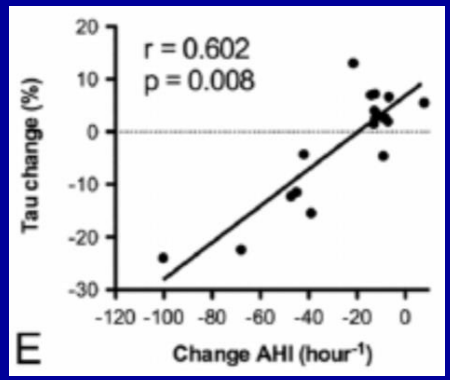
Analysis limited to "**PAP** adherent" subjects

TABLE 1. Effect of Positive Airway Pressure Treatment

	Pretreatment	Post-treatment	*p*
CSF			
Aβ40, pg/ml	12,033 ± 3,972	12,059 ± 3,560	0.944
Aβ42, pg/ml	987 ± 329	977 ± 319	0.733
Tau, pg/ml	184 ± 96	182 ± 102	0.602
Protein, mg/ml	0.857 ± 0.279	0.912 ± 0.235	0.197

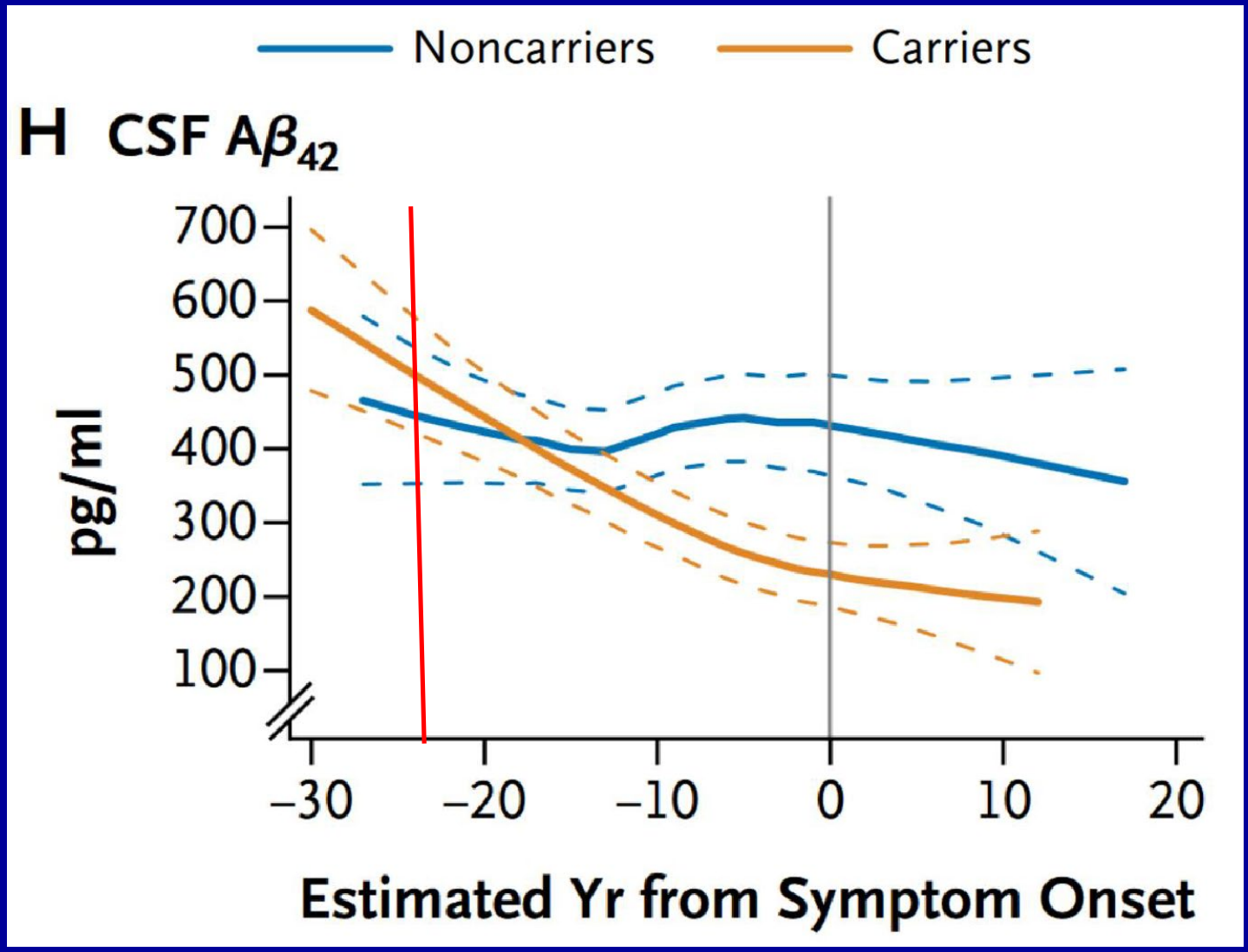






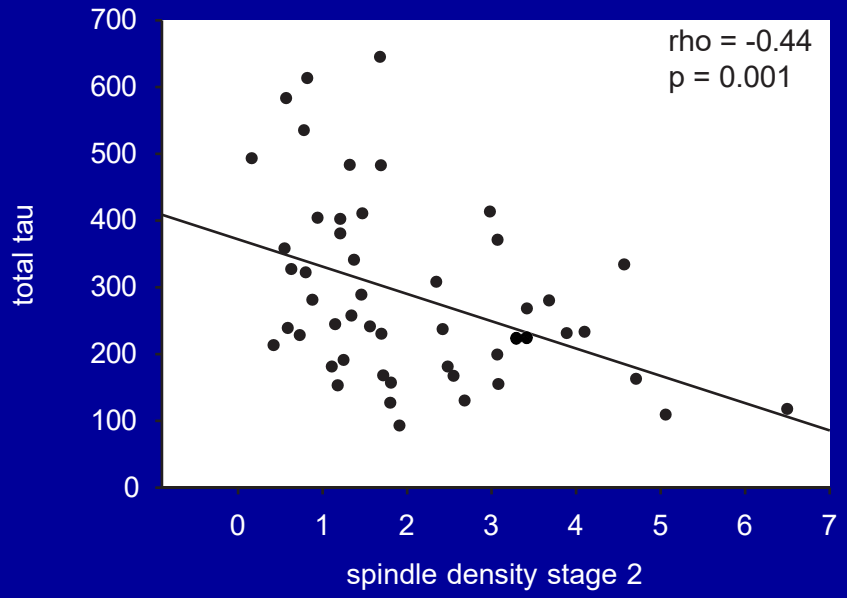
Ju, et al, Annals of Neurology 2019

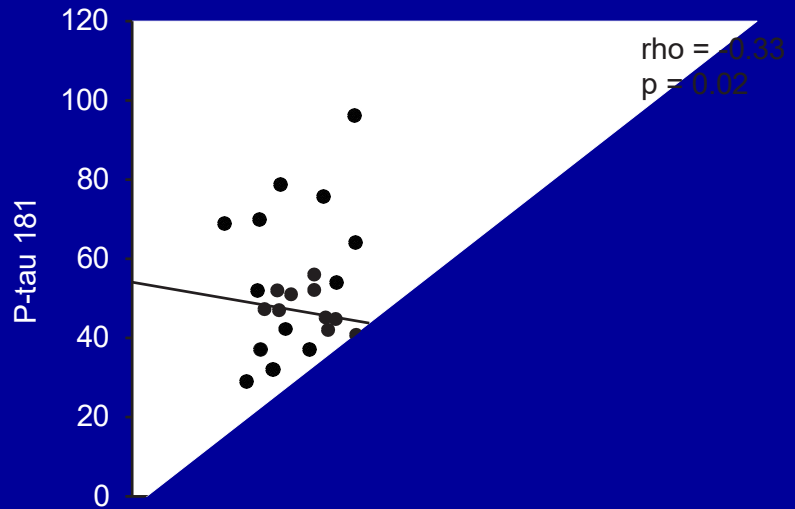
Is elevated CSF $A\beta_{42}$ good or bad?



Bateman, et al, NEJM 2012

High spindle density in stage 2 sleep is associated with low total tau and phosphorylated tau concentrations in cerebrospinal fluid (CSF) in older subjects without OSA

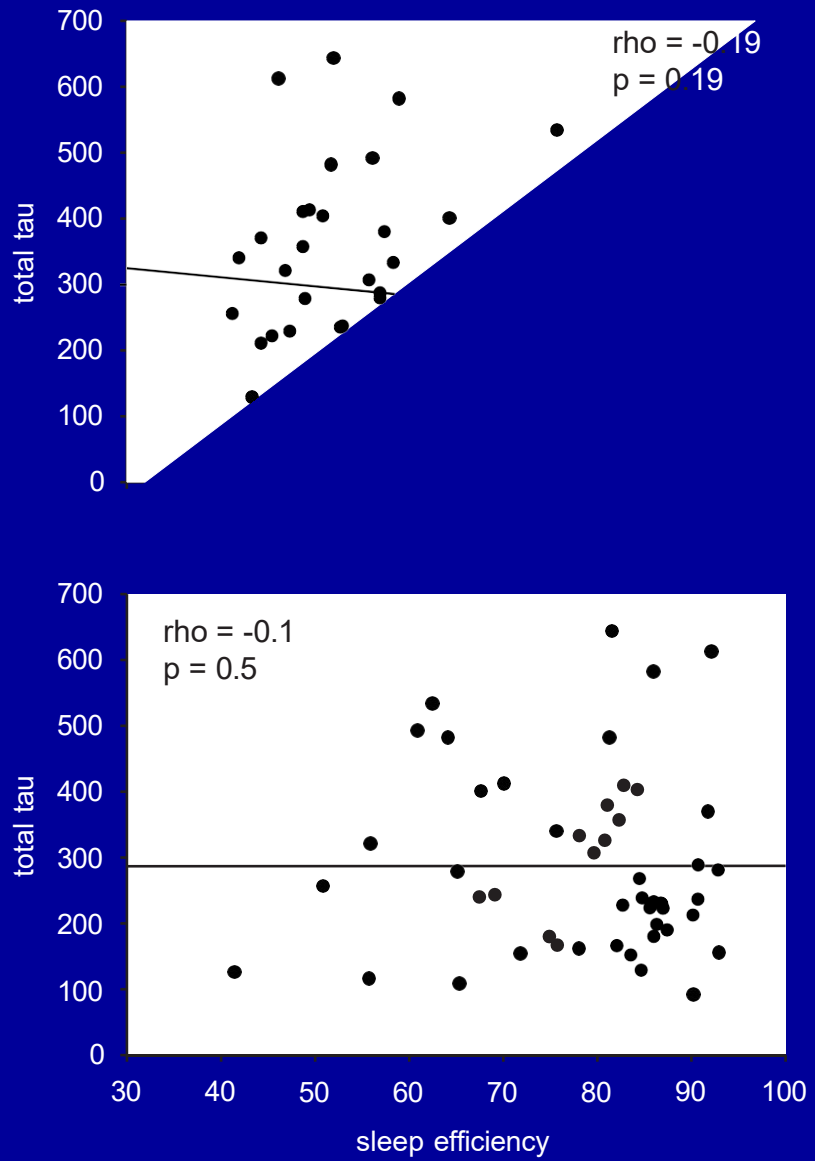


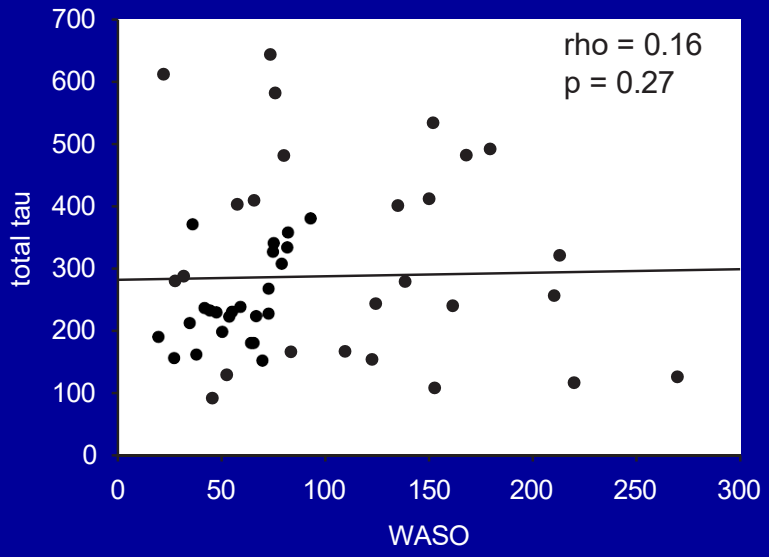


Correlation remains significant when controlling for age and sex

Correlations also present but weaker between tau and spindles in stage 3 or all NREM

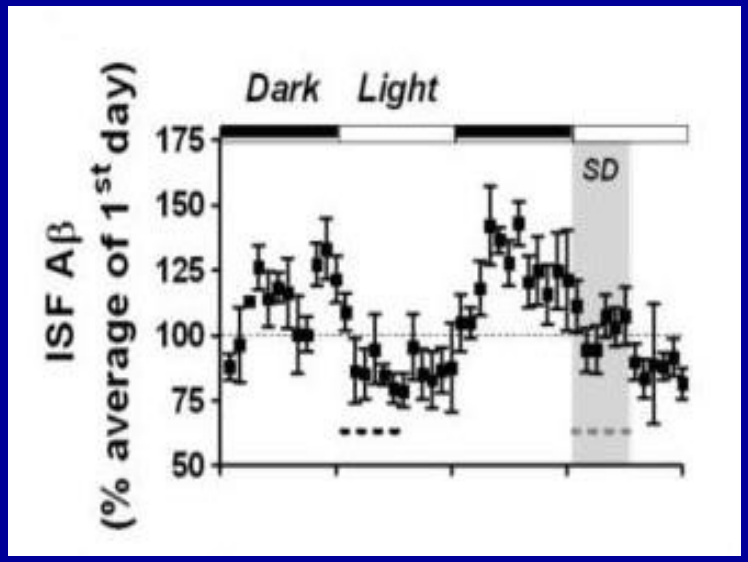
CSF tau does not correlate with general measures of sleep quality

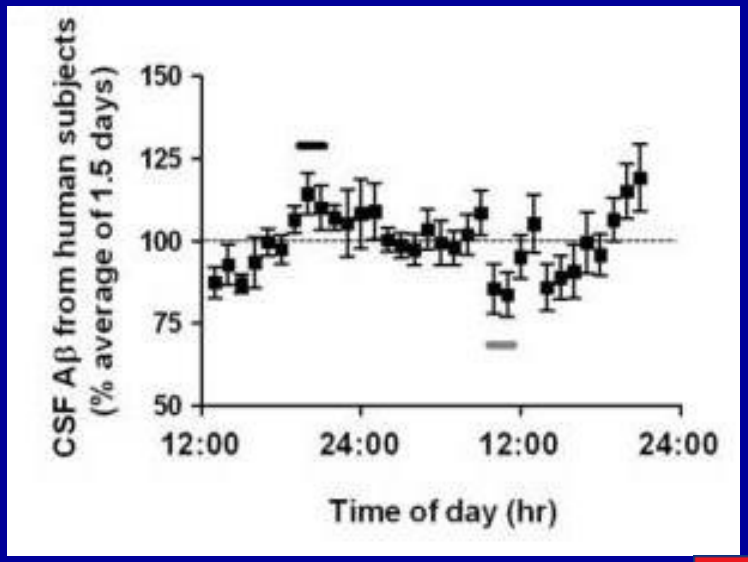




The diurnal fluctuation of Aβ:

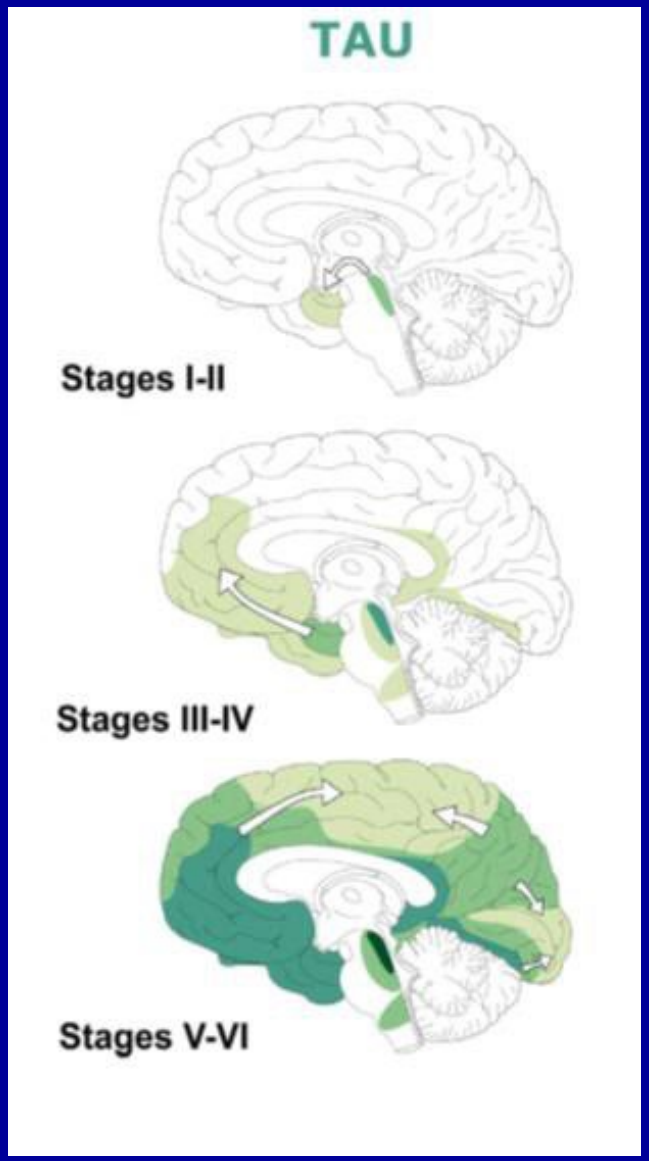
- Neuronal activity regulates Aβ deposition
- There is decreased neuronal activity in SWS
- Aβ shows a diurnal fluctuation in mice/humans





J Kang et al. Science 2009;326:1005-1007

AD neurodegenerative process disrupts sleep (ii):

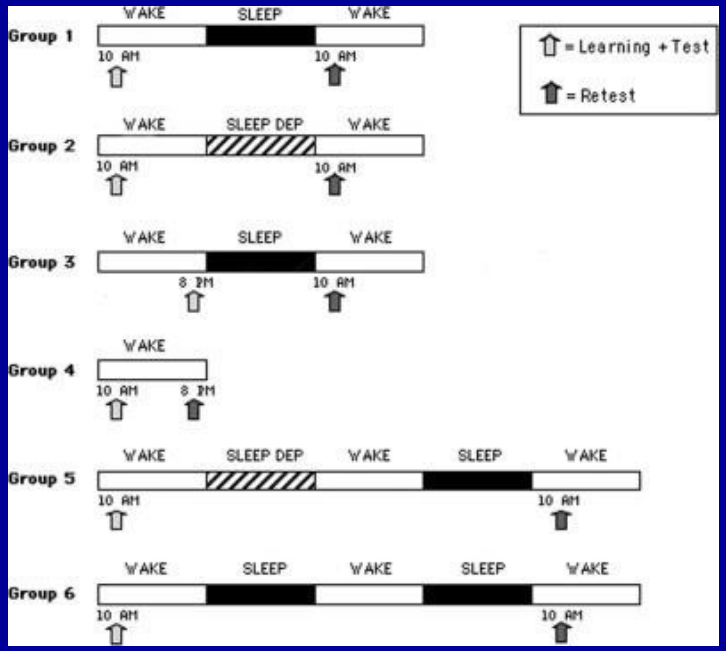


- Tau pathology is seen in LC in over 90% of individuals under 30 years of age.
- Severity of tau pathology in the LC significantly increases with increasing NFT Braak stages
- Better sleep consolidation attenuates the development of neurofibrillary tangles
- Loss of neurons in the intermediate nucleus neurons is accompanied by sleep fragmentation
- AD patients have less intermediate nucleus neurons than those without

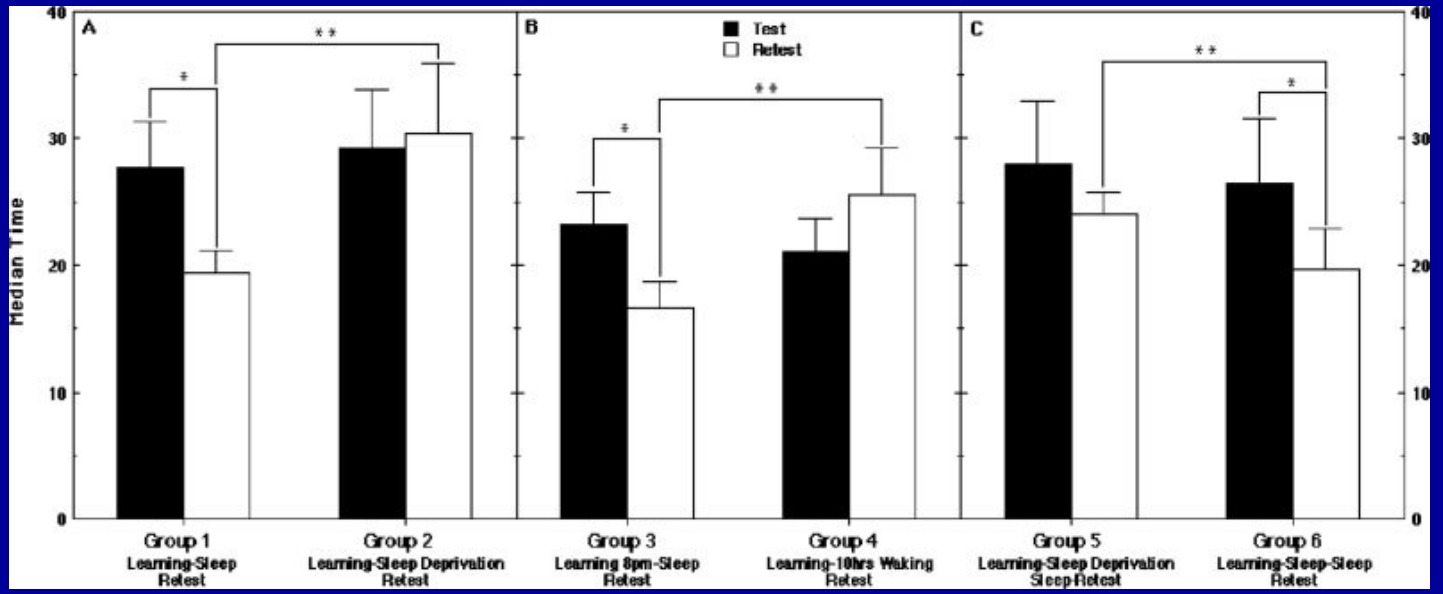
- Using a partial correlation to control for age, we showed a continued significant positive partial correlation between **medial prefrontal cortical volume** and average **relative frontal slow wave activity** ($r = 0.52$, $p = 0.004$), suggesting that controlling for age had little effect on the strength of the relationship between these variables

- A partial correlation controlling for age demonstrated a reduced strength of association between average **relative frontal slow wave activity** and the overnight **percent change in maze completion time** ($rho = 0.3$, $p = 0.056$), suggesting that age has some mediating effect on the relationship between relative frontal slow wave activity and spatial navigational memory

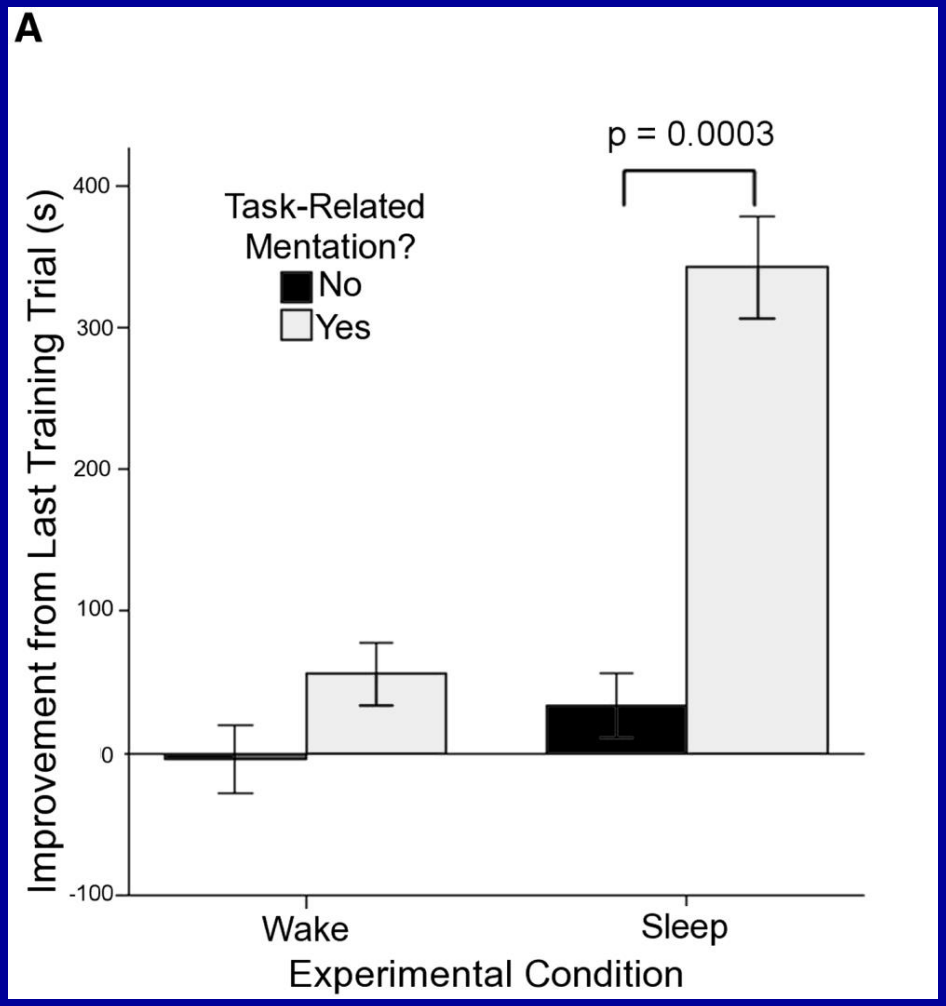
Human Spatial Memory



Ferrara, M, et al, *Hippocampus* 2008

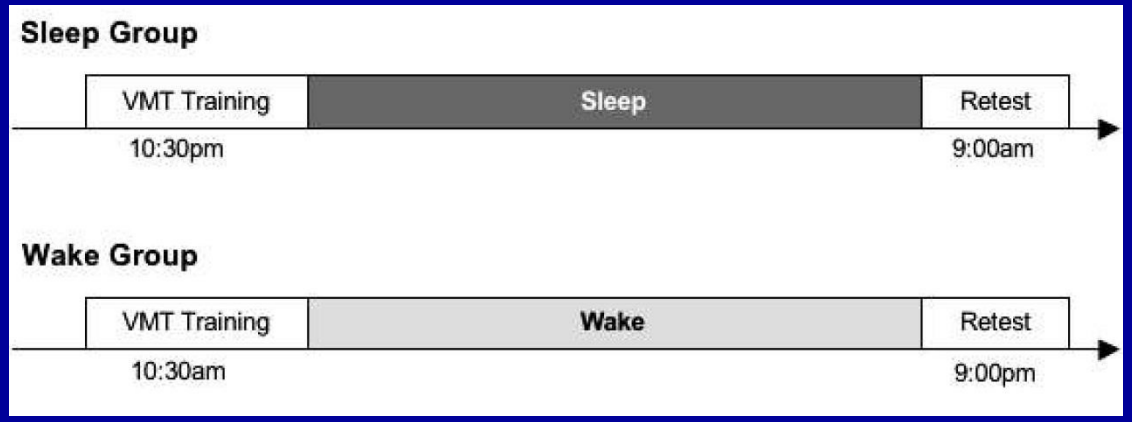


Spatial Navigation Performance is Improved When Subjects Dream About the Maze

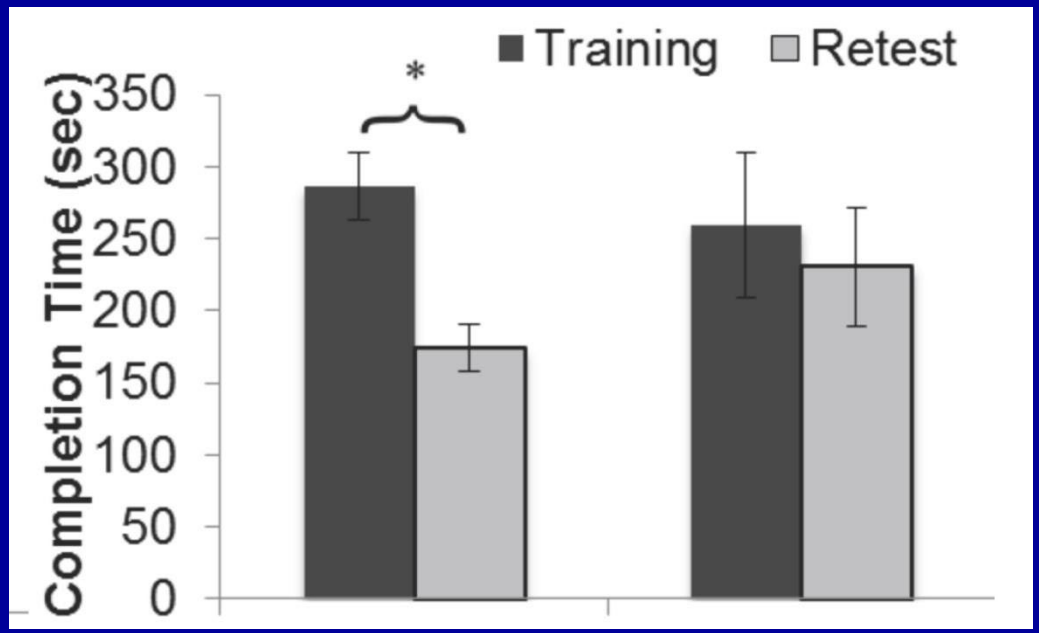


Wamsley, et al, *Curr. Bio.* 2010

Overnight Sleep Enhances Spatial Navigational Memory Versus Equal Wake

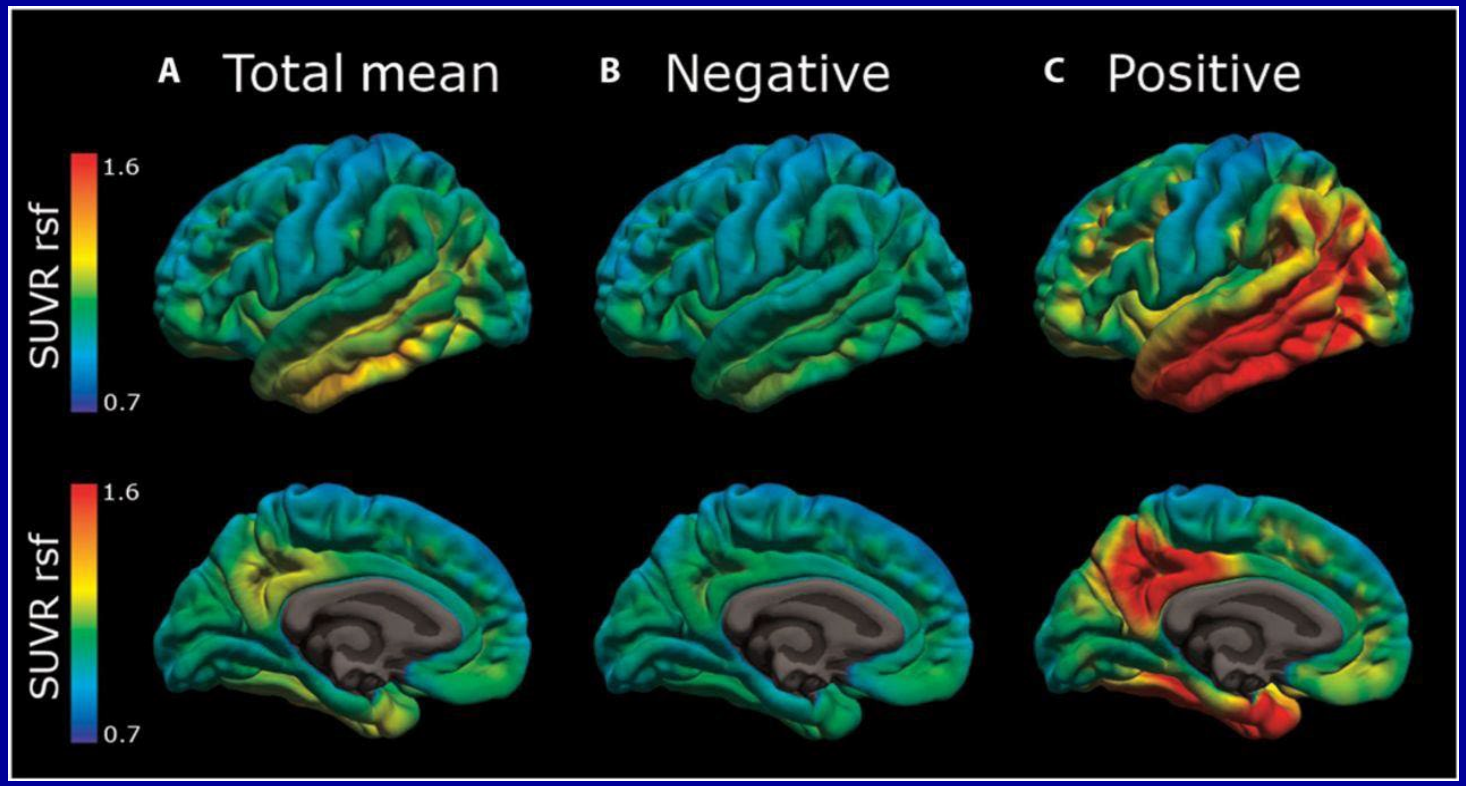


34.7 % Improvement across sleep



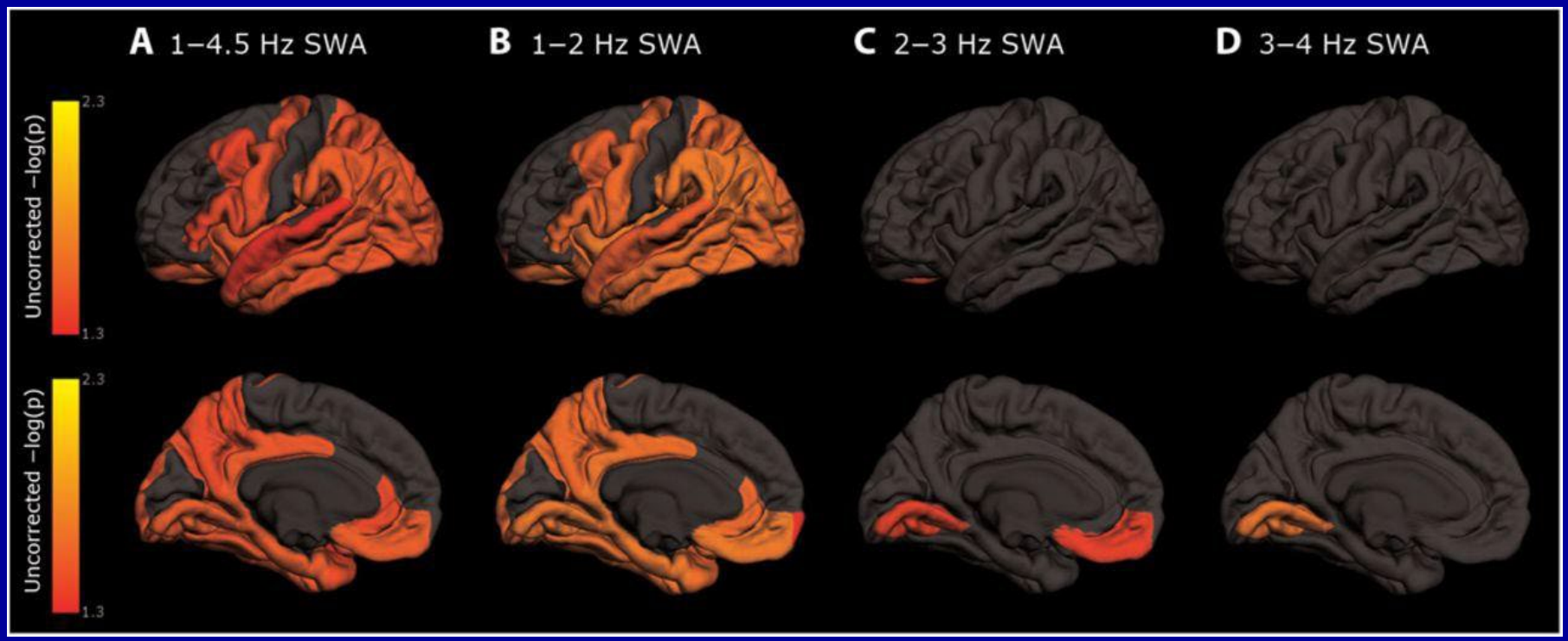
Nguyen, N, et al, *Sleep* 2013

Distribution of tau by PET in cognitively normal elderly



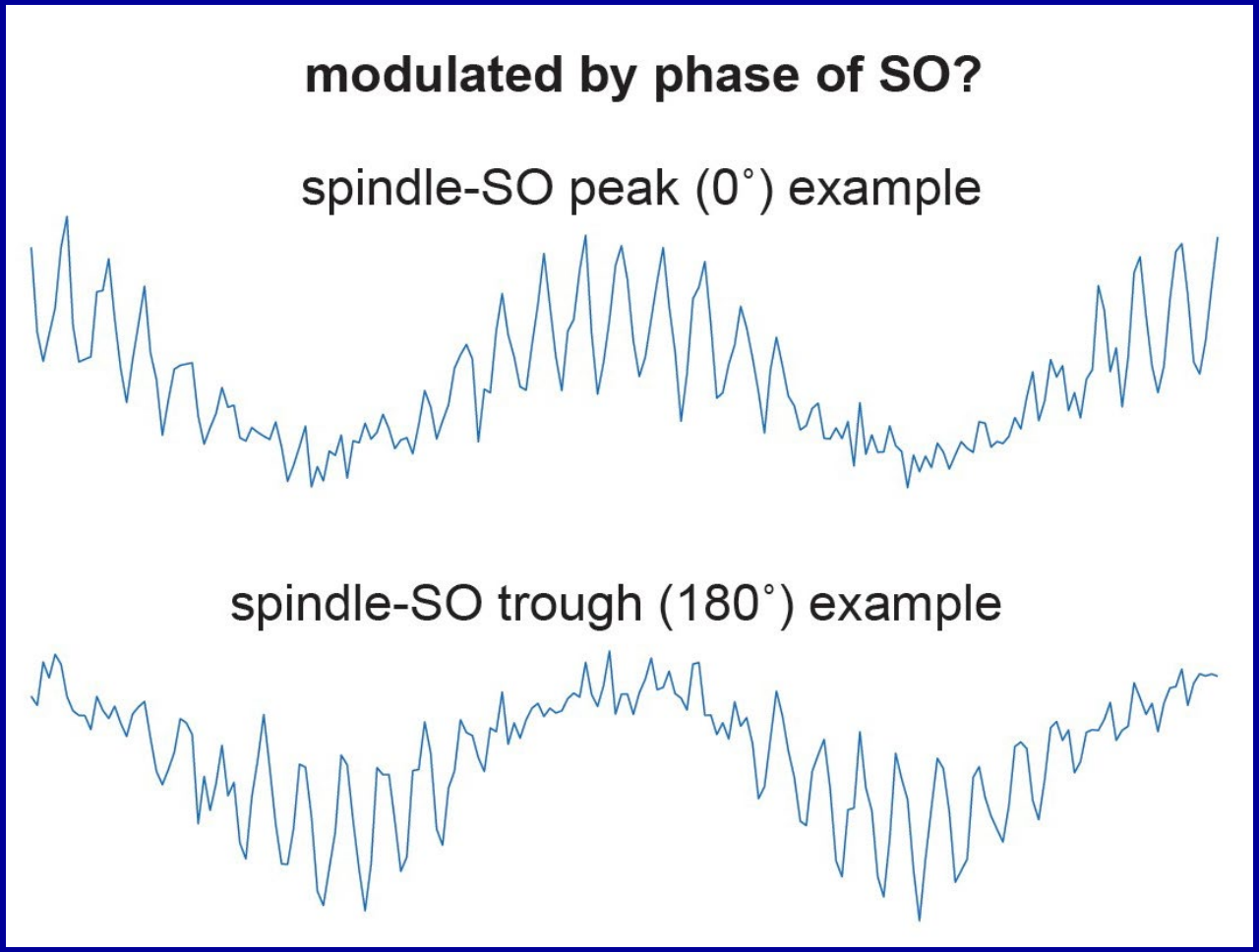
Lucey, et al, Sci Trans. Med 2019

Tau associations with SWA



Lucey, et al, Sci Trans. Med 2019

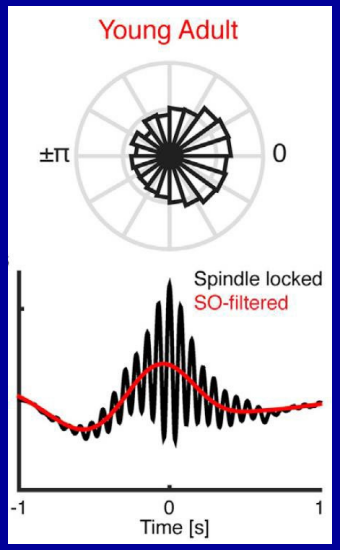
Spindle-SO coupling

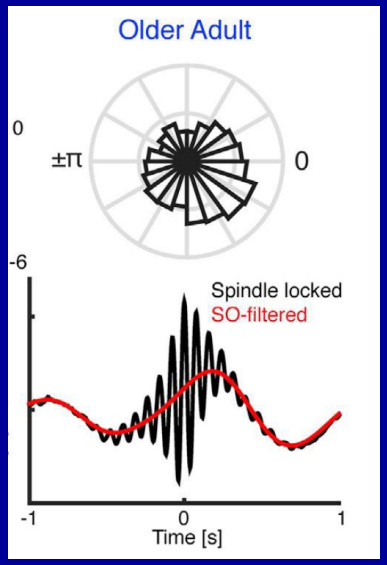


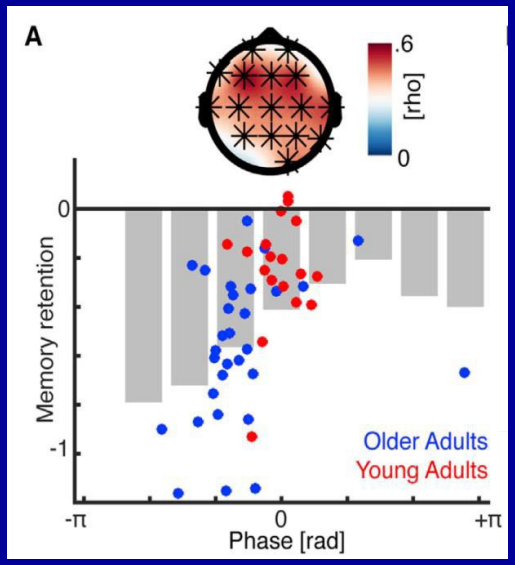
1) Mean Phase Angle

2) Resultant Vector Length

Spindle-SO coupling changes with aging and predicts memory retention







Helfrich, et al, Neuron 2018

Summary

OSA negatively impacts the prospective formation of memories (declarative, spatial navigational)

Mechanism may be related to be reduction/impairment in cortical slow oscillations

Presence of **OSA** is associated with an earlier age of onset of mild cognitive impairment (**MCI**) – impairment of prospective memory and established memories

Greater **OSA** severity is associated with longitudinal decreases in **CSF** Aβ42 and increases in cortical amyloid deposits, thought to increase risk for **MCI** and **AD**

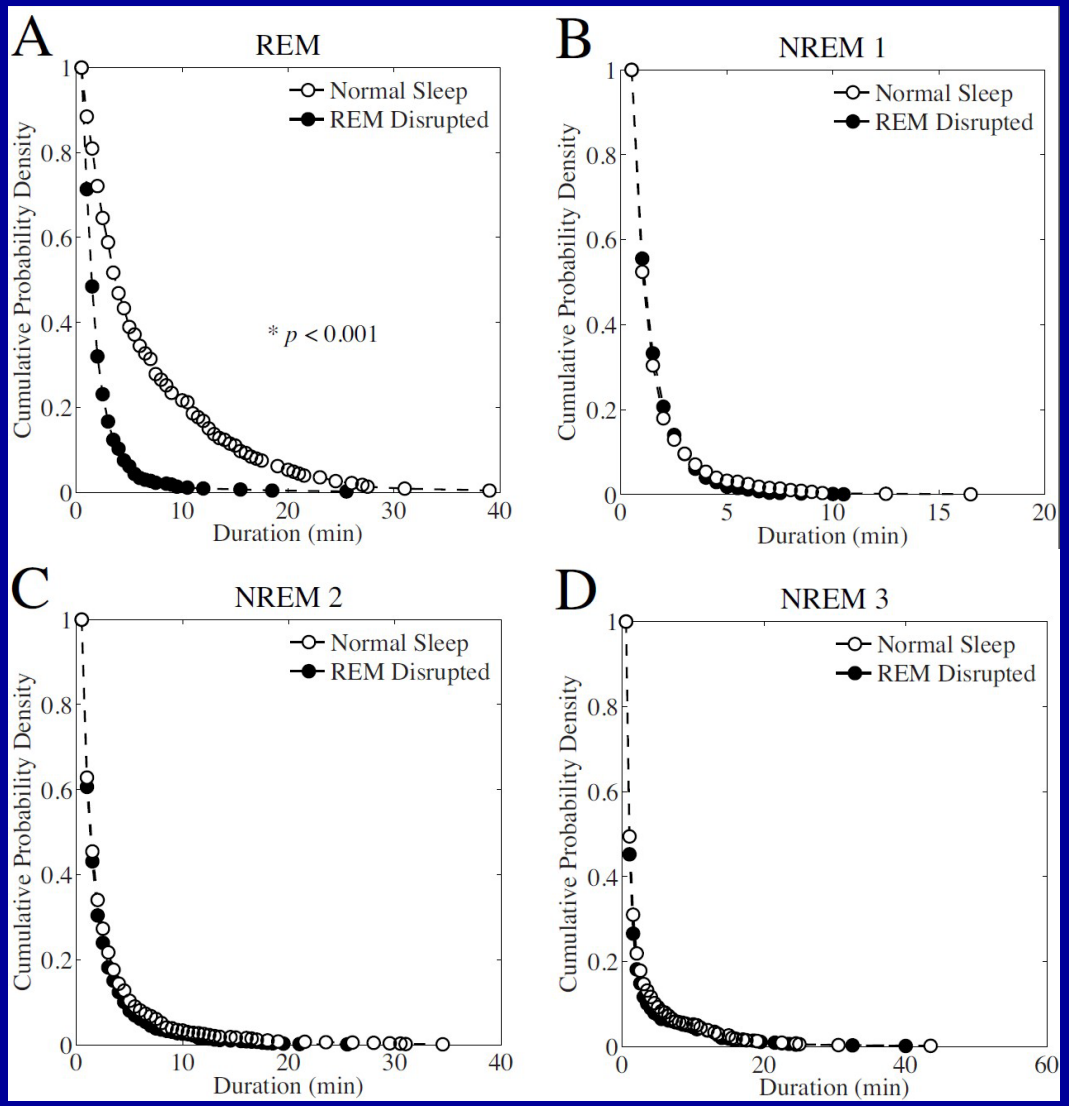
Acute induction of **OSA** via **PAP** withdrawal alters the overnight change in Aβ40 and NfL measured in plasma

Chronic subjective **PAP** use is associated with a later age of onset of MCI (similar to individuals without **OSA**)

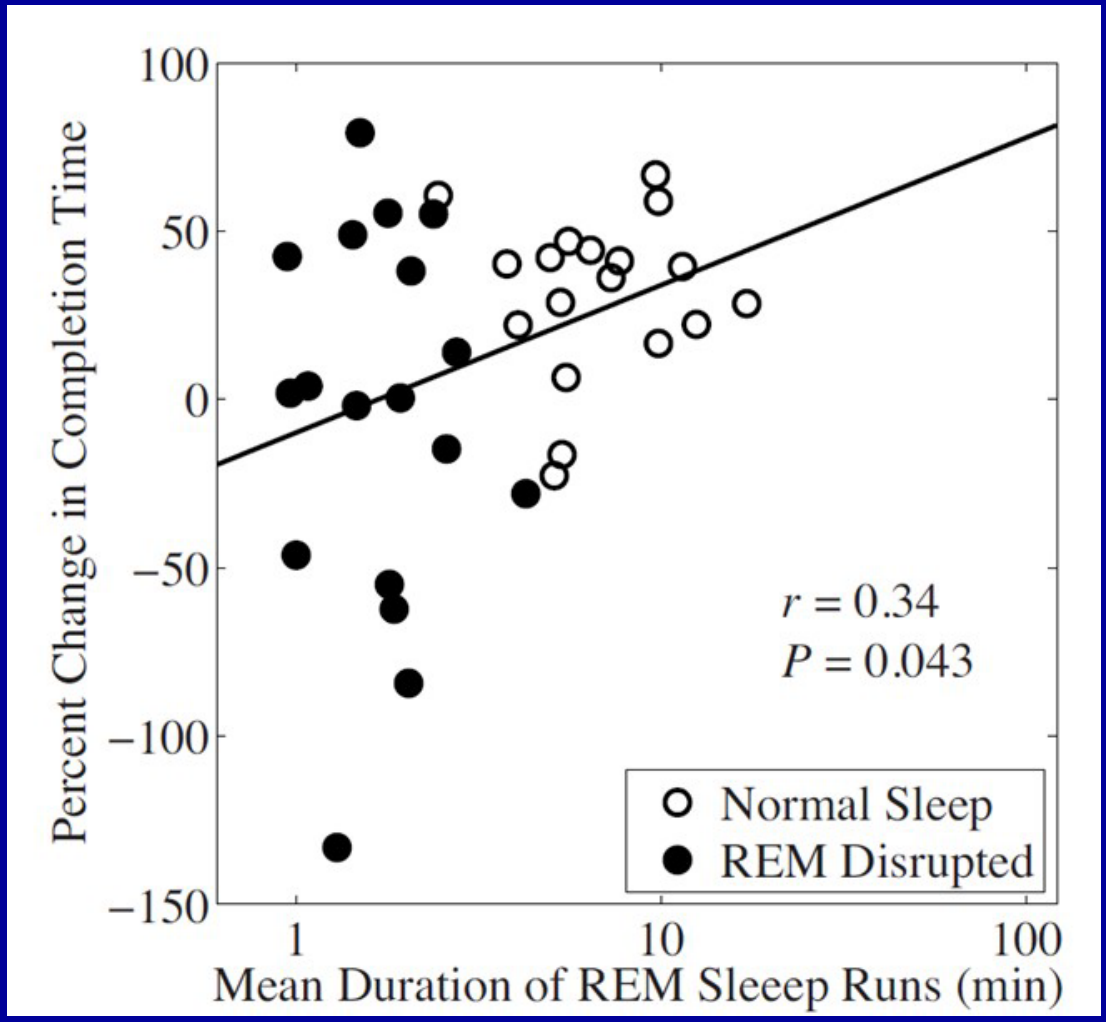
Chronic objective **PAP** use can restore prospective declarative memory formation

Magnitude of change in AHI from chronic **PAP** use correlates with improvements in **CSF** measures of amyloid and tau

OSA in REM increases fragmentation of REM sleep, but not non-REM sleep



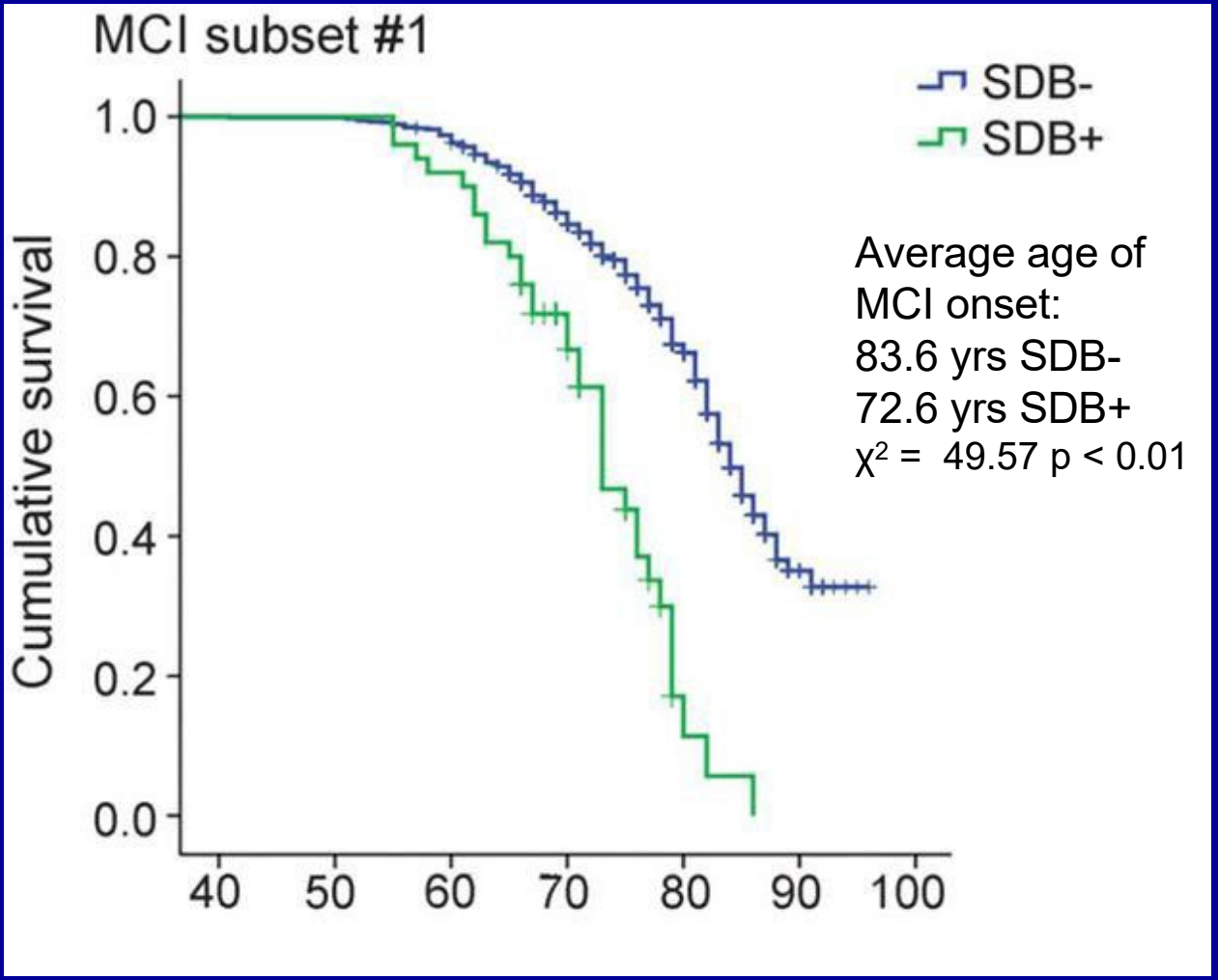
Mean REM run duration correlates with overnight completion time improvement



Mining the Alzheimers Disease Neuroimaging Initiative (ADNI) Cohort

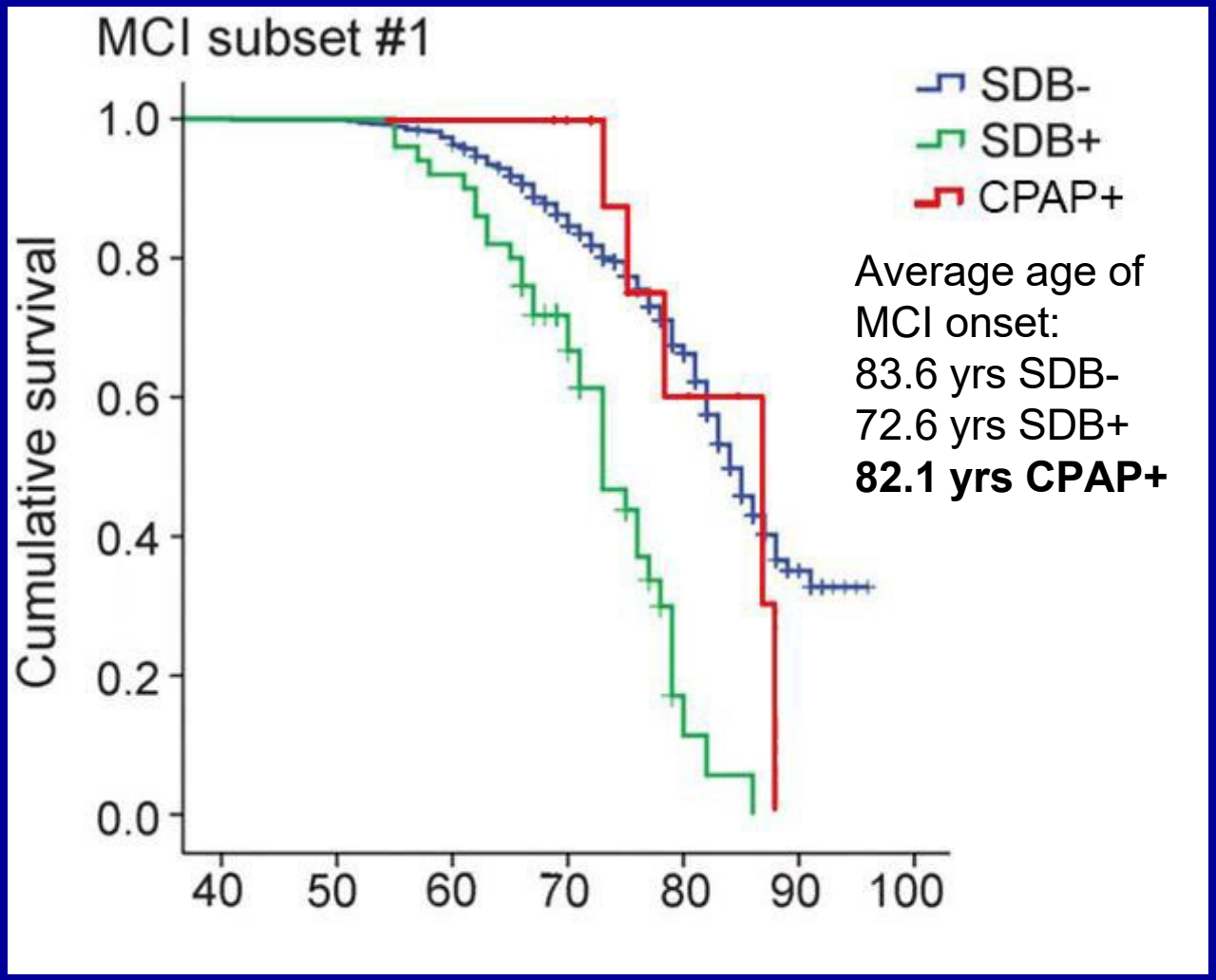
- Active cohort, **2470** subjects at time of analysis, average follow-up **2-3** years, data publicly available
- Subset of **767** subjects for sleep analysis
  - –Subjects completed sleep questionnaires
  - –Sleep apnea (***yes / no***?)
  - –If yes, do you use **CPAP** (***yes / no***?)
  - –Age of mild cognitive impairment (**MCI**) diagnosis could be determined

The age of onset of mild cognitive impairment (MCI) is reduced in older subjects with sleep disordered breathing (SDB)…



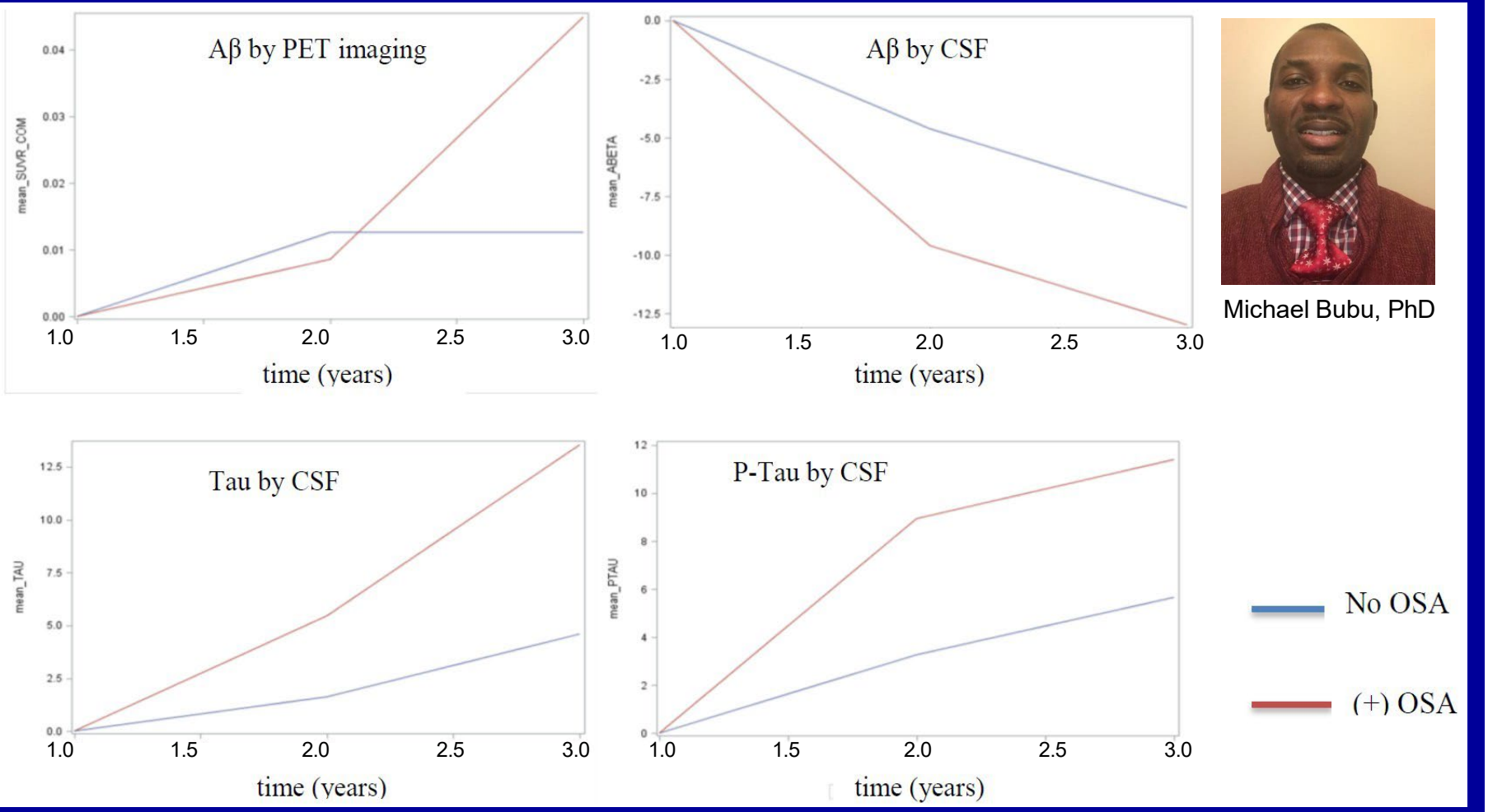
Osorio, et al, *Neurology* 2015

But returns to baseline in subjects with SDB treated with CPAP



Osorio, et al, *Neurology* 2015

ADNI: Self-reported OSA presence is associated with increased longitudinal burden of both Aβ and tau



Michael Bubu, PhD

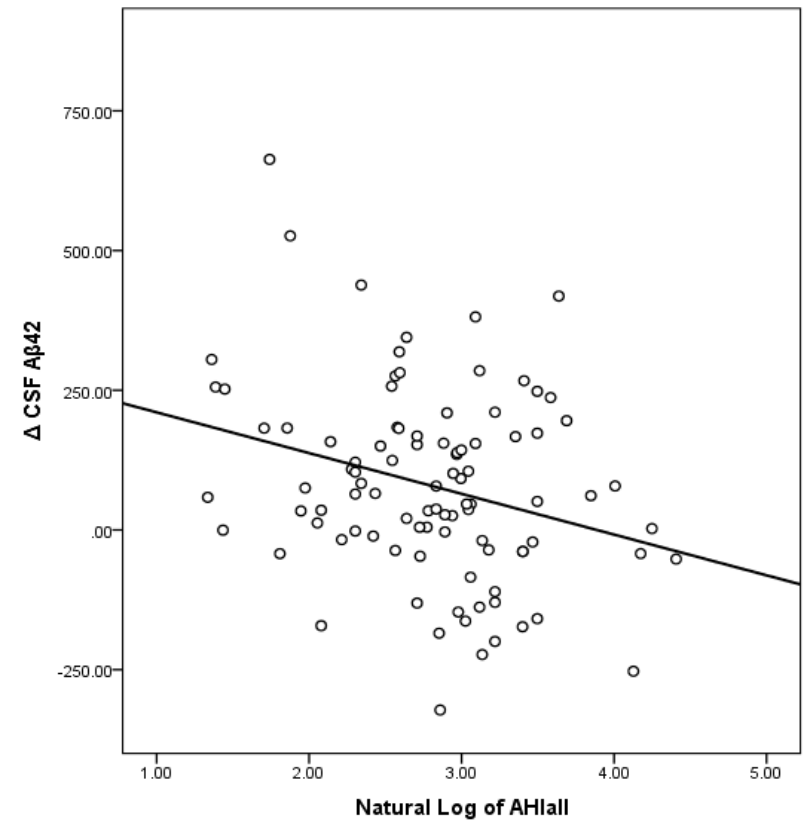
Bubu, et al, *Sleep* 2019

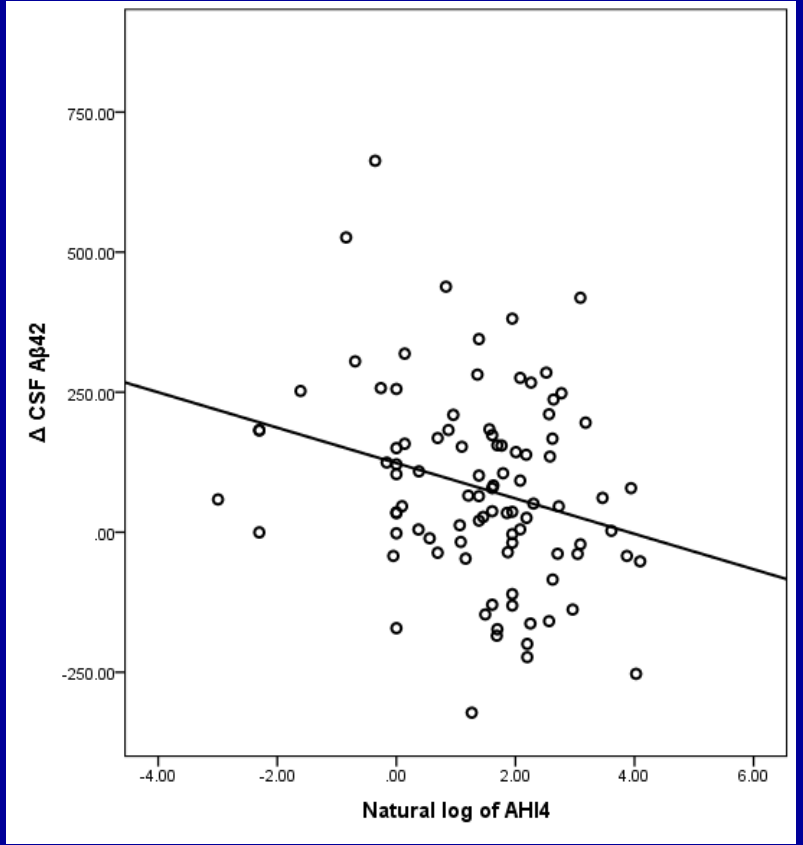
Longitudinal Change in CSF and Imaging AD Biomarkers

- Of the **208** cognitively normal elderly:
  - Subset of 109 subjects completed 2nd **LP 2.42** years (**± 0.88 years**)
  - Subset of **34** subjects completed **2**nd amyloid **PET** scan

2.50 years (± 0.39 years)

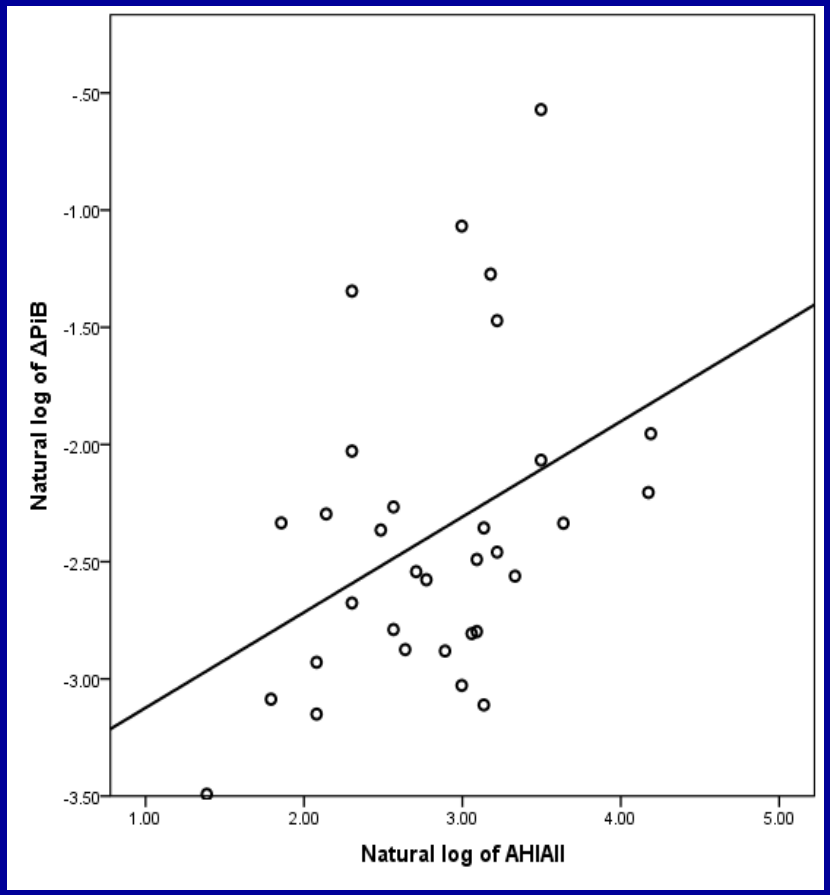
Higher **OSA** severity at baseline is associated with a longitudinal decrease in soluble **CSF** Aβ42

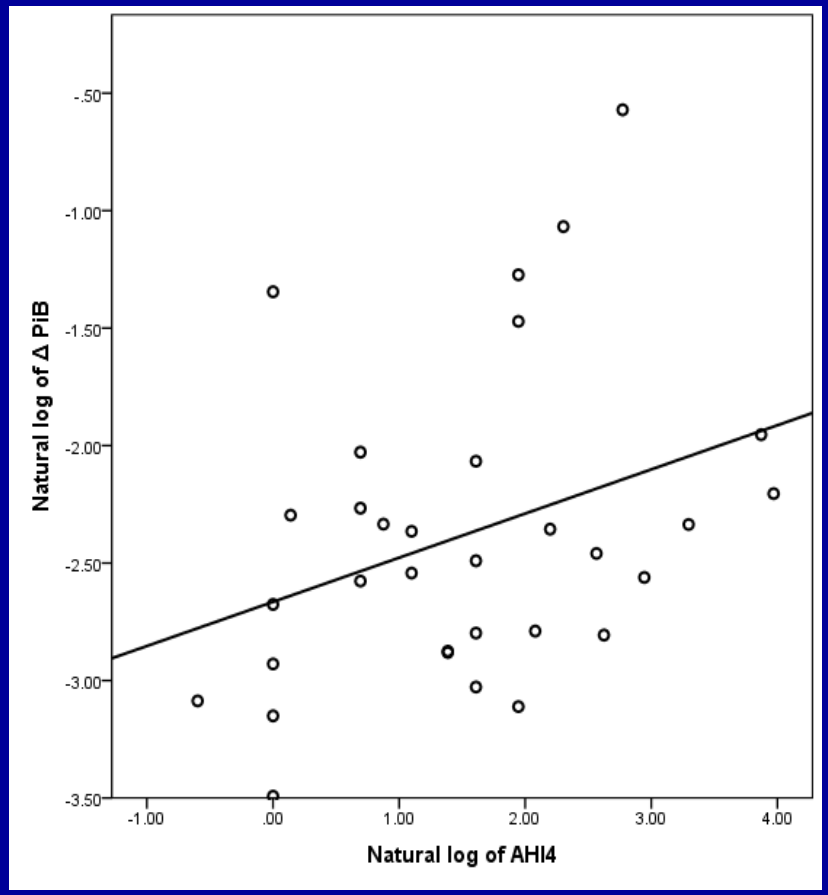




Sharma*, Varga*, et al, Am. Journal Resp. Crit. Care Med. 2018

Higher **OSA** severity at baseline is associated with a longitudinal increase in cortical amyloid deposits by **PET** imaging (**PiB**)





Sharma*, Varga*, et al, *Am. Journal Resp. Crit. Care Med*. 2018 *equal contributions

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PTSD and Sleep Among World Trade Center Responders

Camilo Ruggero, Ph.D.

Brett Messman, MS

University of North Texas, Department of Psychology

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PTSD and Sleep Among World Trade Center Responders

Camilo Ruggero, Ph.D.

Brett Messman, MS

University of North Texas, Department of Psychology

Problem:

Disrupted sleep implicated across psychopathology and **PTSD**

Little work understanding long-term pattern among **WTC** responders

Study:

452 responders **(8% with PTSD)**

Annual assessment across **4 waves**

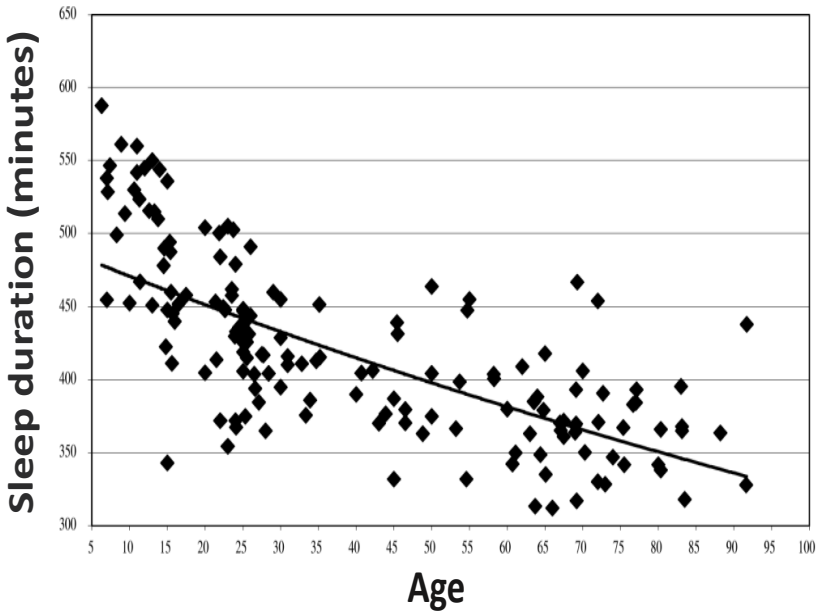
Survey **+ 2-week** sleep diary

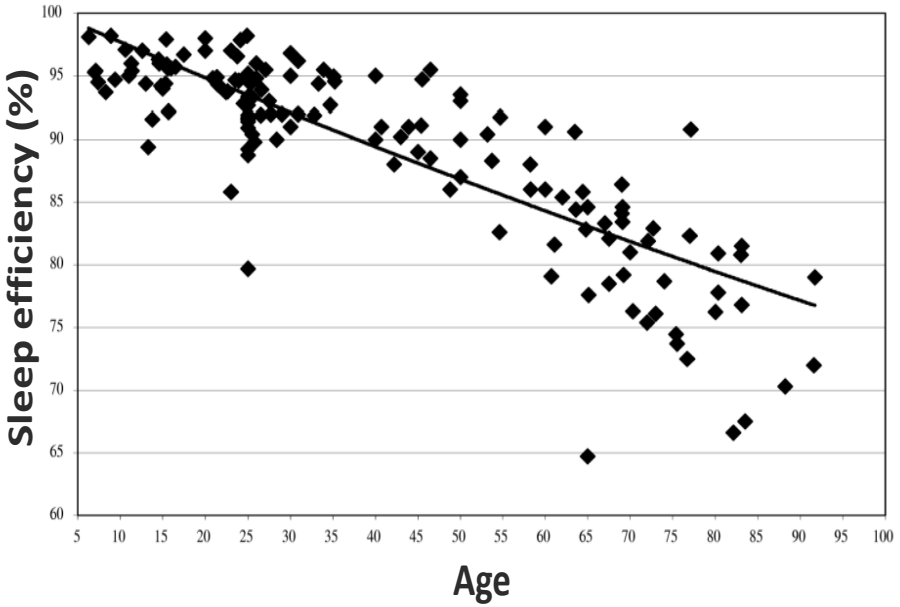
Results from first **3 waves**

Random intercept cross-lagged panel model ***(RI-CLPM)*** *(Stable, trait-like patterns versus change across time from person's own average)*

(Freeman et al., 2020; Colvonen et al., 2018; Germain, 2013)

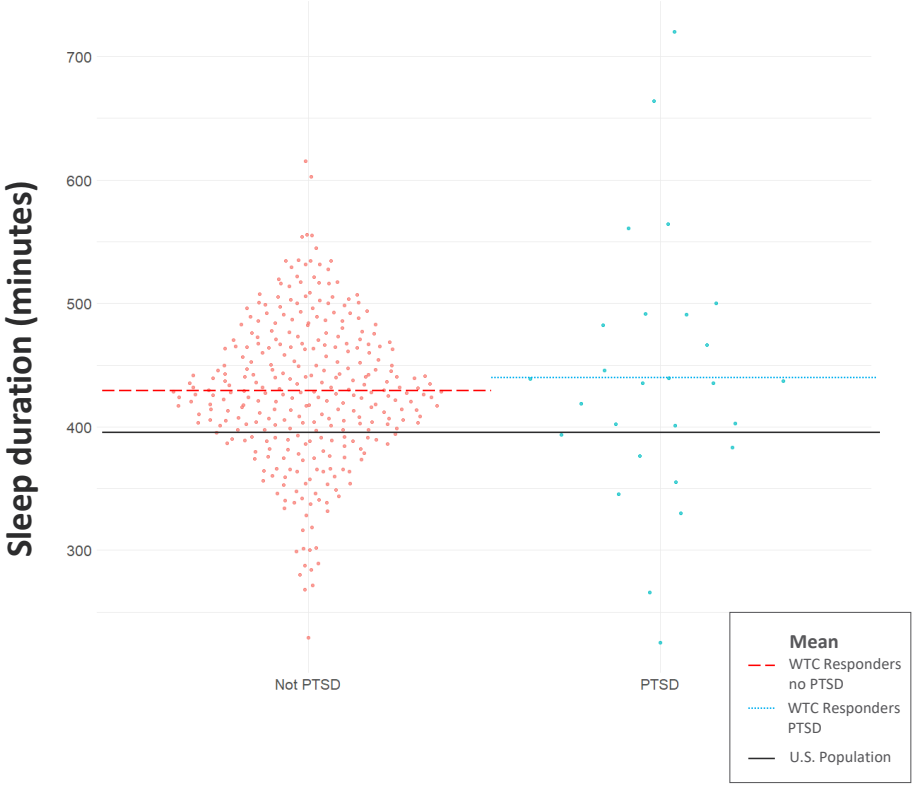
Sleep in US population

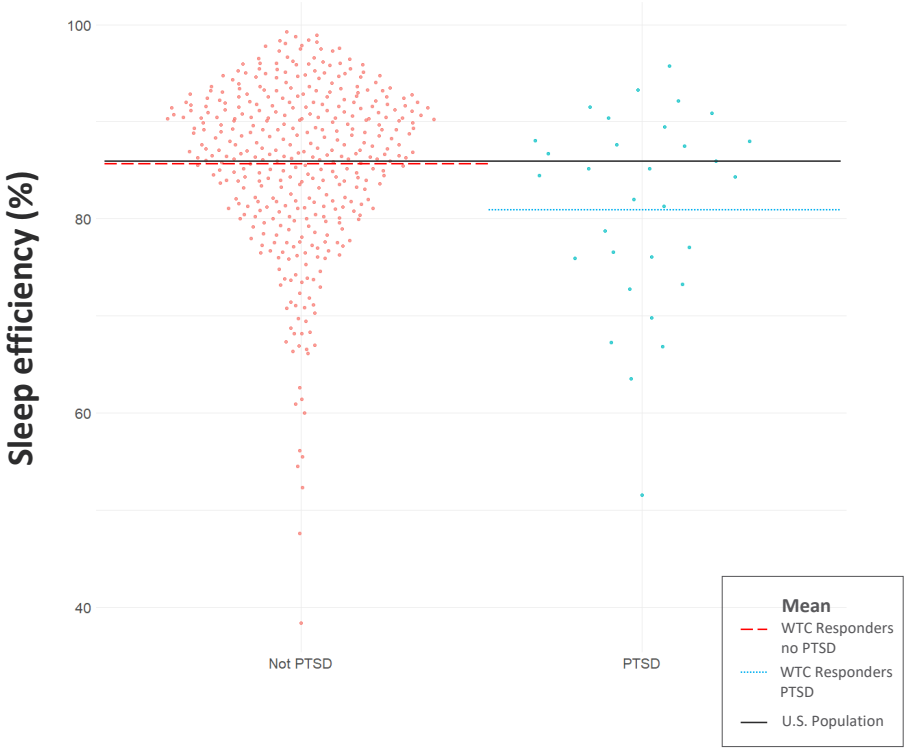




(Ohayon, et al., 2004)

Sleep in WTC responders (with and without PTSD)





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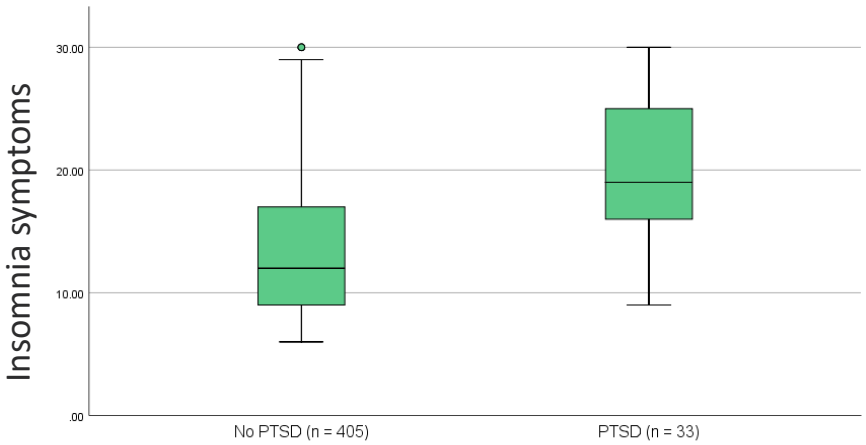
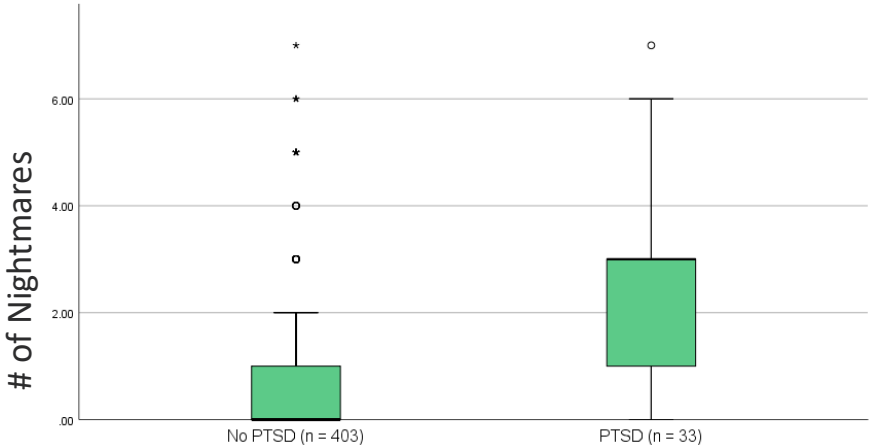
(Slavish et al., 2023)

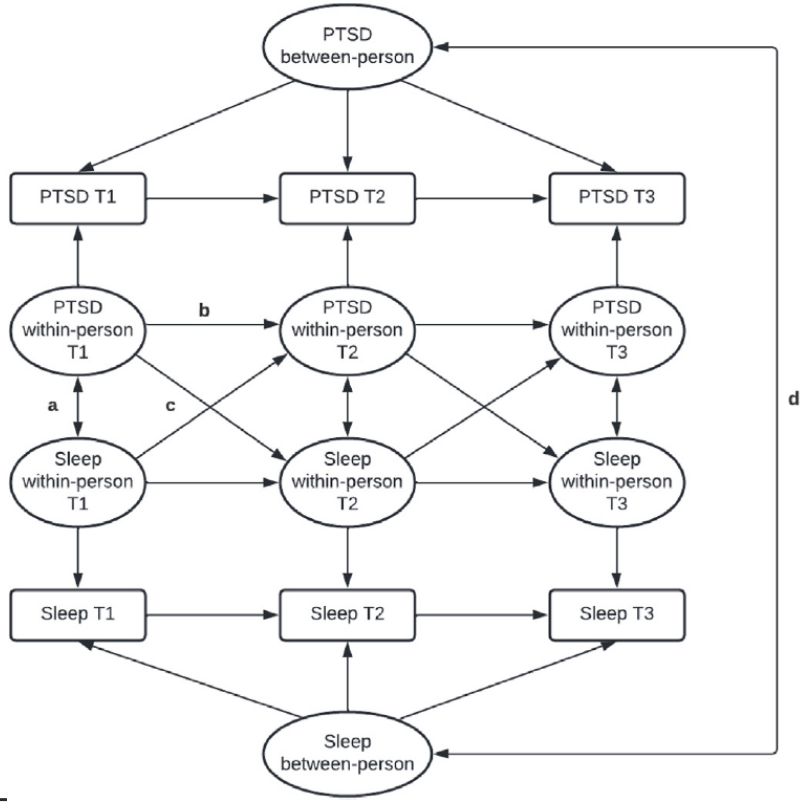
Probable Insomnia (with and without PTSD)

About 5% (with PTSD: >30%)





Sleep disturbances, PTSD across 2 years (N = 452)



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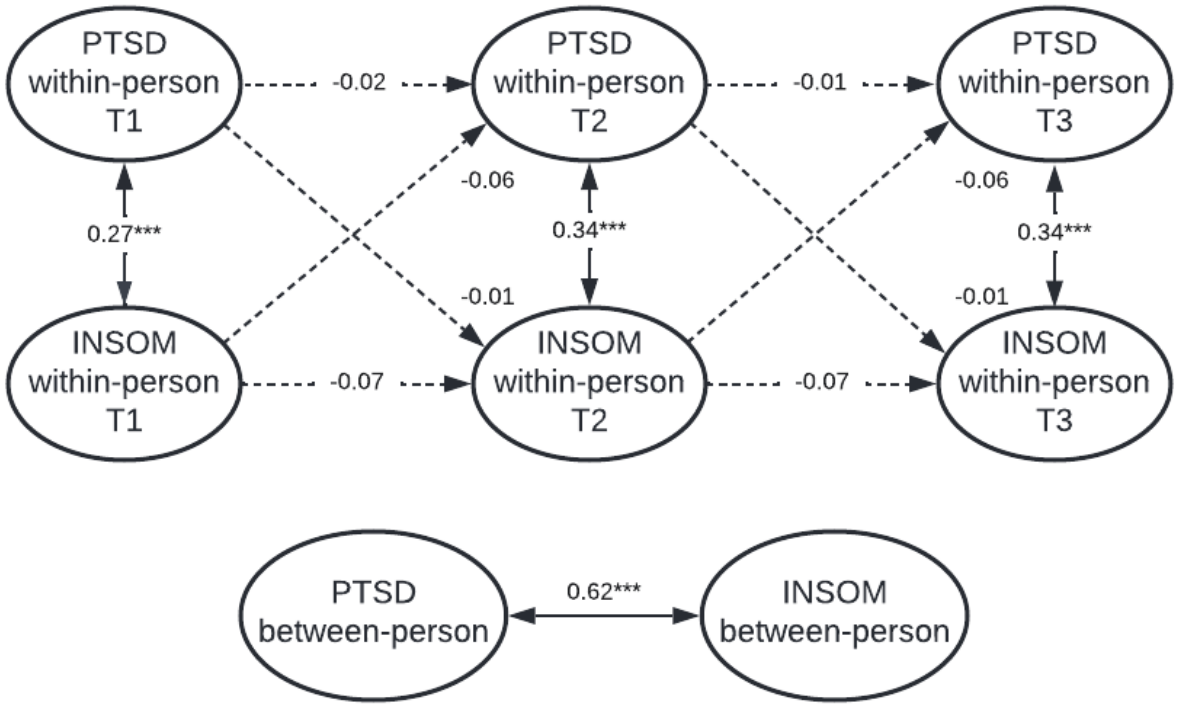
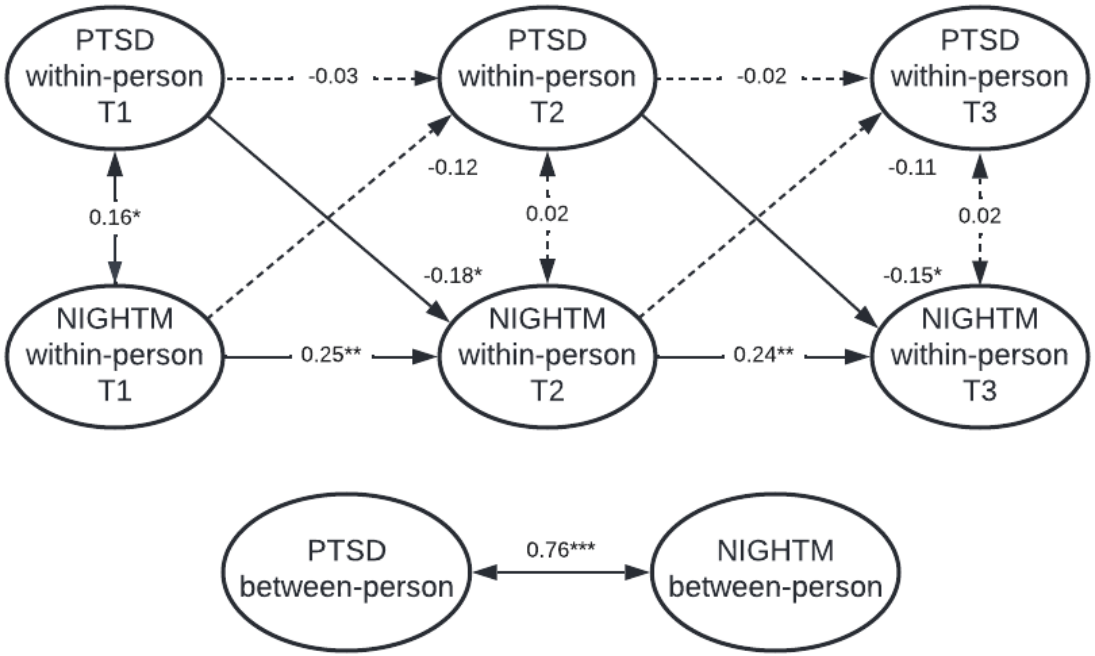
(Slavish et al., 2023)

PTSD and insomnia



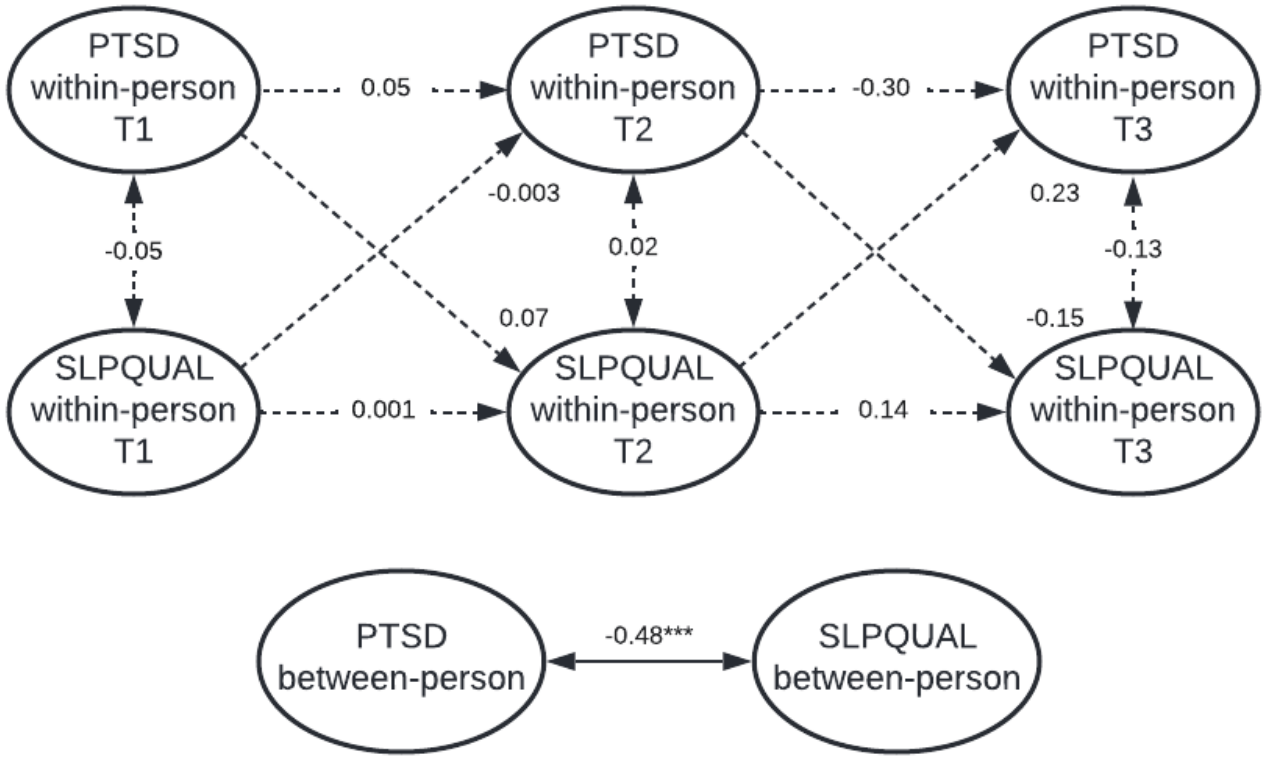
(Slavish et al., 2023)

PTSD and nightmares



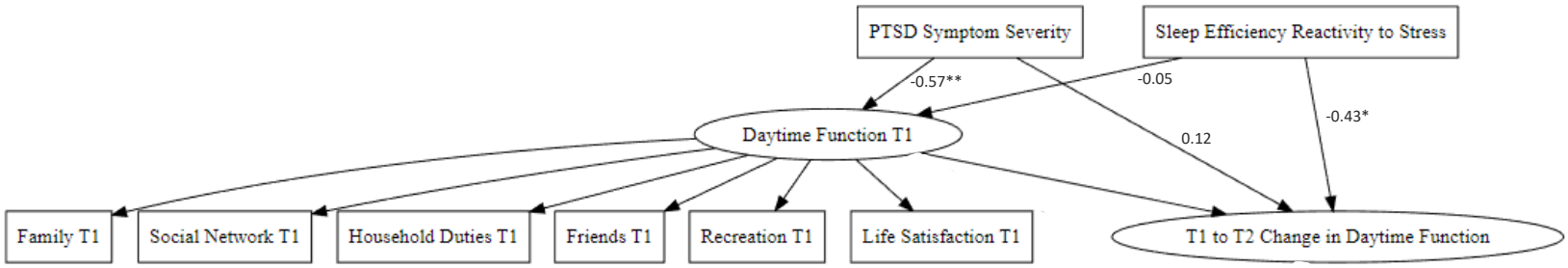
(Slavish et al., 2023)

PTSD and sleep quality



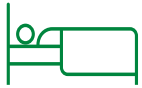
(Slavish et al., 2023)

PTSD and sleep-stress reactivity



(Messman et al., 2023)

Summary



Between-person **PTSD** and disrupted sleep:

Very comorbid: ↑ **PTSD** = ↑ disrupted sleep, nightmares

Highly stable pattern across waves ***(i.e., difficult to disrupt)***

Within-person **PTSD** and disrupted **sleep** :

Within-person ↑ **disrupted sleep, nightmares** = ↑ **PTSD** concurrently

Within person ↑ PTSD = ↓ nightmares

Sleep *reactivity* to daytime stress **= ↓ functioning across time**

Three key finding takeaways

1. Sleep disturbances and **PTSD** symptoms are highly **stable and persist** across time without intervention. Earlier intervention is key to preventing **long-term impact.**

2. **More sleep disturbances** are associated with more severe **PTSD**. Those with this **comorbidity** are in greatest need of care.

3. Strong **sleep reactivity** and fluctuations are a marker for poorer social functioning. Helping address reactivity may promote resilience and prevent onset of other problems.

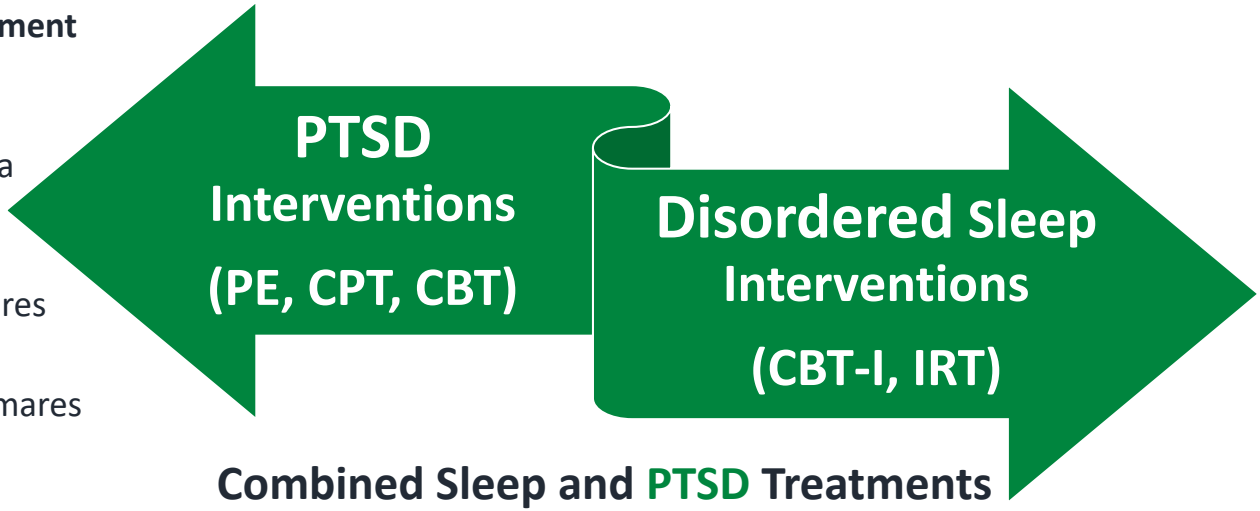
Impact and Implications

Effects of PTSD treatment on disordered sleep

Small-to-moderate reduction in insomnia symptoms

Moderate-to-large reduction in nightmares

Residual insomnia symptoms and nightmares exist post-treatment



Effects of disordered sleep treatment on PTSD

Weak-moderate reduction in PTSD symptoms when treating co-occurring insomnia

Mixed findings in nightmare-specific treatment

Untreated OSA can **interfere** with **PTSD** treatment

Combined Sleep and PTSD Treatments

Treating sleep prior to treating **PTSD** improves overall treatment outcomes

Sleep treatment has less stigma

(Colvonen et al., 2018)

Future Research

Additional research into treatment sequencing (sleep versus **PTSD**) versus integrative approaches

Advancing **ecological momentary interventions (EMI)** and targeting reactivity

Deploying sleep **treatment at-scale**: efficacy of virtual/mobile interventions

Better **identification** of at-risk status for early intervention

Biopsychosocial **mechanisms** linking sleep/**PTSD** and **long-term health impacts**

Acknowledgements

- Danica C. Slavish, Department of Psychology, University of North Texas
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- Benjamin J. Luft, Department of Medicine, Stony Brook University
- Roman Kotov, Department of Psychiatry, Stony Brook University

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Stony Brook University

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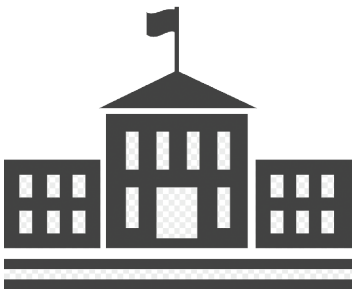
World Trade Center Health Registry Opioid Studies

Robert M Brackbill, PhD, MPH
Research Director

Wednesday, June 28th

NIOSH PI Meeting 2023



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World Trade Center Health Registry Opioid Studies

Robert M Brackbill, PhD, MPH

Research Director

Wednesday, June 28th

NIOSH PI Meeting 2023

Outline

1. Background
2. WTCHR Opioid use questions
3. Two papers on Opioid use
4. AI and Opioid Use

World Trade Center Health Registry Opioid Studies

WTCHR Wave 4 Opioid questions

For the next few questions, please think about prescription pain relievers such as Oxycodone (e.g., Percocet, Endocet, OxyContin) or Hydrocodone (e.g., Vicodin, Norco, Lortab). Do not include "over the counter" medications.

During the last 12 months, has a doctor or other health professional given you a prescription for a pain reliever?

☐ Yes ☐ No

When was the most recent time you took the pain reliever that you were prescribed?

- a. Within the last 30 days
- b. More than 30 days ago
- c. Never – I did not take the pain reliever

Have you ever – even once – taken more of the pain reliever than you were prescribed? This includes taking a higher dosage or taking it more often than directed.

- a. Yes, within the last 30 days
- b. Yes, more than 30 days ago but within the last 12 months
- c. No

During the last 12 months, have you ever – even once – taken a prescription pain reliever that was not prescribed to you?

- a. Yes, within the last 30 days
- b. Yes, more than 30 days ago but within the last 12 months ?

Have you ever stayed overnight or longer at a hospital, rehabilitation facility, or mental health center so you could receive treatment or counseling for alcohol or drug use?

- a. Yes, before 9/11
- b. Yes, after 9/11
- c. Yes, both before and after 9/11 ?
- d. No

World Trade Center Health Registry Opioid Studies

WORLD TRADE CENTER HEALTH REGISTRY

NYC Health

WTCHR Wave 5 Opioid Use Questions

For the next few questions, please think about prescription pain relievers such as oxycodone (e.g., Percocet, Endocet, OxyContin) or hydrocodone (e.g., Vicodin, Norco, Lortab). Do not include "over the counter" medications.

a. During the last 12 months, has a doctor or other health professional given you a prescription for a pain reliever?

- ☐ Yes
- ☐ No

b. During the last 12 months, have you ever – even once – taken the pain reliever that you were prescribed?

- ☐ Yes
- ☐ No

c. During the last 12 months, have you ever – even once – taken more of the pain reliever than you were prescribed? This includes taking a higher dosage or taking it more often than directed.

- ☐ Yes
- ☐ No

d. During the last 12 months, have you ever – even once – taken a prescription pain reliever that was not prescribed to you?

- ☐ Yes
- ☐ No

e. During the last 12 months, on average, how often have you taken a prescription pain reliever that was not prescribed to you?

- ○ More than once a week
- ○ Once a week
- ○ Two or three times a month
- ○ Once a month Less than once a month

Wave 5 Opioid questions (cont'd)

Now think about the last time you used a prescription pain reliever in any way a doctor did not direct you to use. What were the reasons you used the prescription pain reliever the last time?
Select all that apply.

- ☐ To relieve physical pain
- ☐ To relax or relieve tension
- ☐ To experiment or to see what it's like To feel good or get high
- ☐ To help with my sleep To help with my feelings or emotions
- ☐ To increase or decrease the effect(s) of some other drug Because I am "hooked" I I have to have it I used it for some other reason

Have you ever stayed overnight or longer at a hospital, rehabilitation facility, or mental health center so you could receive treatment or counseling for alcohol or drug use?

- ☐ Yes
- ☐ No
- ☐ When did your stay(s) occur?
- ☐ Before 9/11
- ☐ After 9/11 Both before and after 9/11 100.

WORLD TRADE CENTER HEALTH REGISTRY

Registry publications using the Opioid data

- *Takemoto E, Brackbill R, Martins S, Farfel M, Jacobson M.* Post-traumatic stress disorder and risk of prescription opioid use, over-use, and misuse among World Trade Center Health Registry enrollees, **2015-2016**. Drug and Alcohol Dependence, **2020**

- *Garry S, Locke S, Pollari C, Li J, Takemoto E*. Post-traumatic stress disorder and risk of first-time and recurrent opioid-related hospitalizations among World Trade Center Registry enrollees. Submitted to Psychiatric Research **(2023)**

- *Dhanya A, Yung J, Cone JE, Li J.* Association of rheumatoid arthritis with Opioid pain medication overuse among persons exposed to the **9/11** World Trade Center disaster. International Journal of Environmental Research and Public Health, **2023**

WORLD TRADE CENTER HEALTH REGISTRY

Post-traumatic stress disorder and risk of opioid use

- Investigate the association between **PTSD** and use and misuse of opioids
  - Is 9/11-related PTSD associated with recent, overuse, or misuse
  - Are certain symptom clusters associated with opioid use
- Recent use was ***49%*** higher among persons with past **PTSD**, ***83%*** higher among persons with current **PTSD**
- Persons with current **PTSD** were ***178%*** higher risk to overuse compared to never and 204% higher to misuse prescribed opioids
- Arousal symptom cluster had the highest risk for each outcome compared to avoidance and re-experiencing cluster

WORLD TRADE CENTER HEALTH REGISTRY

PTSD and opioid hospitalizations

- Extend the previous study on opioid to objectively define an outcome for assessing a burden through hospitalization
- NYS Statewide Planning and Research Cooperative System ***(SPARCS)*** for patient level opioid hospitalization among **WTCHR** enrollees *(209 Opioid related hospitalizations; 379 total hospitalizations)*
- An individual with **PTSD** had four times the risk of opioid-related hospitalization and recurrent hospitalization

Association of Rheumatoid Arthritis (RA) with Opioid Pain Medication Overuse among Persons Exposed to the 9/11 World Trade Center (WTC) Disaster

IJERPH 2023, *20*(5), 4166
(Special Issue: 9/11 Disaster and Other Man-Made Trauma Events and Their Health Effects)

Ananya Sarker Dhanya, MBBS, MPH
WTCHR, NYC DOH&MH

Wednesday, **June 28th**
NIOSH PI Meeting **2023**

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WTCHR, NYC DOH&MH

Wednesday, **June 28th**

NIOSH PI Meeting **2023**

Background & Rationale

- Various health conditions due to exposure to harmful environmental contaminants and toxic substances in the **WTC** disaster:
  - Acute traumatic injuries, airway & digestive Disorders, cancers, mental Health conditions, musculoskeletal disorders
- Systemic autoimmune diseases ***(SADs)*** is a potentially emerging WTC-related condition, comprised of several diseases ***(i.e., RA, SLE, etc.)***
- **RA** is the most common **SAD** associated with **WTC** disaster exposure ***(Miller-Archie et al, 2020),*** while **PTSD** is the most common mental health problem
- Opioids are the common alternative/supplemental treatment modalities for joint pain ***(40% of all RA patients, Day et al, 2019)***, one of the main complaints of ***SADs/RA***.
- Long-term opioid use results in dependency causing Opioid overuse, which is the initial phase of Opioid overuse disorder ***(OUD)***

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NIOSH PI MEETING 2023

NYC Health

Study Question

- Is there any association of **post-9/11** Rheumatoid Arthritis ***(RA)*** diagnosis with opioid pain medication overuse among **WTCHR** enrollees?

Methods: Study Sample

➢ Inclusion:

- Enrollees who participated in either wave **4** or wave **5** or both.
- **Aged 18** or older on **9/11**
- **Being prescribed** any pain-relieving opioid medication *(e.g., oxycodone or hydrocodone)* in the preceding **12** consecutive months, which were reported in **W4/W5**

➢ Exclusion:

- **Self**-reported **RA** in wave **3**, not confirmed by medical records or treating physicians
- Self-reported **RA** for the first time in either wave **4** or **5** without prior physician's validation
- **RA** diagnosis year: prior to **9/11** or unknown
- Missing value in any of the covariates

- Total analytic sample (**N=10,196**):
  - Clinically confirmed **RA** (**N=46**)
  - **Non-RA** group (**N=10,150**)

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Methods: RA Status (exposure of interest)

- **RA cases:**
  - Used data from the Autoimmune disease in-depth survey conducted in 2013-2014, after wave 3 survey
  - Met at least one of the following three criteria:
    1. The American College of Rheumatology ***(ACR)*** score-based algorithm with a score of **6/10** based on the categories of joint involvement, serology, acute-phase reactants, and the duration of symptoms
    2. received a prescription for medication consistent with an autoimmune disease
    3. received a **RA** diagnosis by a board-certified rheumatologist
  - Positive responses were reviewed independently by Registry research staffs ***(SM-A, JEC (medical director))***
  - Unclear diagnoses were reviewed independently by two board-certified rheumatologists
- **Non-RA:** Enrollees who never reported having a diagnosis of RA in any of the follow-up surveys

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Methods (cont'd)

➢Outcome – Opioid pain medication overuse:

- Overuse: defined if they reported ***"Ever taken that prescribed pain medication at a higher dosage or more often than directed in the last 12 months***"

➢Covariates:

- From the latest survey response ***(either W4 or W5)***
  - Sociodemographic ***(Age, sex, race/ethnicity, marital status, educational attainment, smoking history)***
  - Active **9/11** related **PTSD** symptoms
    - Assessed from enrollees' latest response ***(wave 5 or wave 4),*** using DSM-V criteria ***(a score of 33 or higher out of a total of 80).***
    - In case of wave **4** response ***(responses originally taken in DSM-IV criteria),*** adaptation method was used to correspond DSM-IV response to DSM-V

➢Data analysis:

- Multivariable log-binomial regression

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NYC Health

Results

Table 1. Characteristics by **RA** status

	Enrollees with post-9/11 RA	Enrollees without post-9/11 RA
	N (%)	N (%)
Total	46	10150
Age at 9/11, years		
18-39	14 (30.4)	3941 (38.8)
40-49	22 (47.8)	3595 (35.4)
50-79	10 (21.7)	2614 (25.8)
Gender		
Male	14 (30.4)	6324 (62.3)
Female	32 (69.6)	3826 (37.7)
Race/Ethnicity		
Non- Hispanic White	27 (58.7)	7433 (73.2)
Educational attainment		
>High school graduate	35 (76.1)	8569 (84.4)
Active PTSD symptoms		
Yes	13 (28.3)	1504 (14.8)
No	33 (71.7)	8646 (85.2)
Opioid pain medication overuse		
Yes	13(28.3)	1128 (11.1)
No	33 (71.7)	9022 (88.9)

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Results - Regression Analysis

Association of RA with opioid pain medication overuse

	Unadjusted Risk Ratio	95% CI		Adjusted Risk Ratio*	95% CI
Post-9/11 RA					
Yes	2.54	1.60,4.04		2.13	1.44,3.17
No	**referent**			**referent**	
Active PTSD symptoms					
Yes	2.67	2.39,2.99		2.27	2.03,2.56
No	referent			referent	

**** Adjusted for age, sex, race/ethnicity, marital status, educational attainment, smoking history, and active PTSD symptoms***

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Discussion

- **Main findings**: RA was independently associated with opioid pain medication overuse, after adjusting for covariates
- **RA** patients had at least **4** years of the illness, as they were diagnosed before wave **3**
- Long-term opioid usage could increase pain perception due to sensitization of the pain modulation system in the central nervous system
- **PTSD** may influence the development of **RA** or worsening of the disease progression by disrupting the hypothalamic–pituitary–adrenal ***(HPA)*** axis
- A higher prevalence of **PTSD** in our population may lead to a higher rate of opioid medication use for pain management among those with **RA**

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Limitations

- **Attrition bias** due to 63% of enrollees with self-reported RA did not participate in the in-depth survey or not provided consent for the providers' survey
- **Underestimation of study findings** due to no clinical validation was done among non-RA comparison group
- **Low statistical power** due to small number of RA enrollees
- **Information bias** due to no data on compliance of prescribed pain medication use and reasons for overuse
- **Other confounders** due to lack of data:
  - family history of **RA**
  - personal history of substance misuse, including alcohol, tobacco, and marijuana

Conclusion

- Given the serious consequences of opioids overuse and the vulnerability among RA patients with prior exposure to traumatic events, i.e., WTC-disaster:
  - Closely monitoring the risk of prescribed opioids overuse
  - Clinicians: **PTSD** screening during routine health exam
  - Periodic evaluation and more research on long-term use and management of prescribed opioids
  - Interventions targeting opioid-related harm reduction, such as proper guidelines for prescribing opioids for the providers, education program at patient and public level, prescription Monitoring Program ***(PMP)***

Research Gaps

- **Types of Opioids**
  - Naturally derived (morphine), Semisynthetic (Oxycodone, hydrocodone), Fully synthetic (Fentanyl)
- **Uses of these types are associated with conditions covered by the WTC Health Program**
- **Morphine, fentanyl (mostly in hospital setting, infrequent self intake prescription)-** Severe pain (post-operative, advanced stage cancer, serious injury, bone fracture, etc.)
- **Oxycodone, hydrocodone *(self intake prescription drug)-*** moderate to severe pain (back pain, osteoarthritis, rheumatoid arthritis, some types of cancer, etc.)

➢Are various prescription opioid drugs overuse or misuse patterns (oxycodone/hydrocodone) secondary consequences of treatment for 9/11 conditions?

WORLD TRADE CENTER HEALTH REGISTRY

World Trade Center Health Registry Opioid Studies

NYC Health

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Association of Lung Function Decline with All-Cause and Cancer-Cause Mortality after World Trade Center Dust Exposure

June 2023 WTCHP Research Meeting

David Goldfarb, ***PhD, MPH***

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David Goldfarb, ***PhD***, ***MPH***

Background

- World Trade Center ***(WTC)*** exposures caused lung injury with an immediate decline in forced expiratory volume in one second (FEV_1) in Fire Department of the City of New York ***(FDNY)*** rescue/recovery workers
- For about **11%** of the cohort lung function continued to decline at greater than **64** mL/y (accelerated FEV_1 decline)
- Other population-based studies have evaluated reported increased risk of all-cause mortality among those with accelerated lung function decline
- Joint modeling of longitudinal exposures/predictors and survival outcomes has distinctive advantages over traditional approaches
  - All longitudinal measurements are considered when evaluating the survival event, such that the temporal order of exposure preceding the outcome is preserved
  - Allows for estimation of the association of baseline values and changes from baseline with survival outcomes of interest

Objective

- To evaluate the association of longitudinal lung function with all-cause and cause-specific mortality after exposure to the WTC disaster

Methods

- **Study population**
  - **WTC**-exposed Firefighter and EMS providers
  - Active-duty on **9/11** and responded or worked on the **WTC** rescue/recovery effort between the morning of the attacks and the time which the site closed **7/2002**
  - Informed written consent

Methods

- **Pulmonary Function Testing (PFT): Spirometry**
  - As part of their monitoring exams, participants had spirometry every **12** to **18** months, on average, to assess lung function
  - **FEV_1** was used for all analyses because of its reproducibility and is the most commonly used spirometry measurement in longitudinal analyses
  - Baseline **FEV_1** was defined as the first measurement after **9/11/2001**

Methods

- **Mortality data**
  - Death dates and causes of death were ascertained using data from the National Death Index ***(NDI)***
- **Study outcomes**
  - **Primary**
    - all-cause mortality
  - **Secondary**
    - cancer-cause mortality
    - cardiovascular-cause mortality
    - respiratory-cause mortality

Methods

- **Statistical Methods**
  - Joint longitudinal survival models
    - Using this this method allowed us to evaluate the impact of **FEV_1** and change in **FEV_1** independently in a longitudinal survival analysis
    - Longitudinal sub-model *(evaluating lung function)*
      - Baseline **FEV_1** and change in **FEV_1** were estimated, separately.
        - Change in **FEV_1** was evaluated as a function of years since a participants' first post-***9/11*** **PFT**
    - Survival sub-model (evaluating mortality)
      - Piecewise exponential
    - Controlled for age on **September 11, 2001,** race/ethnicity, smoking, work assignment on **September 11, 2001,** height and **WTC** arrival time

Methods

- **Statistical methods**
  - Sensitivity analyses

    1. Removing PFT measurements within 3 years of the end of the follow-up for an individual to eliminate the potential bias incurred from reverse causality (i.e., removing measurements that were possibly after the onset of impaired lung function caused by incident cancer or other serious disease)

    2. Requiring at least three PFT measurements to assess the extent to which selection bias affected results in the full models

Methods

- **Statistical methods**
  - Additional analyses: Mortality by accelerated **FEV_1** decline
    - Rates of decline were stratified by participants who had accelerated lung function decline, defined **as ≥64 ml/year**
    - Piecewise exponential survival models controlling for age on **9/11**; race/ethnicity; sex; smoking; and **WTC** arrival time were used to estimate mortality hazard ratios ***(HRs)*** of participants with accelerated decline compared with the rest of the cohort
    - Outcomes: All-cause, cancer-cause, cardiovascular disease-cause, and respiratory-cause of death

Cohort characteristics

Variable	Overall (*N* = 12,264)
Age on 9/11/2001, yr	39.7 ± 7.8
PFT examinations	11.2 ± 4.1
Post-9/11 follow-up, yr	19.1 ± 2.6
Race/ethnicity	
White	10,756 (87.7)
Black	696 (5.7)
Hispanic	812 (6.6)
Sex	
Male	11,862 (96.7)
Female	402 (3.3)
Smoking status	
Never	7,819 (63.8)
Current/former	4,445 (36.2)
WTC exposure	
9/11 A.M.	2,076 (16.9)
9/11 P.M.	6,028 (49.2)
9/11 P.M. to 9/12	2,050 (16.7)
9/13–9/24	1,793 (14.6)
9/25 to site close	275 (2.2)
Unknown	42 (0.3)

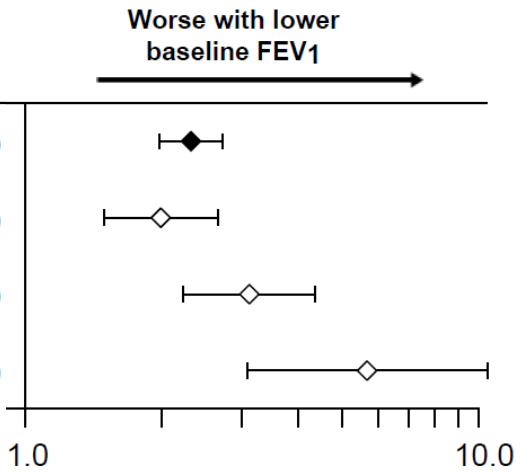
FEV_1 % predicted at baseline and final exam

	Baseline PFT	Last PFT
Strata of FEV_1 % predicted	N (%)	N (%)
0-59	79 (0.6)	309 (2.5)
60-69	204 (1.7)	502 (4.1)
70-79	1011 (8.2)	1457 (11.9)
80-89	2606 (21.3)	2823 (23.0)
90-99	3652 (29.8)	3391 (27.7)
100-109	2822 (23.0)	2422 (19.8)
110-119	1307 (10.7)	1023 (8.3)
120-140	583 (4.8)	337 (2.8)

Joint longitudinal survival models

Evaluating the association between *baseline FEV_1* and mortality

Cause of death (Category)*	HR (95% CI)
All deaths (1−28)	2.32 (1.98, 2.72)
Cancer (2−10)	1.99 (1.49, 2.66)
Heart disease (16)	3.12 (2.23, 4.35)
Respiratory disease (18)	5.67 (3.08, 10.44)

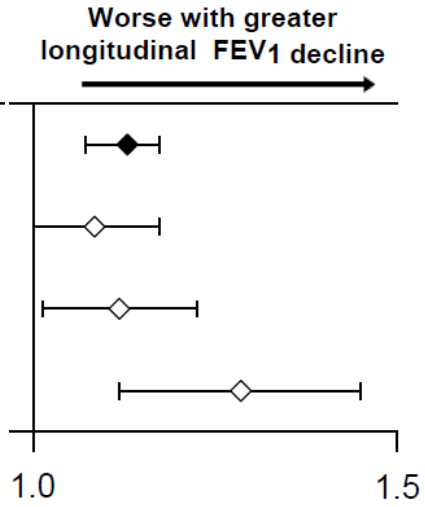


**category corresponds with NIOSH life table analysis system major categories*

Joint longitudinal survival models

Evaluating the association between *change in FEV_1* and mortality‡

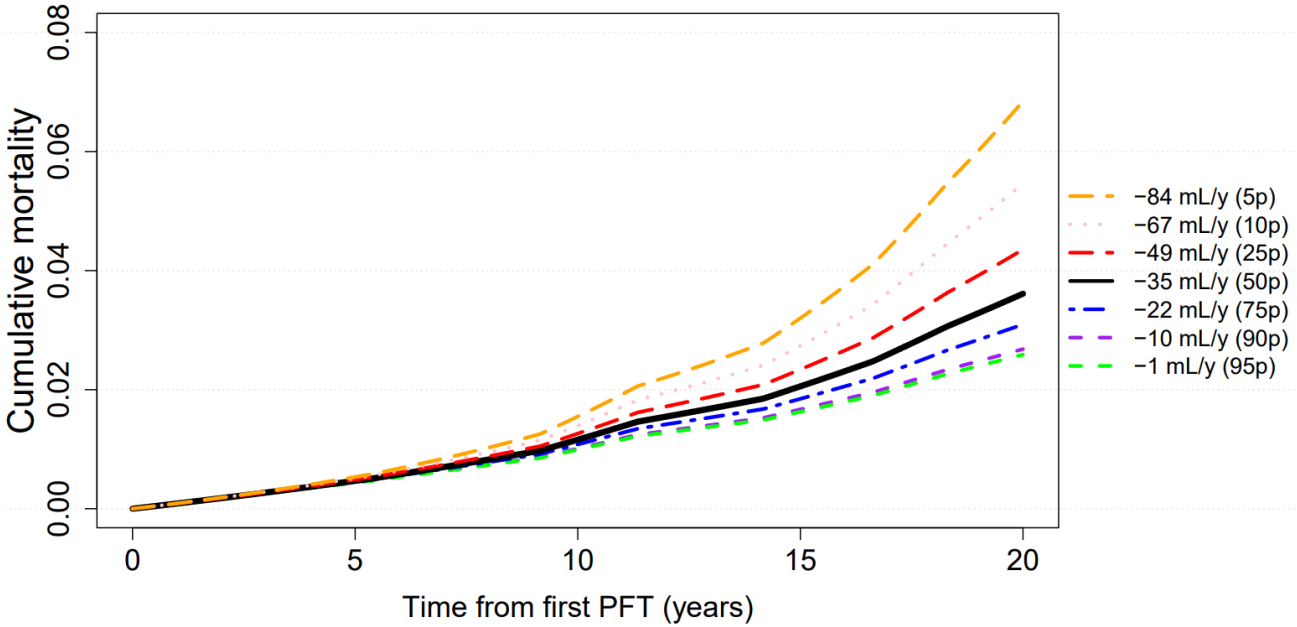
Cause of death (Category)*	HR (95% CI)
All deaths (1–28)	1.11 (1.06, 1.15)
Cancer (2–10)	1.07 (1.00, 1.15)
Heart disease (16)	1.10 (1.01, 1.20)
Respiratory disease (18)	1.26 (1.10, 1.44)



**category corresponds with NIOSH life table analysis system major categories*

‡*Change in FEV1 was analyzed as a continuous variable*

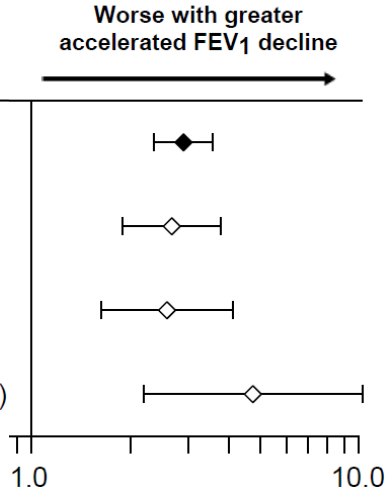
Adjusted all-cause mortality



The model controls for age on **9/11** ***(centered at 40 years),*** race (centered at White), smoking (centered at never), work assignment on **9/11** (centered at firefighters), height ***(centered at 180 cm),*** and **WTC** arrival time **(**centered at initial arrival between ***September 13, 2001***, and ***July 25, 2002*****)**

Accelerated lung function decline and mortality by cause of death

Cause of death (Category)*	FEV_1 <64 mL/y n=10,457 n (%)	Decline ≥64 mL/y n=1,244 n (%)	HR (95% CI)
All deaths (1–28)	332 (3.17)	140 (11.25)	2.91 (2.37, 3.56)
Cancer (2–10)	116 (1.11)	48 (3.86)	2.68 (1.90, 3.79)
Heart disease (16)	68 (0.65)	26 (2.09)	2.59 (1.63, 4.12)
Respiratory disease (18)	15 (0.14)	13 (1.05)	4.74 (2.20, 10.24)



**category corresponds with NIOSH life table analysis system major categories*

Strengths

- Large sample size, cohort retention, repeated measurements for 20 years of follow-up
- Excellent mortality capture
- Rigorous quality assurance, standardization, and consistency for pulmonary function testing procedures
- Joint longitudinal survival methodology accounted for dependencies between the longitudinal exposure process *(lung function)* and the time-to-event outcome process *(death)*
- Further, joint modeling also preserves temporality by allowing each repeated **FEV_1** measurement in the longitudinal model to predict mortality at each respective time interval, thereby reducing biases produced by informative censoring

Limitations

- Underpowered to detect an association between lung function decline and mortality from specific cancer types or other less common causes of death
- Unmeasured confounding, particularly related to continued workplace exposures among firefighters and EMS providers who remained active in the years following 9/11/2001, could not be discounted
- Cannot fully rule out informative missingness in the PFT data
  - However, the short amount of average time elapsed from the last PFT to the end of follow-up (<2 years) demonstrates that it would have not introduced substantial bias

Take-home messages

- Evidence that lung function decline is associated with all-cause mortality and cancer cause mortality after controlling for important confounders.
- Baseline **FEV_1** and change in **FEV_1** over time are associated with all-cause mortality, cancer-cause mortality, and mortality from heart and lung disease.
- Although aspects of the **WTC** exposure are unique, our study design could benefit the monitoring of other cohorts with *occupational/environmental* exposures.

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Equations for Joint Longitudinal Survival Models

$m_i(t) = \beta_0 + \beta_1 t + \sum_{j=1}^{j=m} \delta_j z_{ji} + b_{0i} + b_{1i} t$ This defines a linear mixed model

$h_i(t) = h_0(t) \exp\left\{\sum_{l=1}^{l=q} \gamma_l x_{li} + \alpha_0 m_i(0) + \alpha_1 \left[m_i(t) - m_i(0)\right]\right\}$

$h_0(t) = \sum_{k=1}^{k=7} h_k$ This defines a piecewise exponential survival model with seven periods

$\tau_{k-1} < t \leq \tau_k$

$\tau_0 = 0,$ the time of first FEV_1

τ_7 is maximum follow up

t is follow-up time

z_{ji} are covariates in the longitudinal model: height, race, age, smoking status, service (firefighter vs. EMS), arrival time at site for participant i

x_{li} are covariates in the survival model (same as in the longitudinal model) for participant i

β_0 is the expected value of FEV_1 at the first observed pulmonary function test for a participant 180 cm high, White, 40 years old, never-smoker firefighter who arrived at the site 9/13/2001 or later

β_1 is the expected rate of change of FEV_1 over the follow-up period

b_{0i} is a random effect for FEV_1 at the first observed pulmonary function test for participant i

b_{1i} is a random effect for rate of change of FEV_1 over the follow-up period for participant i

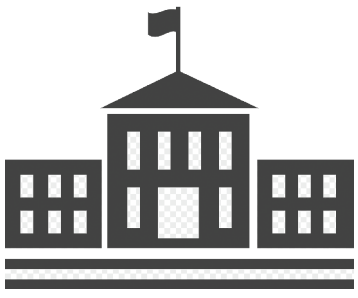
α_0 is the relative hazard for mortality as a function of first FEV_1

α_1 is the relative hazard for mortality as a function of change in FEV_1 over the follow-up period

Survival among World Trade Center Rescue and Recovery Workers

June 2023 WTCHP Research Meeting

David Prezant, MD



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Survival among World Trade Center Rescue and Recovery Workers

June 2023 WTCHP Research Meeting

David Prezant, MD

Background

We know that cancer rates are increased in the cohorts and also know there is a high prevalence of other chronic conditions

Despite increased prevalence of certain illnesses, studies have shown that mortality rates are not necessarily higher than the US population. This raises several questions:

- Is the comparison group appropriate?
- Is it too Early?
- Is it because of the Healthy Worker Effect?
- Is it because of Improved Healthcare access?

These questions are complex.

Two studies we have worked on aim to investigate mortality rates further

Cancer and Mortality Rates

1. WTC Responder Combined Cohort Study

2. Career Firefighter Health Study

WTC Responder Combined Cohort

- Cooperative agreement U01 OH011315/U01 OHO11932
- Collaboration between FDNY, GRC, WTC Health Registry, NYS DOH
- Joint Labor-Management-Government (NIOSH) Initiative

- Investigators included: Charles Hall, Paolo Boffetta , Robert Brackbill, James Cone, Chris Dasaro, Mark Farfel, David Goldfarb, Amy Kahn, Dana Kristjansson, Jiehui Li, David Prezant, Baozhen Qiao, Maria Schymura, Moshe Shapiro, Ankura Singh, Andy Todd, Janette Yung, and Rachel Zeig-Owens

WTC Responder Combined Cohort (continued from the previous)

- NYS DOH Combined and de-duplicated the 3 responder cohorts
- Total of **69,134** WTC-exposed rescue/recovery responders
- Uses previously described combined WTC exposure definitions
- Uses the same reference population as comparison

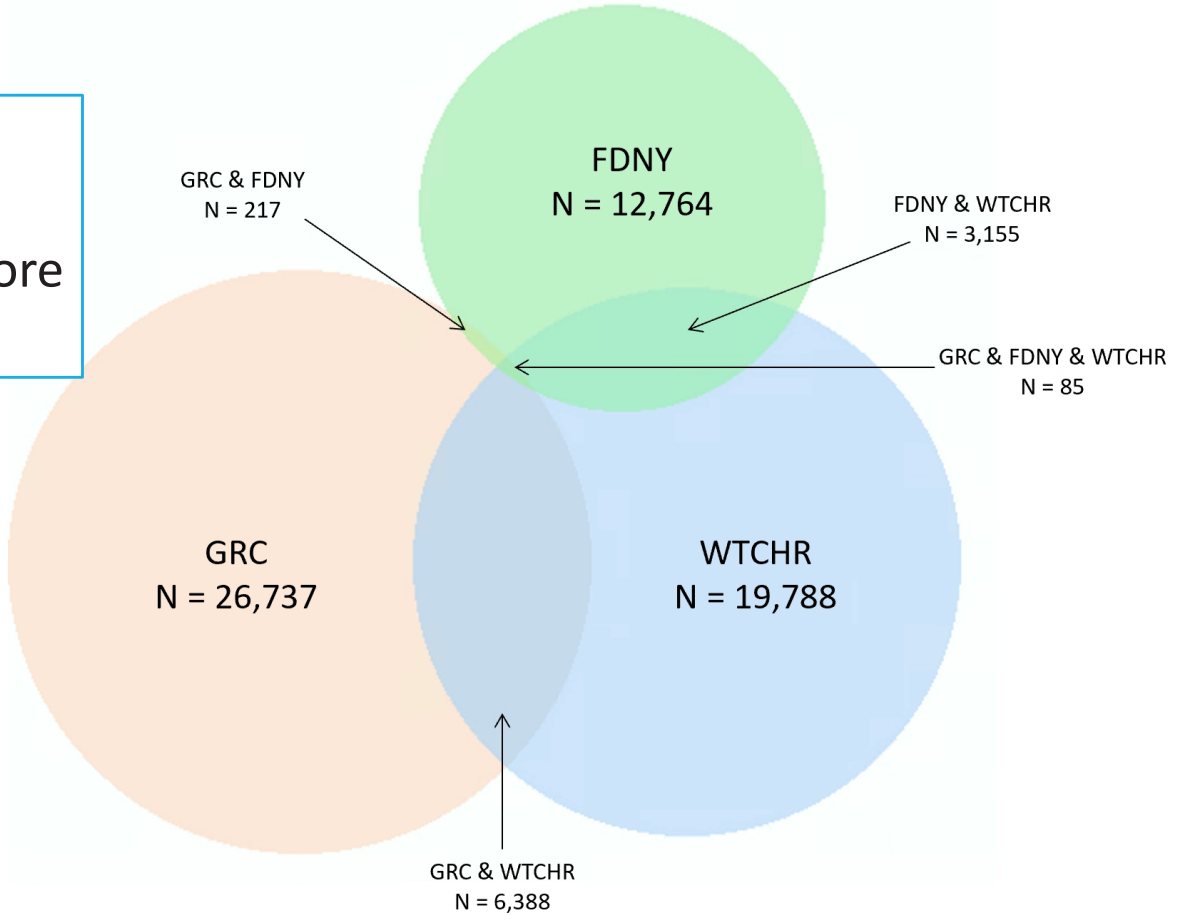
Primary research questions:

- To compare overall cancer incidence, and incidence of specific cancer sites, in WTC rescue/recovery workers to that of the general US population
- To estimate the time after exposure at which the relative risk for specific cancer subtypes significantly increases (or decreases)
- To study mortality rates in WTC rescue/recovery workers with cancer

WTC Responder Cohort Overlap

Total: 69,134

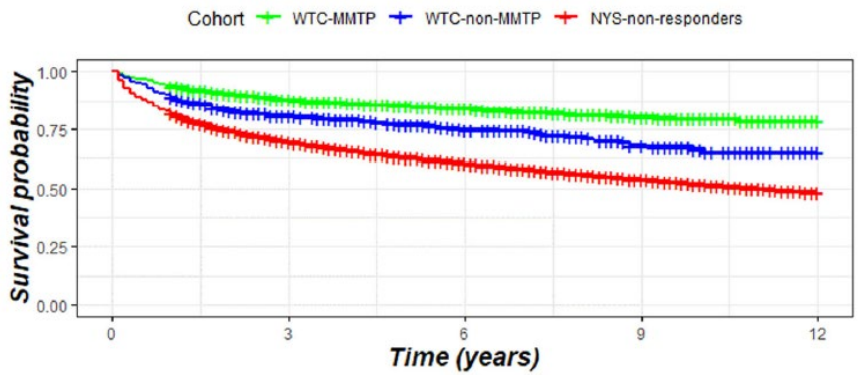
9,845 (14%) in more than one cohort



WTC Responder Cancer Survival

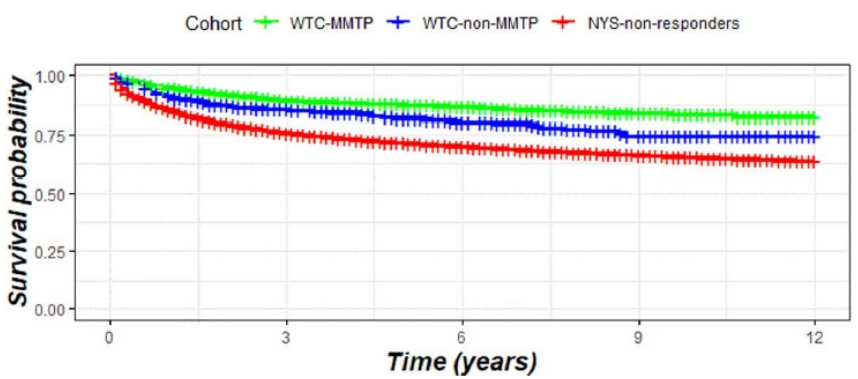
Overall Survival | Cancer Survival

(A) **Overall Survival**



WTC-MMTP vs NYS	HR 0.64 (95% CI 0.58-0.72)
WTC-non-MMTP vs NYS	HR 0.93 (95% CI 0.79-1.10)

(B) **Cancer-specific Survival**



WTC-MMTP vs NYS	HR 0.72 (95% CI 0.64-0.82)
WTC-non-MMTP vs NYS	HR 0.94 (95% CI 0.78-1.14)

Ref: Goldfarb, Zeig-Owens et al AJIM 2021

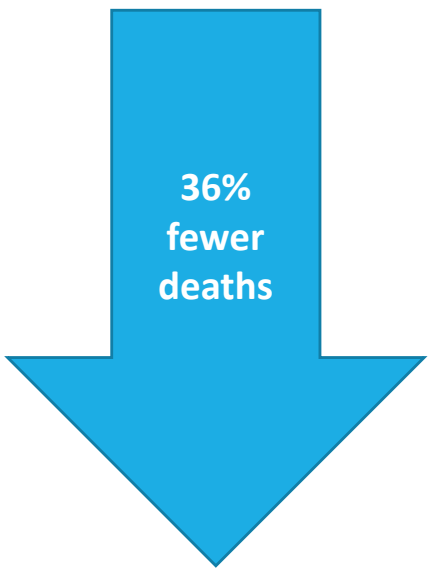
WTC Responder Cancer Survival (continued from previous page)

TABLE 2 All-cause mortality risk among cases of selected cancers

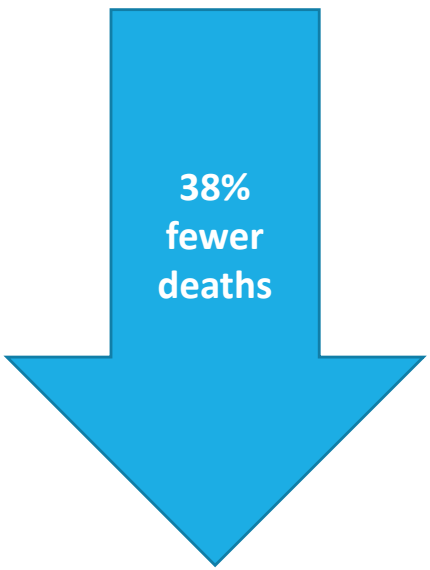
All-cause mortality by cancer site	WTC-MMTP versus NYS-non-responders HR (95% CI)	WTC non-MMTP versus NYS-non-responders HR (95% CI)
(A) All-cause mortality risk by cancer site: Follow-up time starts at diagnosis date		
Prostate	**0.62 (0.44, 0.88)**	0.92 (0.54, 1.55)
Lung and bronchus	**0.74 (0.56, 0.97)**	0.88 (0.60, 1.28)
Esophagus	0.65 (0.36, 1.18)	1.15 (0.55, 2.43)
Colon and rectum	**0.48 (0.31, 0.74)**	1.11 (0.60, 2.06)
Myeloma	0.49 (0.22, 1.10)	0.50 (0.16, 1.54)
Pancreas	**1.66 (1.15, 2.39)**	1.18 (0.61, 2.27)
Brain and other nervous system	1.11 (0.70, 1.76)	0.87 (0.42, 1.83)
Liver	0.74 (0.44, 1.22)	1.00 (0.50, 2.01)
Melanoma of the skin	0.54 (0.27, 1.08)	0.82 (0.20, 3.27)
Kidney and renal pelvis	**0.36 (0.16, 0.79)**	1.23 (0.51, 2.96)

WTC Responder Cancer Survival

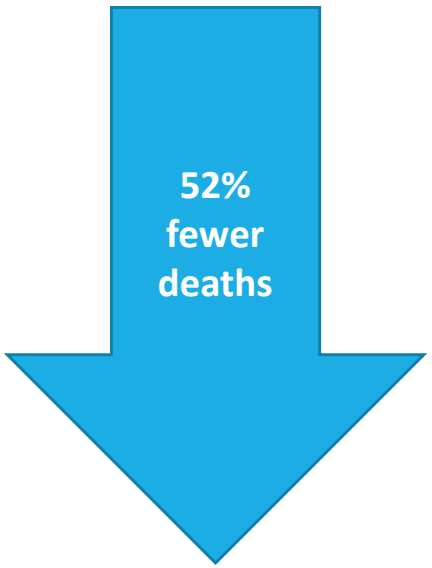
WTC Health Program enrollees **with** Any Cancer



WTC Health Program enrollees **with** Prostate Cancer



WTC Health Program enrollees **with** Colon Cancer



Lower All-cause Mortality Risk in **WTC Health Program Responders (FDNY & GRC)** compared to **NYS** population with same **Cancer**

All-cause Mortality by cancer site	WTC MMTP vs. NYS non responders
	HR (95%CI)
Prostate	0.62 (0.44, 0.88)
Lung and bronchus	0.74 (0.56, 0.97)
Esophagus	0.65 (0.36, 1.18)
Colon and rectum	0.48 (0.31, 0.74)
Myeloma	0.49 (0.22, 1.10)
Pancreas	1.66 (1.15, 2.39)
Brain and other nervous system	1.11 (0.70, 1.76)
Liver	0.74 (0.44, 1.22)
Melanoma of the skin	0.54 (0.27, 1.08)
Kidney and renal pelvis	0.36 (0.16, 0.79)

	WTC MMTP (n=2,037)	NYS non-responders (n=574,075)
Deaths n (%)	303 (14.9)	224,040 (39.0)
Cancer deaths n (%)	248 (12.2)	158,645 (27.6)
Survival rate n (%)		
1 year survival	1,916 (94.1)	474,895 (82.7)
3 year survival	1,346 (88.3)	326,959 (69.6)
5 year survival	919 (86.1)	228,933 (62.8)

Follow-up time starts at diagnosis date, males only, adjusted for age and date of diagnosis

Combining Three Cohorts of WTC Rescue/Recovery Workers for Assessing Cancer Incidence and Mortality. Int. J. Environ. Res. Public Health. 2021

Cancer survival among WTC Rescue/Recovery Workers: a collaborative cohort study. Am J Ind Med. 2021

WTC Responder Cancer Survival (continued on next Slide)

For **WTC Health Program** Responders –

Does Improved Healthcare Access Improve Survival?

WTC Responder Cancer Survival (continued from previous Slide)

While it would seem that the WTC Health Program does improve survival rates there remain potential confounders:

- Is the comparison appropriate?
- All WTC Responders are Not Equal
  - Healthy Worker Effect is not identical across all WTC Responders
    - FDNY has the most stringent health standards
  - Non-WTC Exposures (pre-, post-WTC) are not identical across all WTC Responders
- Healthcare Disparities
  - Socioeconomic and Racial/ethnic Disparities
  - Education, Health-specific education
  - Employer Health Care Programs
  - Non-WTC Healthcare insurance
  - WTC Health Program surveillance bias

Career Firefighter Health Study (continued from previous Slide)

- Cooperative agreement **U01 OH011309/U01 OH011934**
- Collaboration between FDNY, Chicago, Philadelphia and San Francisco
- Joint Labor-Management-Government (NIOSH) Initiative
- Aims
  - Identify prevalence and mortality rates in career firefighters
  - Provide a more appropriate comparison control group for WTC firefighter studies
    - Thereby differentiating the impact of WTC exposure from usual firefighter exposures
    - "Eliminating" the Healthy Worker Effect
    - Reducing the impact healthcare disparities, access and possibly surveillance bias
- Investigators include: Robert D Daniels, Charles B Hall, David G Goldfarb, David J Prezant,, Joke Salako, Ankura Singh, Suzanne Triplett, Mayris P Webber, and Rachel Zeig-Owens

Career Firefighter Health Study (continued from previous Slide)

Original **NIOSH** cohort of **29,992** professional firefighters employed any time between **1950-2009** from the San Francisco **(5,313),** Chicago **(15,184),** and Philadelphia **(9,495)**fire departments.

- Originally assembled by **NIOSH** to study cancer and mortality.
  - *Daniels RD et al., Occup Environ Med, 2014*

- Now includes **FDNY** firefighters
  - **13,833 WTC**-exposed
  - Will soon add **~10,000** non-**WTC** exposed

Totals over **50,000** firefighters

Linkages *(State tumor registries, National Death Index Registry)* Web-based survey for health characteristics & self-reported diseases

Career Firefighter Health Study Cancer Results

Updates original **NIOSH** study and adds **FDNY** **WTC** firefighters

Adds a Web-based survey for firefighters to report health characteristics and self-report health conditions

Focused on cancers diagnosed between **9/11/2001-12/31/2016** in male firefighters who were **actively employed on 9/11/2001**.

Received confirmed cancer data from **15** state tumor registries

Compared cancer rates in **WTC**-exposed & non-**WTC**-exposed firefighters to **US** males

- Standardized Incidence Ratios ***(SIRs)*** presented: Observed number of cancer cases in the firefighter population vs. number of cases *expected* based on the **US** male cancer rates.

Cancer Incidence in World Trade Center-Exposed and Non-Exposed Male Firefighters, as Compared with the US Adult Male Population: 2001 – 2016. *Occup Environ Med, 2021*

	Male WTC-exposed FDNY firefighters actively employed on 9/11/2001	Male non-FDNY, non-WTC-exposed firefighters actively employed on 9/11/2001
Total N	10,786	8,813
Age on 9/11, mean ± SD	40.4±7.5	43.9±9.2
Race/ethnicity, N (%)		
Non-Hispanic White	10,121 (93.8)	6,117 (69.4)
Non-Hispanic Black	282 (2.6)	1,589 (18.0)
Hispanic	353 (3.3)	736 (8.3)
Othera	30 (0.3)	371 (4.2)
Smoking status, N (%)		
Current	373 (3.5)b	189 (6.6)c
Former	3,233 (30.2)b	1,056 (37.0)c
Never	7,117 (66.4)b	1,611 (56.4)c
WTC exposure/site arrival time, N (%)		
Morning of 9/11	1,741 (16.1)	
Afternoon of 9/11	5,683 (52.7)	
9/12/2001	1,873 (17.4)	
9/13-9/24/2001	1,315 (12.2)	
After 9/24/2001	174 (1.6)	
Deceased by 12/31/16, N (%)	261 (2.4)	605 (6.9)
Follow-up years, mean ± SD	15.2 ± 1.1	14.9 ± 2.0
Total follow-up years	163,583.4	130,971.0

A Includes Asian and Native American race categories;
B N=10,723 who self-reported smoking status;
C N=2,856 who completed Career Firefighter Health Study survey

19,599 Firefighters employed on **9/11/2001**

Note: throughout this presentation **CFHS** includes only males due to low numbers of females. Next phase should enable their inclusion

Career Firefighter Health Study Cancer Results

Standardized Incidence Ratios (SIRs) of cancers in male WTC-exposed and non-WTC-exposed firefighters vs. US males

	Observed case count			Observed case count		
All cancer sites[ab]						
Kidney	39	0.93	(0.67-1.28)	55	1.19	(0.90-1.56)
Non-Hodgkin Lymphoma	55	1.39	(1.06-1.83)	43	1.04	(0.77-1.41)
Melanoma (skin)	96	1.59	(1.30-1.96)	70	1.39	(1.07-1.79)
Thyroid	46	2.37	(1.78-3.17)	15	1.01	(0.61-1.67)

[a]All malignant cancers (multiple primaries), and in situ bladder cancers;
[b]Excludes non-melanoma skin cancers

Career Firefighter Health Study Cancer Results WTC vs. Non-WTC

- We compared incidence rates in **FDNY WTC**-exposed male firefighters to incidence rates to the non-**WTC**-exposed male firefighters (CFD, PFD, SFFD)

		FDNY WTC-exposed vs CFD, PFD & SFFD non-exposed
		Webber et al, 2021 *Data through 2016*
	All cancer	1.13 (1.02-1.25)
	Thyroid	2.53 (1.37-4.70)
	Prostate	1.39 (1.19-1.63)
	Lung	0.87 (0.57-1.33)
	Skin Melanoma	1.12 (0.80-1.57)

- ***WTC**-exposed male firefighters had significantly higher rates of cancers especially thyroid, and prostate compared to Non-WTC male Firefighters*

Ref: Webber et al OEM 2021

Career Firefighter Health Study Cancer Results

For cancers diagnosed between **9/11/01** and **12/31/2016**

WTC-exposed **FDNY** male firefighters had higher rates of cancer **(15%)** when compared with similar **US** males.

- Site-specific cancers that were statistically elevated include:
  - Thyroid, Prostate, Melanoma, and Non-Hodgkin Lymphoma
- Lung cancer was significantly decreased

WTC-exposed **FDNY** male firefighters had higher rates of cancers **(13%)** when compared with **Non-WTC** male **Firefighters** from the **3** collaborating cities

- Site-specific cancers that were statistically elevated include:
  - **Thyroid** and **Prostate**

Career Firefighter Health Study Mortality Rates

Both **WTC**-exposed and non-exposed male firefighters had lower than expected all-cause mortality compared with **US** males.

Standardized Mortality Ratios (SMRs) of all-cause and cause-specific mortality in male WTC-exposed FDNY and PFD firefighters vs. US males active on 9/11/2001						
Cause of death (NIOSH major category)	FDNY			3 City		
	N	SMR	95% CI	N	SMR	95% CI
All	261	0.30	0.26-0.34	191	0.64	0.55-0.73
All cancers	86	0.40	0.32-0.49	32	0.45	0.31-0.63
Heart diseases	52	0.27	0.20-0.35	62	0.72	0.55-0.92

Cancer incidence in WTC-exposed and non-exposed male firefighters, compared with the US adult male population: 2001-2016. Occup Environ Med. 2021 Oct;78(10):707-714

All-cause and cause-specific mortality in a cohort of WTC-exposed and non-WTC-exposed firefighters. Occup Environ Med. 2023 Mar 27:oemed-2022-108703. doi: 10.1136/oemed-2022-108703

Career Firefighter Health Study Mortality Rates

Table 2: Standardized Mortality Ratios (SMRs) of all-cause and cause-specific mortality in male WTC-exposed FDNY and non-WTC-exposed non-FDNY firefighters vs. US males, 9/11/2001-/12/31/2016

Cause of death	FDNY count	FDNY SMR	95% CI	Non-FDNY count	Non-FDNY SMR	95% CI
All	261	**0.30**	**0.26-0.33**	**605**	**0.60**	**0.55-0.65**
All cancer	86	**0.40**	**0.32-0.49**	**206**	**0.73**	**0.65-0.83**
Oral cancer	1	**0.15**	**0.07-0.36**	5	0.65	0.25-1.70
Digestive cancer	37	**0.54**	**0.43-0.68**	**57**	**0.65**	**0.53-0.80**
Respiratory cancer	12	**0.19**	**0.08-0.44**	**55**	**0.63**	**0.55-0.74**
Male genital cancer	4	0.54	0.28-1.02	12	0.91	0.60-1.39
Kidney or bladder cancer	3	**0.25**	**0.13-0.50**	15	1.01	0.66-1.54
Other/unspecified cancer	15	**0.40**	**0.30-0.53**	37	0.87	0.66-1.15
Blood cancers	14	0.74	0.39-1.38	25	1.03	0.80-1.33
Diabetes	4	**0.14**	**0.06-0.35**	**14**	**0.38**	**0.27-0.53**
Heart disease	52	**0.27**	**0.21-0.34**	**120**	**0.51**	**0.43-0.59**
Other circulatory disease	8	**0.18**	**0.10-0.31**	**24**	**0.38**	**0.25-0.57**
Respiratory disease	14	**0.31**	**0.22-0.42**	**36**	**0.57**	**0.45-0.72**
Digestive diseases	8	**0.13**	**0.06-0.28**	**24**	**0.42**	**0.29-0.61**
Intentional self-harm (suicide)	17	**0.36**	**0.20-0.65**	31	1.01	0.76-1.34

Career Firefighter Health Study Mortality Rates

- We compared mortality rates in WTC-exposed firefighters to rates in non-WTC-exposed firefighters

Cause of death	Adj. RR (95% CI)
All cause	0.54 (0.49-0.59)
All cancers	0.72 (0.65-0.79)
Diseases of the heart	0.61 (0.55-0.67)
Diseases of the respiratory system	0.69 (0.62-0.77)
Diseases of the digestive system	0.54 (0.48-0.60)
Other injury	0.90 (0.81-1.01)

Ref: Singh A et al OEM 2023

Summary:

WTC Responder Combined Cohort Study:

- Confirms that Cancer rates are increased and that this is driven by specific sites
- Cancer Survival benefit from being in the WTC Health Program
- Not able to dissect influence of multiple confounders

Career Firefighter Health Study: WTC-exposed vs Non-WTC exposed

- Not just a healthy worker effect
  - Confirms that Cancer rates are increased and that this is driven by specific sites
    - Is this due to increased surveillance (Thyroid and Prostate)
  - Cancer Mortality is lower than other career firefighters
  - Lower mortality rates is not just due to cancer
    - See this also for Cardiac and Respiratory

Next Steps:

1. Update cancer and mortality rates for the WTC Responder Combined Cohort

2. Include diseases other than Cancers.

3. Update and Expand Relevant Comparison Groups

3A. Career Firefighter Health Study Cohort

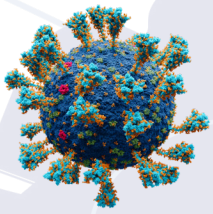
- Already reached out to current cities - **Chicago, Philadelphia, San Francisco, FDNY**
- Expand to include firefighters hired after **12/31/2009**
  - Employees post 2009 are likely different
- Expand to include firefighters from other cities
- Ongoing negotiations with Miami-Dade County, Boston, Indiana
  - Demographics – more females, more persons of color
  - Even lower smoking rates, other health characteristics may be different?
  - Firefighters exposed to new toxins – PFAS, etc.

3B. Career Law Enforcement – Buffalo Police Department

WORLD TRADE CENTER HEALTH PROGRAM COVID-19 STUDIES

The Impact of World Trade Center Related Medical Conditions on the Severity of COVID-19 Disease and Its Long-Term Sequelae. Polygenic risk scores for asthma and allergic disease associate with COVID-19 severity in 9/11 responders. Assessment and Characterization of Cognitive Decline in SARS-CoV-2 Infection.

ZENNUR SEKENDIZ MD MPH
DEPARTMENT OF MEDICINE-WTCHP
STONY BROOK MEDICINE, STONY BROOK, NY



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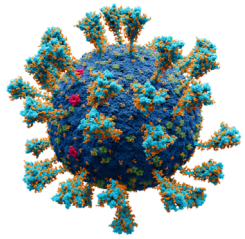


Introduction

COVID-19

- Caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-COV-2)
- Initially identified with respiratory symptoms but effects many organs such as brain, heart and kidney
- Increased mortality with severe disease

Risk Factors for Severe COVID-19

- Older age, Obesity, Male sex, Smoking,
- Chronic Obstructive Pulmonary Disease, Cardiovascular Disease, Immunocompromised Status and Malignancy

Vaccination found to be protective for reinfection and symptomatic disease

Global prevalence of Post-Acute Sequalae of **SARS-CoV-2 (PASC) is 43%**

According to a systemic review and meta-analysis **poor quality of life experienced** by **59%** of people with **PASC**

COVID-19 Forecasting Team, 2023/Chen et al., 2022/Malik et al.,2022/Wasczuk et al., 2023/Lhuillier et al.,2022

Introduction

PASC:

Definitions: At least 4 weeks of symptoms after initial **SARS-CoV-2** infection (**CDC**),

Common Symptoms: Fatigue, Dyspnea, and Cognitive impairment

Neurologic Symptoms of PASC ***(****e.g., brain fog, headache****,*** *loss of taste and smell****)***

Risk Factors:

- Severity of Acute **SASRS-CoV-2**, Female sex, **BMI,**
- Asthma, **Chronic Obstructive Pulmonary** disease, Anxiety, Depression, Diabetes,
- Immunosuppressed Status and **Ischemic Heart Disease**

Treatment: Symptomatic, there is no effective treatment for Fatigue and Cognitive impairment

Vaccination: Decreasing the risk of PASC and severity of **COVID-19**

Introduction

Nervous system invasion-SARS-Cov-2

1-The nerve root,

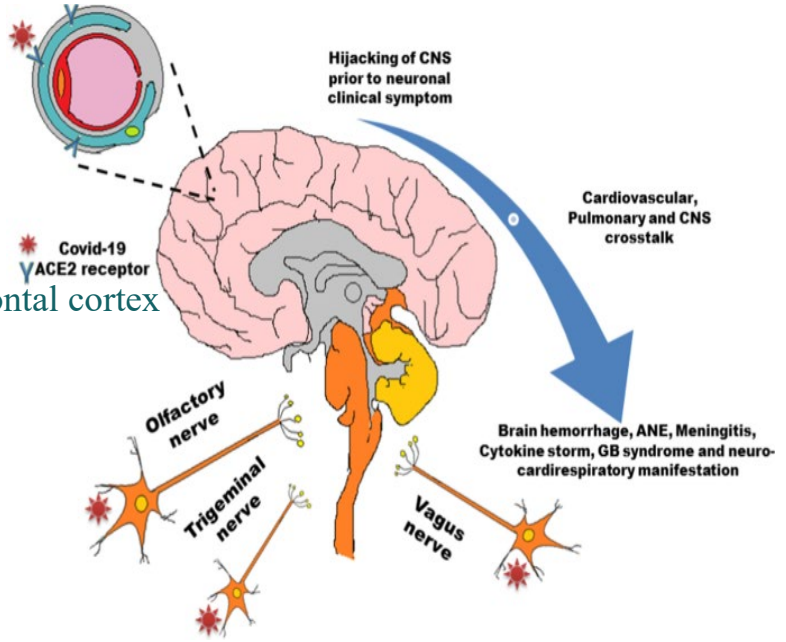
2-The circulatory system,

ACE2

NRP1 and **Basigin (BSG);** highly expressed in the prefrontal cortex

Purposed Mechanism

- Direct invasion by the virus,
- Indirectly by inflammation, epigenetic changes,
- Autoimmune process or hypercoagulation



Chaudhury et al., 2021

Introduction

Host genetics in COVID-19

- Genetics contribute to individual differences in **COVID-19** outcomes
- Polygenic Risk Scores(PRS) for susceptibility to infection *vs* **COVID-19** severity
- Previous work: **COVID-19** severity **PRS** predicted death and severe respiratory failure in patient population **(OR=1.70)**
- Null findings using **PRS** for relevant conditions, e.g., Asthma

World Trade Center First Responders Cohort

- **WTC Health Program** established in **2002**, and
- Monitors more than **13,000 9/11** first responders for **WTC** exposure related health conditions
- In **Long Island, NY, USA**

Wasczuk et al.,2023

Introduction

Some of the Medical Conditions associated with 9/11 events being certified and coded as below;

- adjustment disorder **(ADJ),**
- anxiety **(ANX),** depression **(DEP), PTSD**, substance abuse **(SA),**
- extremity **(EXT),** head trauma **(HT)**, spine **(SP),**
- gastroesophageal reflux disorder **(GERD),**
- interstitial lung disease **(ILD),** obstructive airway disease **(OAD),** sarcoid **(SRC),** and upper respiratory disease **(URD)**

Multiple chronic conditions place responders at potential risk for severe COVID-19 and PASC

Lhuillier et al., 2022

Introduction

Lhuillier *et al.*, 2022

Objective

Examined if **WTC** related and other health conditions were associated with **COVID-19** severity and **PASC** presence among individuals who endorsed any **COVID-19** infection

Wasczuk *et al.*,2023

Objective

Investigated whether polygenic vulnerabilities to **COVID-19** hospitalization, asthma, related allergic diseases, coronary artery disease, and type II diabetes, were associated with **COVID-19** severity and **PASC**

Sekendiz *et al.*, current

Objective

To determine whether cognitive decline emerges with the onset of **COVID-19** and whether it is more pronounced in patients with **PASC** or severe **COVID-19.**

Materials and Methods

Table 1. COVID-19 Severity in 9/11 responders

Asymptomatic	Mild	Moderate	Severe
• A positive test result, but no symptoms.	• At least 1 symptom of **COVID-19**. • No shortness of breath or difficulty breathing. • Medically managed mostly at home, with some initial healthcare facility visit a for medical treatment and/or testing.	• Shortness of breath and/or diagnosis of lower respiratory disease (pneumonia/bronchitis) during clinical assessment or imaging. • Maintained **SpO2 ≥ 94%** on room air at sea level.	• Proven or endorsed **SpO2 < 93%** on room air, and/or respiratory rate **> 30 breaths/min**, and/or heart rate greater than **100** beats per minute, • And /or acute respiratory distress syndrome, septic shock, cardiac dysfunction, or an exaggerated inflammatory response in addition to pulmonary disease and/or severe illness causing cardiac, hepatic, renal, central nervous system, or thrombotic disease during **COVID-19** illness. • Hospital admission, supplemental oxygen use, **ICU** admission, or death

Material and Methods

Lhuillier et al., 2022

- **1549** Patients who answered ***"yes"*** to indicate a positive test result for **COVID-19** between March **2020** and January **2022** ,through **PCR** testing, antigenic testing, or antibody testing
- Asymptomatic ***(N = 129),*** mild ***(N = 511),*** moderate ***(N = 536),*** and severe ***(N = 104).***

Analytic sample 1280, responders with confirmed infection
Statistical Analysis: Logistic regression, Multivariable Poisson Regression Models

Waszczuk et al., 2023

- **983 WTC** responders with confirmed **COVID-19**
- Asymptomatic ***(N = 92, 9.4%),*** mild ***(N = 378, 38.5%)***, moderate ***(N = 408, 41.5%)***, and severe **(N = 75, 7.6%).**

Analytic sample 813
European ancestry responders with confirmed infection and available DNA data
Statistical Analysis: Logistic regression

Sekendiz et al., current

- **614** with cognitive assessments from November **2015** to November **2021** from **WTCHP** cohort
- **256** Cases: Reported to Have **COVID-19** symptoms and a positive **COVID-19** Antibody, antigen and **PCR** test
- 217 controls
- Mild **(N = 121, 47.21%),** moderate **(*N* = 104, 40.63%),** and severe **(*N* = 31, 12%).**

Analytic sample 473
256 Cases, 217 controls
Statistical Analysis: Linear longitudinal mixed models

Results

Lhuillier et al., 2022		Waszczuk *et al.*, 2023		Sekendiz *et al.*, current	
Age		**Age**		**Age**	
Mean (SD)	56.9 (7.37)	Mean (SD)	56.06 (7.37)	Mean (SD)	55.75 (6.4)
Gender		**Gender**		**Gender**	
Male	91.4%	Male	95%	Male	94.85%
Female	8.6%	Female	5%	Female	5.15%
Race/Ethnicity		**Participants with European ancestry**		**Race/Ethnicity**	
White	87.3%			White	80.88%
Black	5.6%			Black	2.94%
Hispanic	5.3%			Hispanic	6.62%
Other	1.8%			Other	9.56%

Results

Table 2

Correlates of COVID-19 severity using ordinal logistic regression model.

	OR	95% CI	FDR-p
Age [a]	**1.21**	**(1.06, 1.38)**	**0.015**
Female	1.15	(0.78, 1.70)	0.583
Race: Black	**2.01**	**(1.24, 3.27)**	**0.015**
Race: Hispanic	1.22	(0.76, 1.95)	0.583
Race: Other	1.55	(0.72, 3.30)	0.408
Gastroesophageal Reflux Disorder	1.27	(1.00, 1.60)	0.131
Obstructive Airway Disease	**1.86**	**(1.46, 2.38)**	**<0.001**
Upper Respiratory Disease	1.16	(0.91, 1.48)	0.396
Obesity	1.16	(0.94, 1.45)	0.332
Hypertension	1	(0.78, 1.29)	0.999
High Cholesterol	0.94	(0.74, 1.18)	0.615
Heart Disease	1.13	(0.78, 1.62)	0.583
Diabetes	1.15	(0.80, 1.67)	0.583
Depressive Symptoms [a]	**1.27**	**(1.12, 1.43)**	**<0.001**

Lhuillier et al. **(2022)** *Int J Environ Res Public Health*

Results

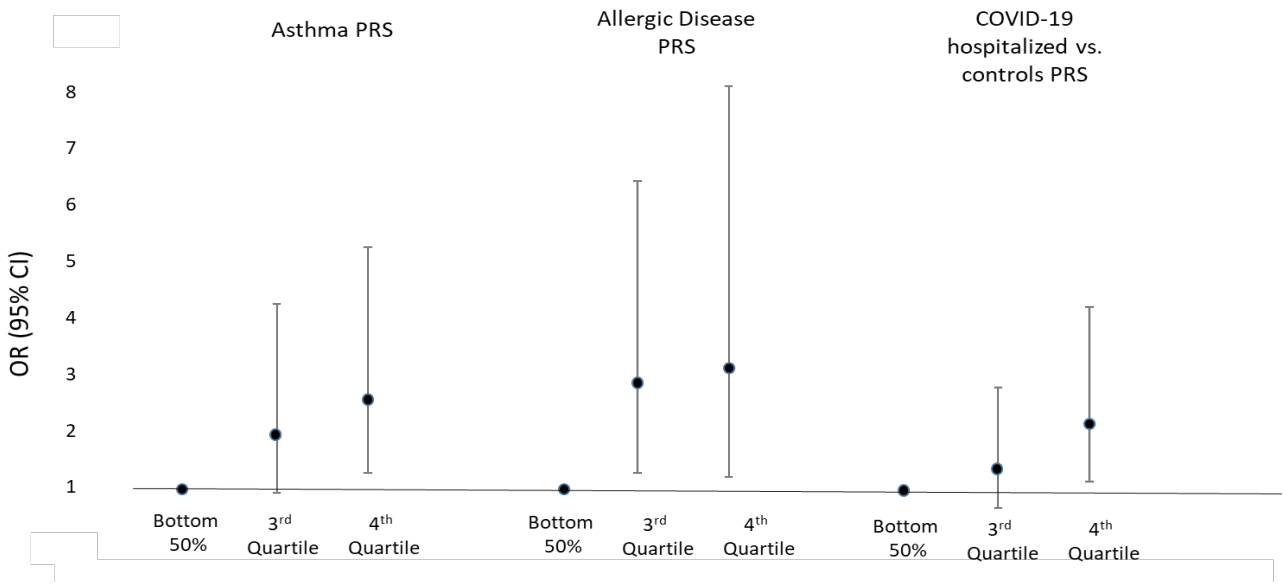
Table 3

Multivariable-adjusted risk ratios and 95% confidence intervals predicting the presence of Post-Acute COVID-19 Syndrome in World Trade Center responders.

aRR	95% CI	FDR-p	
Severity Asymptomatic	**0.13**	**(0.04, 0.41)**	**0.002**
Severity Moderate	**1.82**	**(1.47, 2.26)**	**<0.001**
Severity Severe	**2.87**	**(2.23, 3.71)**	**<0.001**
COVID-19 Report Status: Incomplete	1.13	(0.95, 1.34)	0.327
Age [a]	0.98	(0.89, 1.08)	0.853
Female	1.12	(0.84, 1.49)	0.615
Race: Black	0.99	(0.70, 1.40)	0.971
Race: Hispanic	1.10	(0.81, 1.50)	0.708
Race: Other	0.71	(0.31, 1.64)	0.615
Gastroesophageal Reflux Disorder	1.22	(1.01, 1.48)	0.128
Obstructive Airway Disease	1.02	(0.85, 1.22)	0.954
Upper Respiratory Disease	1.19	(0.97, 1.46)	0.259
Obesity	1.00	(0.84, 1.19)	0.971
Hypertension	0.98	(0.81, 1.19)	0.954
High Cholesterol	0.91	(0.75, 1.09)	0.490
Heart Disease	**1.34**	**(1.07, 1.67)**	**0.037**
Diabetes	1.2	(0.95, 1.53)	0.295
Depressive Symptoms	1.07	(0.99, 1.16)	0.259

Lhuillier et al. **(2022)** Int J Environ Res Public Health

Results



Covariates included: age, sex, and lower **+** upper respiratory symptoms associated with **9/11** exposure

Waszczuk et al. (2023) *PLOS ONE*

Results

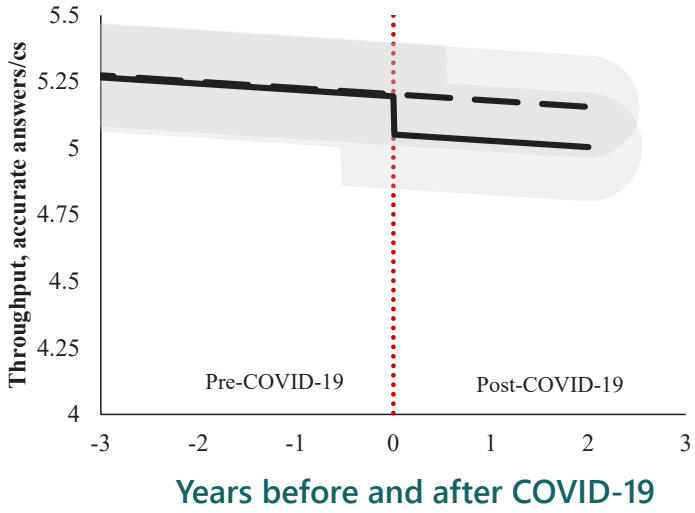


Figure 1. Trajectory plot showing expected reaction speeds before and after Start of **COVID-19** symptoms

Abbreviations: cs, count per second

Conclusion

Lhuillier *et al.*, 2022

COVID-19 severity predicted by:
- **Older age**, male gender,
- **Black race**
- Upper Respiratory Disease,
- **Obstructive Airway Disease**
- **GERD**, Obesity, Hypertension, Diabetes
- **Depression**

Post-acute COVID-19 sequel predicted by:
- **Acute COVID Severity**
- Upper Respiratory Disease, Obstructive Airway Disease
- **GERD**, **Heart Disease**
- Depression

Not much **COVID-19** symptom-specificity

Waszczuk *et al.*, 2023

COVID-19 severity predicted by:
- **Asthma Polygenic Risk Score (PRS)** (β=.09)

COVID-19 severe category predicted by:
- **Asthma PRS** (OR=1.61, CI: 1.17-2.21)
- **Allergic Disease PRS** (OR=1.97, CI: 1.26-3.07)
- **COVID-19 Hospitalization PRS** (OR=1.35, CI: 1.01-1.82)

No genetic prediction by **T2D PRS** and coronary artery disease **PRS**

No genetic prediction of post-acute **COVID-19**

Sekendiz *et al.*, current

- **COVID-19**-induced neuroinflammation was most likely the cause of the observed cognitive decline

What have we learned

- Respiratory illness is a key predictor for **COVID** severity, and emerged as the main predictor in terms of genetic risk
- Other important predictors: heart disease and depression - but the effects at genetic level are not detected
- **PASC** is much harder to predict, main predictors were heart disease and severity of **COVID-19**
- **COVID-19-**induced neuroinflammation was most likely the cause of the observed cognitive decline

Future Directions and Recommendations

- Understanding the pathophysiological mechanisms behind **PASC** and the **SARS-CoV-2**-induced neurocognitive sequelae
- Additional research to detect genetically vulnerable individuals for severe **COVID-19** and **PASC**
- Determining the long-term prognosis of cognitive impairment
- People who have a history of severe **COVID-19** and **PASC** should be monitored with more vigilance
- Screening patients for **COVID-19** complications based on risk factors

Acknowledgements

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The nursing and medical team of **WTCHP**

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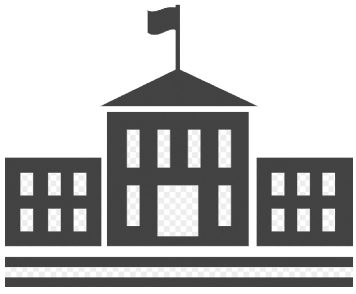
On overview of cancers in Survivors in the WTC EHC with a focus on breast cancer

Joan Reibman, MD

Professor of Medicine and Environmental Medicine, **NYU Langone Medical Center**

Medical Director, **H+H WTC** Environmental Health Center



Disclaimer: Funding for this conference was made possible *(in part)* by the **Centers for Disease Control and Prevention**. The views expressed in written conference materials or publications and by speakers and moderators do not necessarily reflect the official policies of the **Department of Health and Human Services**, nor does the mention of trade names, commercial practices, or organizations imply endorsement by the **U.S. Government**.

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NYC HEALTH+ HOSPITALS

On overview of cancers in Survivors in the WTC EHC with a focus on breast cancer

Joan Reibman, MD

Professor of Medicine and Environmental Medicine, **NYU Langone Medical Center**

Medical Director, **H+H WTC** Environmental Health Center

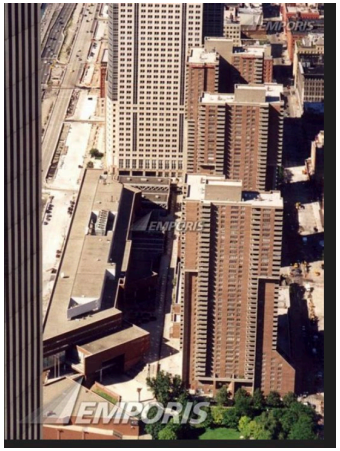
Goals of the talk

- **Brief** description of the **WTC Environmental Health Center: Survivor Center of Excellence** in the **WTC** Health Program
- **WTC EHC Pan Cancer Database** – what it is and its use as resource
- **Describe Cancers** in the **WTC EHC**
- **Breast Cancer** in the **WTC EHC**
- **Next** steps

Diverse area around the WTC towers

Battery part city (West)

Tribeca (North)



Chinatown, NYCHA housing, other (East)

Wall Street et al. (South/East)

3 Div

WTC towers sat in the midst of an active residential and working community

- 300,000 local workers/commuters
- 60,000 residents
- 15,000 students
- Major commuter/tourist area

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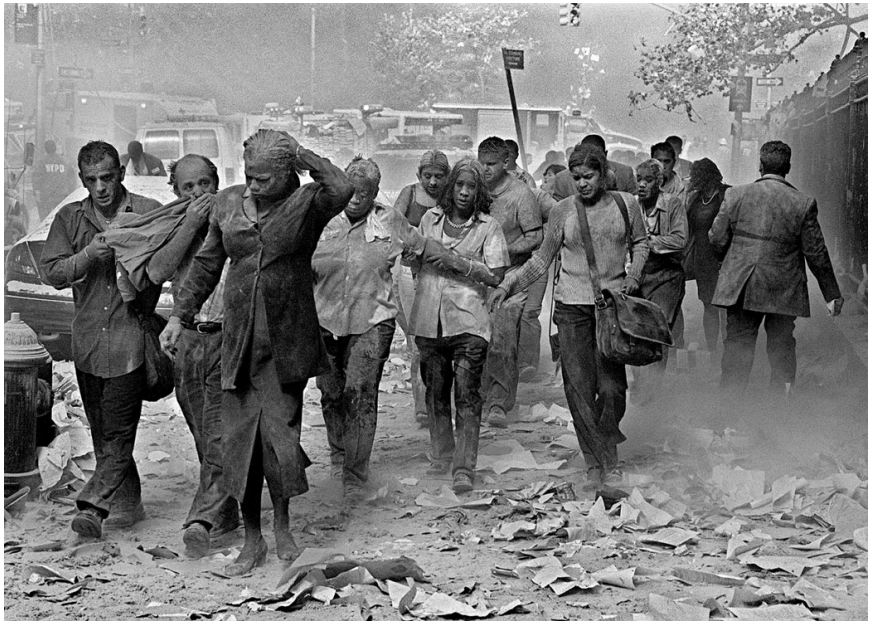
Acute exposures

- **Dust** cloud or heavy dust exposure on **9/1/01**
  - **Tower evacuees**
  - **Office building evacuees**
  - **Store/restaurant workers**
  - **Tunnels** *(Brooklyn Battery tunnel)*
  - **Commuters/passing by**
  - **Residents**



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Chronic exposures

- Local workers returned 9/17/01
- Homes/schools/workplaces breached
- Chronic exposures from resuspended dust and fires/fumes

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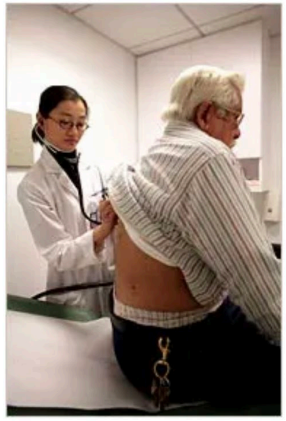
Creation of the WTC Environmental Health Center

- **Bellevue Hospital** – treatment program
  - **2002** community collaborative pilot program for treatment of residents/area workers in the **Bellevue Hospital** Asthma clinic
- **WTC** Environmental Health Center – **treatment** and **surveillance** program
  - **Grant** - **2005** American Red Cross Liberty **Disaster Relief Fund**
  - **Grant** - **2006** funding from City of **New York**
  - **Grant** - **2008** first Federal funding **(CDC-NIOSH)**
  - Contract under the **WTC** Health Program - 2011 James Zadroga **9/11** Health and Compensation Act

WTC Environmental Health Center – Center of Excellence for Survivors within the WTC Health Program

- Local residents/children, in utero
- Local workers
- Students
- Those passing by on **9/11** *(commuters, tourists)*
- Clean-up workers



Dr. Stephanie Lau examined Manuel S. Bruno, 82, at the W.T.C. Environmental Health Center at Bellevue Hospital.
Nicole Bengiveno/The New York Times

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WTC Environmental Health Center – Center of Excellence for Survivors

- Multidisciplinary program for **treatment** and **surveillance of** community members with **WTC** certified conditions
- **Very significant differences compared to the Responder Programs / WTC Health Registry programs** – these differences influence our data analyses**:**
  - Enrollment in the **WTC EHC requires** the presence of a certified condition, not a screening program for those without illness
  - Treatment in the **WTC EHC requires** coordination of benefits with the WTC Health Program as the final payor

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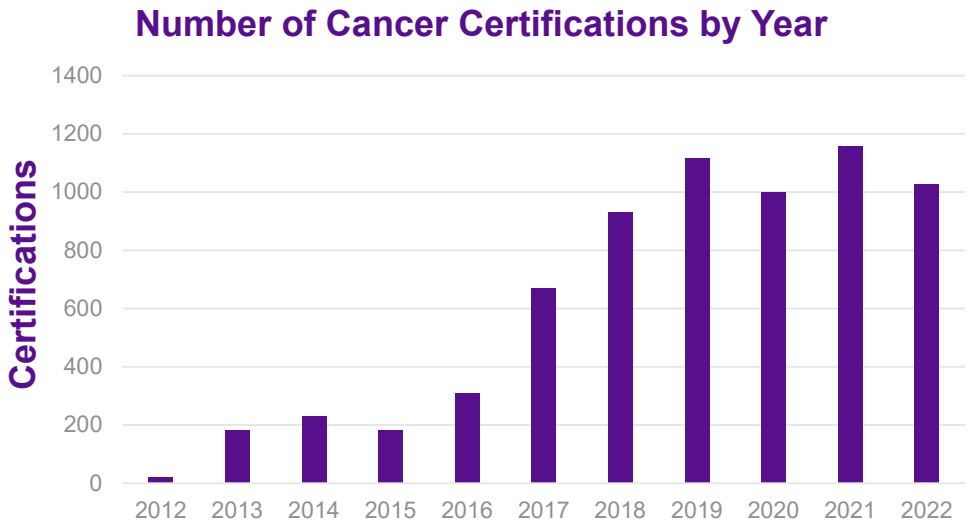
Yearly cancer certifications in the WTC EHC

- Self-referred population for **WTC** Health Program certification. As such, cannot assess prevalence
- Goal to understand characteristics within specific cancer groups and across cancer groups



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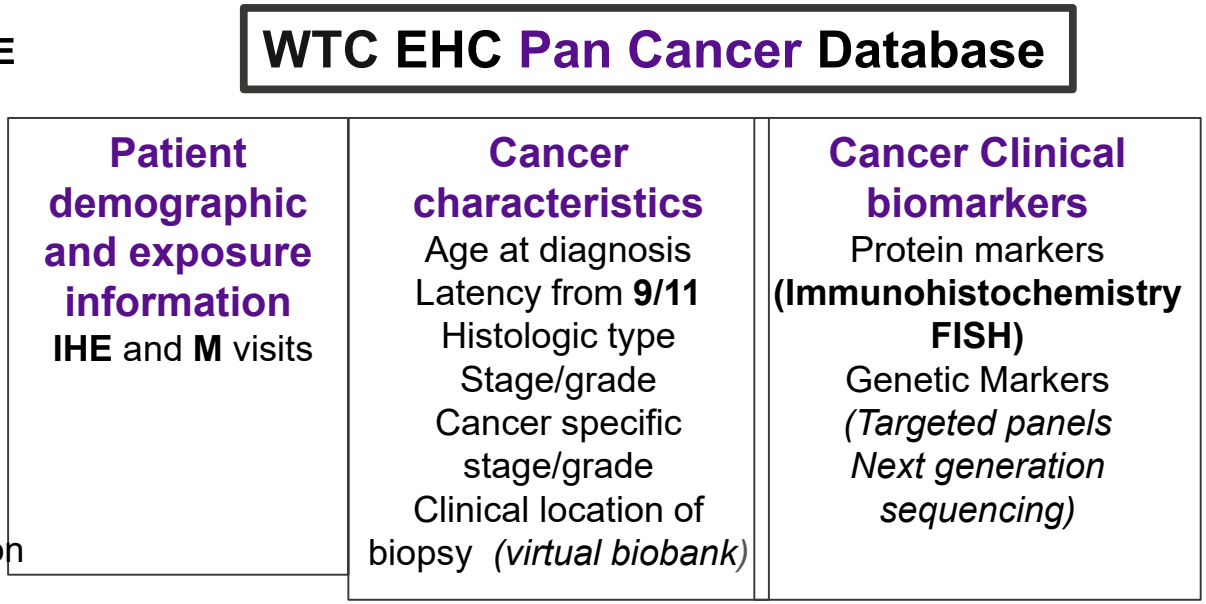
WTC EHC Pan Cancer Database

- Demographic/exposure information obtained from **IHE** and **M** visits
- **Cancers** identified from patient self-referral and/or state registry linkages. All confirmed with pathology/cytology
- **Cancer** characteristics obtained from chart review
- **Clinical** biomarker information obtained from chart review



Durmus et al. *Int J Environ Res Public Health.* **2020**
Shao et al. *Int J Environ Res Public Health.* **2021**

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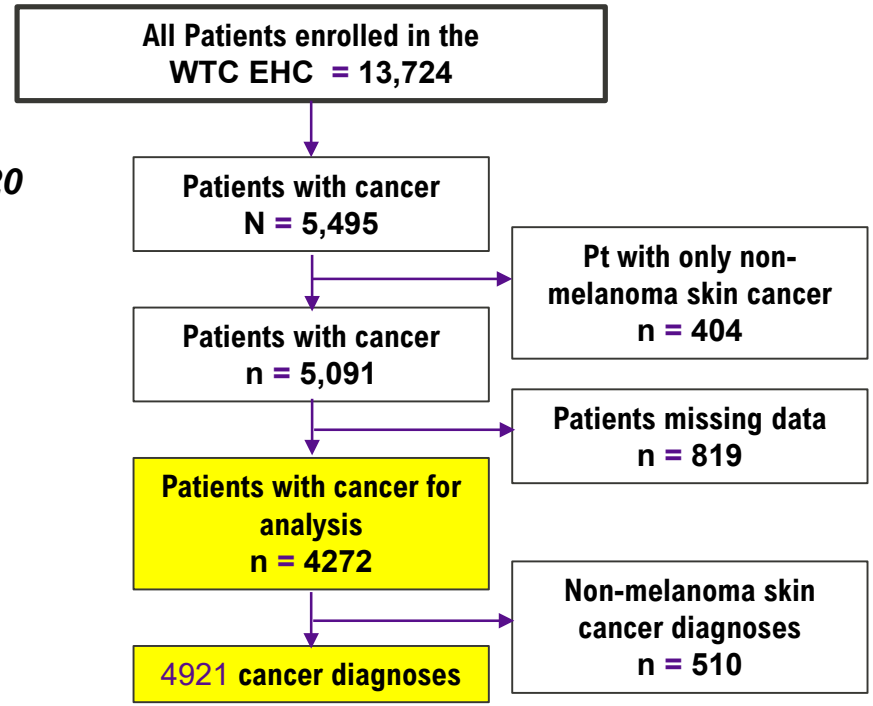
Overview of cancer patients in the WTC EHC (12/2022)

- We previously presented data on **2561** patients with cancer as of **12/2019**

  Durmus et al. *Int J Environ Res Public Health.* ***2020***

  Shao et al. *Int J Environ Res Public Health.* ***2021***

- **50%** increase in patients with cancer since **2019**
- We now report on **4921** patients with complete data *(excluding patients with non-melanoma skin cancer)*



Most common certified cancers in the WTC EHC (data as of 12/2022, excluding non-melanoma skin cancer)

- Breast cancer is the most common cancer (16 cases in men)
- Frequency distribution does not differ significantly from that reported in Durmus Int J Environ Res Public Health. 2020.
- Rare cancer - 5 cases of mesothelioma (3 peritoneal mesothelioma)

Demographic characteristics of the WTC EHC with and without cancer as of 12/2022

- 50% women
- 1% of those with cancer were less than 20 on 9/11
- 8% of those with cancer were less than 30 on 9/11
- Diverse race/ethnicity

		Non-Cancer	Cancer
n*		6,228	4,272
Sex, n (%)	F	3159 (51)	2048 (48)
	M	3069 (49)	2224 (52)
Age on 9/11 (years), median [IQR]		41.21 [33, 49]	45.94 [39, 53]
Race/Ethnicity, n (%)	Hispanic	1709 (28)	532 (13)
	NH-White	2416 (40)	2215 (53)
	NH-Black	1241 (20)	841 (20)
	Asian	700 (12)	567 (14)
	Native American	17 (0.3)	6 (0.1)
Education, n (%)	≤ High school	2007 (32)	1100 (26)
	> High school	4205 (68)	3165 (74)

*excludes those who did not sign consent and those with only non-melanoma skin cancer

Cancer risks in the WTC EHC

- Similar distribution of basic cancer risks of **BMI** with slight increase in tobacco use in those with cancer
- Nearly **50%** with acute exposure – similar in both groups
- Most exposed as local workers with many residents

		Non-Cancer	Cancer
BMI, kg/m2, median **[IQR])**		28 [24, 32]	28 [25, 32]
Tobacco pack-year, n (%)	**<5 p-y**	4804 (78)	3120 (74)
	>5 p-y	1328 (22)	1120 (26)
Dust cloud exposure, n (%)	**No**	2916 (47)	2165 (51)
	Yes	3259 (53)	2100 (49)
Type of Survivor, n (%)	Worker	3378 (54)	2817 (67)
	Resident	1441 (23)	1053 (25)
	Student	165 (3)	95 (2)
	Clean-up Worker	670 (11)	49 (1)
	Other	550 (9)	218 (5)

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Age at cancer diagnosis in patients in the WTC EHC

- Median age at diagnosis –58
- Most cancers diagnosed at ages 40-70

Age at cancer diagnosis (years), median [IQR]		58 [51,66]
Age at cancer diagnosis (years), n (%)		
	<20	3 (0.1)
	20-29	38 (1)
	30-39	202 (5)
	40-49	655 (17)
	50-59	1224 (32)
	60-69	1183 (31)
	70-79	439 (12)
	>=80	66 (2)

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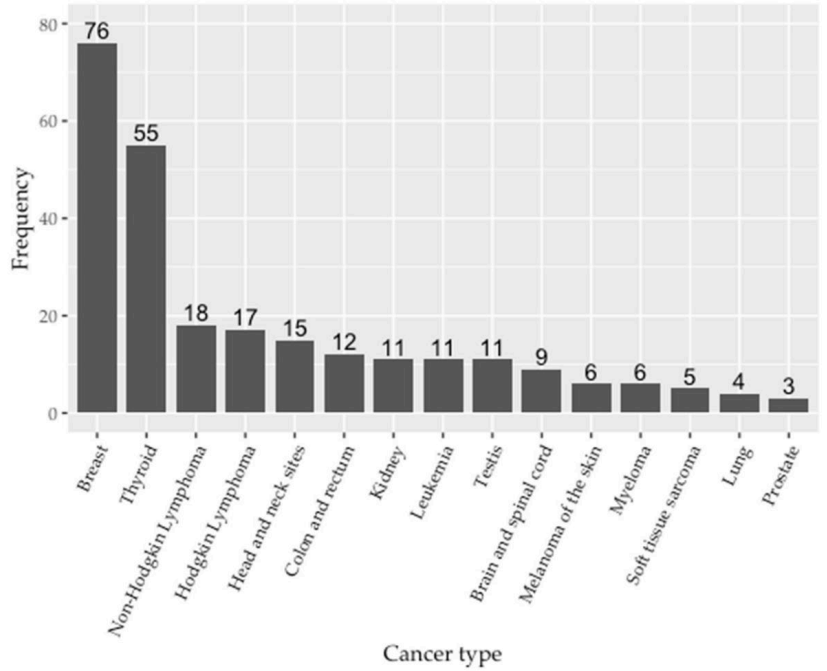
Breast cancer most common cancer in total population and in those exposed at a young age (≤30 years) (data as of 7/2021)



Florsheim et al. Int J Environ Res Public Health 2022

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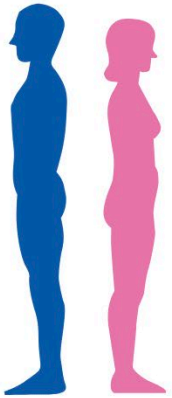
Cancer Stats in US population in 2023 by sex

Estimated New Cases

Males				Females		
Prostate	288,300	29%		Breast	297,790	31%
Lung & bronchus	117,550	12%		Lung & bronchus	120,790	13%
Colon & rectum	81,860	8%		Colon & rectum	71,160	8%
Urinary bladder	62,420	6%		Uterine corpus	66,200	7%
Melanoma of the skin	58,120	6%		Melanoma of the skin	39,490	4%
Kidney & renal pelvis	52,360	5%		Non-Hodgkin lymphoma	35,670	4%
Non-Hodgkin lymphoma	44,880	4%		Thyroid	31,180	3%
Oral cavity & pharynx	39,290	4%		Pancreas	30,920	3%
Leukemia	35,670	4%		Kidney & renal pelvis	29,440	3%
Pancreas	33,130	3%		Leukemia	23,940	3%
All Sites	**1,010,310**	**100%**		**All Sites**	**948,000**	**100%**



- **Breast cancer is most common newly diagnosed cancer in women in the US and in the WTC EHC (**Siegel et al. 2023**)**
- **Are there differences in the breast cancer characteristics in women in the WTC EHC?**

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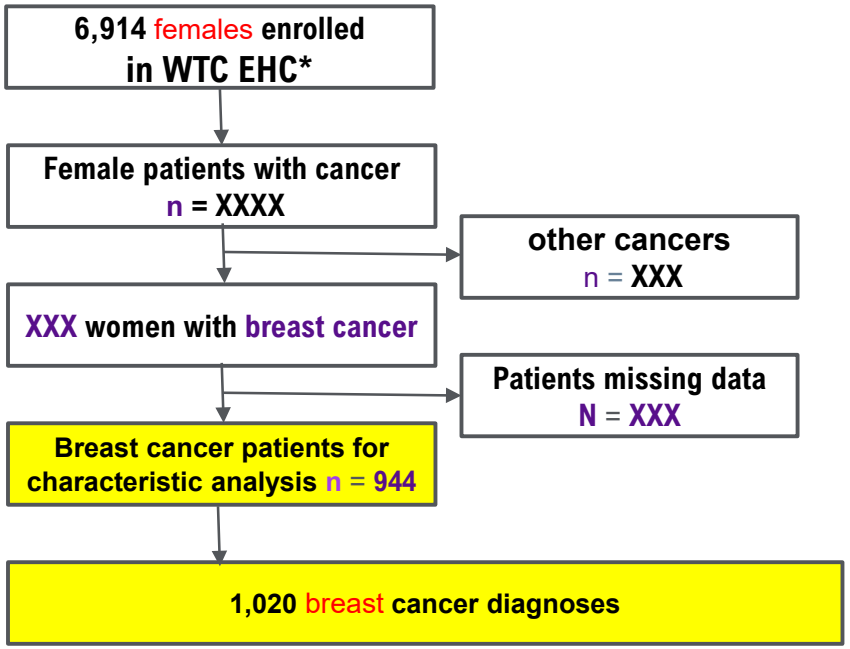
Breast cancer in women in the WTC EHC (12/2022)

- We previously reported on our women as of 2018 (Arslan et al. In J Environ Res Public Health 2021)
- Now report on patients as of 12/2022 with characteristics data
- XXX women enrolled in the WTC EHC
- XXX percent of these have certified breast cancer (ductal, lobular, mixed carcinomas)



*excludes those with incomplete data and those with only non-melanoma skin cancer

Characteristics of women with and without breast cancer the WTC EHC (data as of 12/2022)

- Median age on **9/11** was **42**
- High rates of Hispanic and **Black/African-American** women in both groups, with suggestion of fewer **Hispanic** women and more **Asian** women with Breast Cancer

		Non-Cancer	Breast Cancer
n		**3159**	**944**
Sex, n (%)	**F**	**3159 (100)**	**944 (100)**
Age on 9/11 (years), median [IQR]		**42 [34, 49]**	**43 [36, 51]**
Race/Ethnicity, n (%)	**Hispanic**	**867 (28)**	**137 (15)**
	NH-White	**1062 (35)**	**375 (41)**
	NH-Black	**829 (27)**	**258 (28)**
	Asian	**306 (10)**	**150 (16)**
	Native American	**10 (0.3)**	**0 (0.0)**
Education, n (%)	**≤High school**	**918 (29)**	**230 (24)**
	> High school	**2235 (71)**	**713 (76)**

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Cancer risk and exposure characteristics in women in the WTC EHC with / without breast cancer

- **No** differences in history of tobacco use or **BMI**
- **No** difference in acute dust cloud exposure
- **More** local worker women with Breast Cancer

		Non-Cancer	Breast Cancer
n		3159	944
BMI, kg/m2, median [IQR])		28 [24,32]	27.35 [24, 32]
Pack year, n (%)	<=5 p-y	2523 (81)	775 (83)
	>5 p-y	588 (19)	162 (17)
Dust cloud exposure, n (%)	No	1476 (47)	479 (51)
	Yes	1662 (53)	462 (49)
Type of community members, n (%)	Worker	1786 (57)	617 (66)
	Resident	759 (24)	251 (27)
	Student	95 (3)	29 (3)
	Clean-up worker	292 (10)	4 (0.4)
	Other	215 (7)	31 (3)

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Age of cancer diagnosis in women with breast cancer the WTC EHC *(data as of 12/2022)*

- **Median** age of breast cancer **dx** in the **WTC EHC** is **55**
- **No** difference in **age** of breast **cancer** diagnosis by race/ethnicity ***(data not shown)***

		Breast Cancer with IVQ
n		944
Age at cancer diagnosis (years), median [IQR]		55 [48,63]
Age at cancer diagnosis (years), n (%)	<20	0 (0.0)
	20-29	2 (0.2)
	30-39	57 (6)
	40-49	237 (25)
	50-59	329 (35)
	60-69	231 (25)
	70-79	76 (8)
	>=80	9 (1)

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Stage *(published data in yellow just included now for our interest)*

- **Most** patients diagnosed with **Stage 1 Breast cancer**

Stage (cancer 1) (%)	0		248 (19)
	I		637 (50)
	II		241 (19)
	III		51 (4)
	IV		14 (1)
	Unknown		95 (7)

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Grade of breast cancer in women in the WTC EHC

- Most patients with moderately differentiated Breast cancer
- Large number with poorly differentiated *(poorer prognosis)*

Grade (cancer 1) (%)	**G1.** Well-differentiated	**171 (13)**
	G2. Moderately differentiated	**516 (40)**
	G3. Poorly differentiated	**371 (29)**
	G4. Undifferentiated	**2 (0.2)**
	GX. Grade of differentiation cannot be assessed	**36 (3)**
	Unknown	**190 (15)**

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Molecular characterization of breast cancer

	ER	PR	Her2	SEER % 2020*	WTC EHC n (%)
Luminal A (Group 1)	pos	pos	neg	82.2	578 (45)
Luminal B (Group 2)	pos	neg	pos	12.6	118 (9)
Her2 (Group 3)	neg	neg	pos	5.1	39 (3)
Group 4 (basal-like)	neg	neg	neg	13.2	114 (8.9)
Unknown				7	287 (22)
Luminal/ missingHer2					150 (11.7)

- **Molecular characterization of breast cancer using 4 major subtypes described in the literature, important for therapy – chemotherapy, hormonal therapy, therapy targeting Her2 receptor**

*https://seer.cancer.gov/statfacts/html/breast-subtypes.html

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Genome-wide methylation profiles of WTC breast cancer cases and WTC unexposed breast cancer cases

- Increase in global **DNA** hypermethylation
- Some of the top differentially methylated genes previously implicated in breast cancer
- Promoters of several known tumor suppressor genes all hypermethylated *(associated with gene silencing)* in **WTC-exposed BC** cases compared to unexposed.
- Gene pathways enrichment analysis - potential upregulation of several immune and cancer-related pathways in **WTC-exposed** breast cancer cases compared to the unexposed group, including viral carcinogenesis, **T** cell receptor signaling, and the **B** cell receptor signaling pathways.

Tuminello et al. Int J Environ Res Public Health. 2022

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Summary

- As cancer case enrollment increases in the **WTC Health Program**, the **WTC EHC Pan-Cancer Database** serves as a potential resource for studies of cancer characteristics in the **WTC** Survivor population, including ***"virtual biobank."***
- In contrast to the Responder populations, breast cancer is the most common cancer in the **WTC EHC**, consistent with the large number of women in the program
- Age of diagnosis of breast cancer is younger than expected in patients in the **WTC EHC**
- Early analyses suggest differences in breast cancer characteristics including more advanced grade and molecular subtype
- Pilot genome-wide methylation studies of blood samples suggest differences compared to non-**WTC**-exposed breast cancers

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Conclusion

- Data from the **WTC** **EHC Pan-Cancer** database begin to suggest differences in cancer behaviors in **WTC** exposed Survivors compared to the general population. These differences may have implications for cancer screening and support recent draft revisions in **U.S.P.T.F** for breast cancer screening reducing the screening age to **40**.

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Yongzhao Shao **Ph.D.**

Nedim Durmus **MD**

Alan Arslan **MD**

Yuyan Wang **MS**

Qiao Zhang **MS**

Yian Zhang **Ph.D.**

Sultan Pehlivan **MD**

Stephanie Tuminello **MS**

Maria Elena Fernandez Beros

Guy Frazier

Michele Hyde

Sharon Abbott

Ramazan Alptekin **MD**

Muhammed Yilmaz **MD**

Sefa Keserci **MD**

Community organizations
WTC EHC Steering Committee

NYC HEALTH+ HOSPITALS

Cognitive Function among WTC-Exposed Community Members with Mental Health Symptoms

Rebecca Rosen, Ph.D.

Director of Mental Health

WTC EHC Clinical Center of Excellence

H+H: Bellevue, Gouverneur, Elmhurst

Clinical Associate Professor of Psychiatry

Grossman School of Medicine | June 28, 2023

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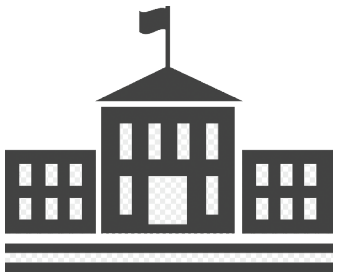

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Cognitive Function among WTC-Exposed Community Members with Mental Health Symptoms

Rebecca Rosen, Ph.D.

Director of Mental Health

WTC EHC Clinical Center of Excellence

H+H: Bellevue, Gouverneur, Elmhurst

Clinical Associate Professor of Psychiatry

Grossman School of Medicine | June 28, 2023

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Study and Goals of Talk

R. Rosen, Y. Shao, Q. Zhang, J. Bao, Y. Zhang, A. Masurkar, T. Wisniewski, N. Urban and J. Reibman; International Journal of Environmental Research and Public Health, March 2022

- **Describe study and its findings**
- **Discuss impact and where we go from here**

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Why Study Cognitive Functioning in Survivor Cohort

- **Cognitive impairment *(CI)*** has been extensively described and found to be associated with psychopathology and toxic exposure in:
  - **First Responder cohort** *(e.g., Clouston, et al, 2022; Huang et al, 2021; Kritikos et al, 2021)*
  - **Other populations** *(e.g., Richard et al, 2013; Patel et al, 2021)*
- **Cognitive functioning in Survivors not yet systematically described using objective measures.**
  - **Self reported memory loss/confusion studies on Registry population** *(Alper et al, 2020 and Seil et al, 2019)*

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Cognitive impairment in the WTC EHC

- Little is known about **cognitive** functioning the **Survivor** population
- Many patient **complaints** and **worries** about memory

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Study Goals

- Describe **cognitive** status in subgroup of **Survivor** cohort referred for mental health evaluation **(N-480)**
- Examine association of **cognitive** status with **WTC** exposures and covariates such as **psychopathology** screener **scores** and **demographics**

Methods

Inclusion criteria

- Signed consent for analysis
- Med/MH IV/MV between 8/2012 – 12/2018
- Diagnostic evaluation with MoCA administration

Measures - Administered at Screening (IV) and Monitoring (MV):

- Standardized, multi-dimensional interviewer administered questionnaires on: **9/11** Exposures, Medical symptoms, MH symptoms

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Standardized evaluations-Initial (IV), Surveillance (MV)

Physical health evaluation

- Physical exam, pulmonary function tests, bloodwork
- Standardized questionnaire with demographic, physical symptom and exposure questions

Mental health evaluations

- **PCL 17: PCL+ = ≥ 44** *("Probable PTSD" or "PCL+" or "PTSD")*
- Hopkins Symptom Checklist for ***depression/anxiety: ≥ 1.75 ("Probable Depression/Anxiety" or "depression" / "anxiety")***
- **CAGE –** for lifetime alcohol – score of **2** positive

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Inclusion criteria – Diagnostic Evaluation

Diagnostic evaluation with MoCA administration

- Administered at **MH** diagnostic evaluation:
  - **PCL 17**
  - **PHQ-9: none (0-4), mild (5-9), moderate (10 – 14), mod-severe (15-19), severe (20-27)**
  - **Montreal Cognitive Assessment**
    - **MoCA≥ 26** probable unimpaired cognition
    - **MoCA 26** probable cognitive impairment ***(CI without probable now)***

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Reason for Evaluation

- **People** who had elevated scores on **PTSD, dep,** and **anxiety during monitoring** who agreed to be evaluated**.**
  - **Interested in treatment**
  - **Interested in certification only**

- **Self** referred
- **WTC EHC** Clinician referred

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Salient Demographic Characteristics

Demographic characteristics, n (%)	Total (N= 480)
FEMALE Gender	259 (54)
AGE (Median)	56.4
HISPANIC Race/ethnicity	170 (35)
NON-HISPANIC WHITE Race/ethnicity	187 (39)
SPANISH Language	80 (17)
>HIGH SCHOOL Education	346 (72)
≤$30k/YEAR Income	234 (49)
POSITIVE PCL-17	347 (72)
MODERATE–SEVERE DEPRESSION PHQ-9	333 (70)
WORKER Exposure Category	318 (66)
YES Dust Cloud	294 (61)

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Lower MoCA scores associated with:

Univariate regression

- Age, race/ethnicity, language associated with lower **MoCA** scores
- As is education, income *(not shown)*
- And **PCL** score

Demographic characteristics	MoCA≥ 26 (n=199)	MoCA<26 (n=281)	P-Value
Gender, n (%)			0.56
Female	111 (43)	148 (57)	
Male	88 (40)	133 (60)	
Age			**0.02**
Median	56.4	56.9	
Race/ethnicity, n (%)			**<0.001**
Hispanic	54 (32)	116 (68)	
Non-Hispanic white	104 (56)	83 (44)	
Non-Hispanic black	27(30)	64 (70)	
Asian	9 (45)	11 (55)	
Other	2 (40)	3 (60)	
Language, n (%)			**<0.001**
English	184 (46)	214 (54)	
Spanish	14 (17.5)	66 (82.5)	

Lower MoCA scores associated with:

Univariate regression

….PCL score

Demographic characteristics	MoCA≥ 26 (n=199)	MoCA<26 (n=281)	P-Value
PCL-17, n (%)			0.35
Negative	53 (45)	64 (55)	
Positive	138 (40)	209 (60)	
PCL-17 score			0.01
Median	50	55	
PHQ-9, n (%)			0.36
None (0-4)	13 (37)	22 (63)	
Mild (5-9)	48 (46)	56 (54)	
Moderate (10-14)	50 (40)	75 (60)	
Mod. Severe (15-19)	55 (45)	68 (55)	
Severe (20-27)	28 (33)	57 (67)	
PHQ-9			0.16
Median	13	14	

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Lower MoCA scores associated with:

Univariate regression

Exposure category and **Dust Cloud** exposure also associated with lower **MoCA** scores

Demographic characteristics	MoCA≥ 26 (n=199)	MoCA<26 (n=281)	P-Value
Exposure, n (%)			<0.001
Worker	124 (39)	194 (61)	
Resident	54 (61)	35 (39)	
Clean-Up Worker	6 (15)	33 (85)	
Other	15 (45)	18 (55)	
Dust Cloud, n (%)			0.03
No	87 (48)	96 (52)	
Yes	109 (37)	185 (63)	

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Multivariate logistic regression on status of MoCA <26

	Odds Ratio	2.5%	97.5%	P-Value
Age	1.04	1.02	1.06	0.001
Race				
Asian	2.38	0.83	6.88	0.11
Hispanic	1.80	1.01	3.19	0.05
NH-Black	3.08	1.68	5.68	0.000
Other	2.36	0.36	15.29	0.37
NH-White (reference)	1.00			
Language				
Spanish	1.59	0.65	3.87	0.31
Education				
≤High school	2.01	1.12	3.63	0.02
Income				
≤$30k/year	1.76	1.12	2.77	0.01
PHQ 9	0.98	0.93	1.04	0.51
PCL	1.02	1.0	1.04	0.133
Exposure categories				
Worker	1.62	0.93	2.83	0.089
Clean up Worker	3.02	0.78	11.74	0.11
Other	1.40	0.53	3.66	0.50
Resident (reference)	1.00			
Dust Cloud Exposure				
Yes	1.59	1.01	2.49	0.04

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MH Symptoms as Mediator?

- **Singh et al, 2020:** Study of self reported cognitive complaints in Firefighters
  - PCL scores mediated the association between WTC exposures and subjective CI.
- **Survivors:** – perhaps mediation, but…
  - Dust cloud exposure seems to be independent risk factor for CI in the presence of PCL and PHQ-9 scores as potential mediators
  - WHY discrepant?
    - Used **MoCA** rather than self reported subjective **CI**
    - Exposure profiles are different
    - **HEALTH impact is different for Responders and Survivors** – Responders mostly healthy men of working age, survivors include women, children, elderly, any medical status
    - **Referral process –** enriched with **depression/PTSD**, potentially reducing the effect

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Summary

- **High** rates of probable **CI: 59%** of study population.
- **Associated** with age, race/ethnicity, education, income, depression and **PTSD**.
- **Caught** in dust cloud significantly associated with **CI** even after controlling for all of these.
- **Results** suggest association of cognitive disfunction with exposure to dust/fumes and psychological stress from attacks.

Limitations

- **No** unexposed comparison group
- **Other Variables:**
  - Pre and **Post 9/11** Trauma
  - Other med conditions, such as Respiratory Conditions
- **Selection bias:** Help seeking subgroup of help seeking population – unknown how representative of larger survivor population
- **No baseline** cognitive function

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Further study needed - Ageing cohort

- **20+** years after **9/11**, ageing cohort
- **Cognitive** decline increasing health concern
- **Average** age of **WTC EHC** patient: **63**
- **Therefore, Important to understand:**
  - **Rates**
  - **Risks**
  - **Mechanisms**
  - **Modifiable health conditions**

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Survivor Studies

- Consistent with existing studies of **WTC** Responders
  - Support hypothesis that the **WTC** dust toxins and the traumatic experience have had an adverse impact on cognitive function

- Need in-depth, systematic studies on cognitive status of **WTC** Survivors
  - Salient differences from the **General Responder** and **FDNY** populations

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Diverse Population

- Potentially different rates and risks of **CI** as the survivor population is:
  - **50%** female
  - Many races/ethnicities
  - Range of education and socio-economic status
  - Range of ages at time of **9/11**
  - Untrained for disasters/emergencies
- **Indeed**, in both univariate and multivariable analysis, age, race/ethnicity, low income and low education attainment remained associated with probable **CI**.
- This finding is consistent with current research in which these factors are associated with the presence of **CI** *(e.g., Perales-Puchalt et al, 2021; Koster et al, 2005)*
- Reinforces the need to include these factors in analysis of **CI** in an exposed race/ethnically diverse population.

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Exposures

- Potentially different rates and risks as the survivor population has different exposure profile, e.g., all ages, varying premorbid health status

  – Dust cloud significant in both univariate and multivariate analysis

  – Chronic exposure of residence – **24/7**: We found evidence that **WTC** chemicals from chronic exposures were more detectible in blood **12** years after 9/11 than chemicals from acute dust cloud exposures among affected children ***(Khan et al, 2018)***

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Medical Conditions/Medications

- Other variables can impact cognitive functioning
  - Comorbid respiratory symptoms – asthma *(e.g., Rosencranz et al., 2021)*
  - Neurological symptoms *(e.g., Marmor et al., 2020)*
  - Cardiovascular disease and diabetes *(e.g., Plassman et al, 2010)*
  - Genetic and epigenetic factors such as **ApoE** genotype known to modify risk/rate of cognitive decline; might impact probable **CI** via gene-environment interactions *(e.g., Chen et al., 2021)*
  - Medications *(van der Meulen et al., 2022)*

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Larger Survivor Cohort; Control Group

- **NON MH**-symptomatic survivors in **WTC EHC**:
  - Univariate analyses: significant association between **CI** and **MH** sx.
  - BUT high proportion of patients with elevated mental health scores due to the referral process.
- **NON 9/11** exposed group:
  - to compare the **CI** in this group with those of a non exposed, ageing cohort.

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Longitudinal; Objective Measures

- **Longitudinal study**
  - within patient change
  - is change consistent with other cohorts
- **Objective measures; neuropsychological instruments**

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Cognitive decline among WTC survivors with chronic mental and physical disorders

- **U01** Funded by the **CDC/NIOSH**
  - **NYU** Alzheimer's Disease Research Center:
    - Yongzhao Shao, **Ph.D.**
    - Thomas Wisniewski, **MD**
  - **WTC EHC**:
    - Joan Reibman, **MD**

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Aim 1

- Assess association of **WTC** exposures, mental health and physical health comorbid conditions and the rate of cognitive decline among **WTC EHC** Survivors.

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Aim 1

- **500** patients
- **Assessed 3** Separate occasions – **12-18** months time lag
- **"T-COG"** Telephone-based assessment
  - **t-MoCA (MOntreal Cognitive Assessment)**
  - Craft Story Recall
  - Number Span Forward and Backwards
  - Category Fluency
  - Verbal Fluency
  - Geriatric Depression Scale **(GDS)**
  - Clinical Dementia Rating Scale **(CDR)**
- Demographic questionnaire
- **PHQ-9**

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Aim 2

- Assess association of blood-based biomarkers with rate of cognitive decline among **WTC EHC** Survivors and compare with non-**WTC** exposed historical control data from **NYU ADRC (NYC data)** and Alzheimer's Disease Neuroimaging Initiative (**ADNI**; national data).

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Aim 2

- **240** patients
- **Assessed** in-person
  - Physical **Exam**
  - **Blood** samples for biomarkers: Inflammation and neurodegeneration in person assessment
  - **MoCA (MOntreal Cognitive Assessment),** Craft Story Recall, Number Span Forward and Backwards, Category Fluency, Verbal Fluency, Geriatric Depression Scale **(GDS),** Clinical Dementia Rating Scale **(CDR),** Demographic questionnaire, **PHQ-9**

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Summary

- The **WTC EHC** remains a program for surveillance and treatment of physical and mental health conditions.
- Initial data suggested high rates of **PTSD** symptoms with comorbid physical symptoms.
- **PTSD** symptom scores are associated with markers of inflammation **(CRP)** and **PTSD** mediates the association of the **WTC** cloud on inflammation.
- Persistent **PTSD** symptom scores are associated with lower respiratory symptoms and exposures.
- Measure of cognitive impairment associated with demographic characteristics, psychological distress and **WTC** dust cloud exposure.
- The **WTC EHC** serves as a resource to further our understanding of environmental, traumatic events and mental health symptoms.

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- **CDC/NIOSH** Contract 200 – 2017 – 93327 **HHC WTC** Data Center **CDC-NIOSH**
- **CDC/NIOSH** Contract 200 – 2017 – 93427 **HHC CCE**
- **1 U01 OH012486-01** Cognitive decline among **WTC** survivors with chronic mental and physical disorders

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Jia Bao, ***Ph.D.***

Yian Zhang, ***Ph.D.***

Yongzhao Shao, ***Ph.D.***

Joan Reibman, ***MD***

WTC EHC Clinical and Administrative staff

WTC EHC Research Staff

WTC EHC Data Center staff