Obstructive Sleep Apnea severity and Other Sleep Disorders Impact on Alzheimer's Disease

Omonigho Michael Bubu, MD, PhD, MPH

Associate Professor
Department of Psychiatry
Department of Population Health
NYU Grossman School of Medicine

NYU Langone Health

Disclosures

RESEARCH SUPPORT

- NIH/NIA K23AG068534 (PI: Bubu)
- NIH/NHLBI PRIDE: R25HL105444 Small Research Project (PI: Bubu)
- NIH/NIA CIRAD P30- AG059303 Pilot Grant (PI: Bubu)
- NIH/NIA NYU ADRC 1P30AG066512-01 Developmental Grant (PI: Bubu)
- American Academy of Sleep Medicine (AASM) Foundation Bridge to Success Award for Early Career Investigators (PI: Bubu)
- NIH/NIA R01AG056031 (PI: Osorio)
- NIH/NIA1R01AG056531 (MPI: Osorio, Jean-Louis)

OTHER GRANTS

- None

SPEAKERS BUREAU

- None

CONSULTANT

- None

STOCKS IN PHARMACEUTICAL COMPANY

- None

ADDITIONAL DISCLOSURE

- None

NYU Langone Health

Summary of Sleep and Alzheimer's Disease

Individuals with dementia have disturbed sleep

Multiple studies have associated numerous sleep parameters with AD pathology and/or future risk of cognitive impairment

Self Report

- Daytime sleepiness (Carvalho et al., 2018)
- Total sleep time (Tworoger et al., 2006; Spira et al., 2013)
- Sleep disorders (Sprecher et al., 2015)
- Sleep quality (Sprecher et al., 2017)

Objective Sleep Parameters

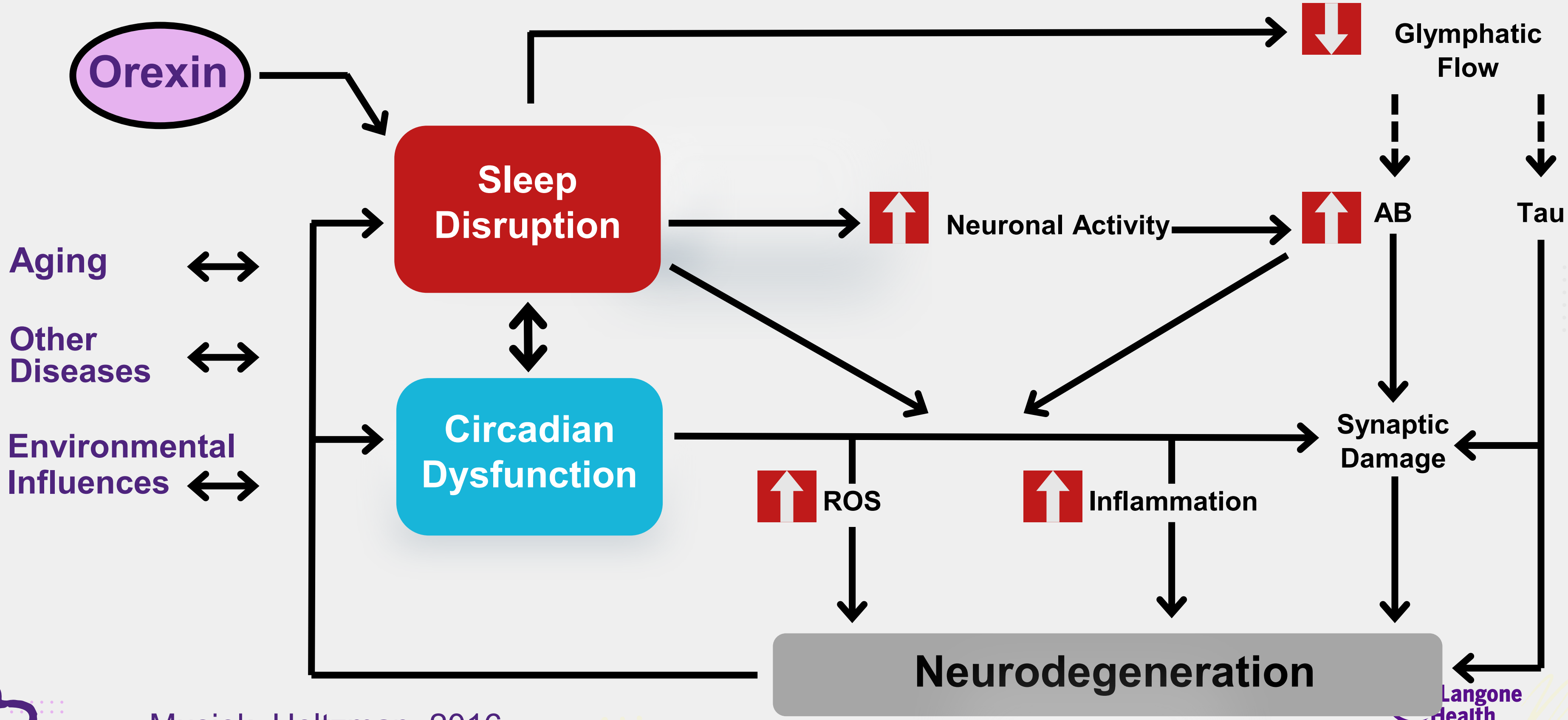
- Total sleep time (Blackwell et al., 2011)
- Sleep efficiency (Blackwell et al., 2006; Ju et al., 2013)
- Sleep onset latency (Brown et al., 2016; Branger et al., 2016)
- NREM slow wave activity (Mander et al., 2015; Lucey et al., 2019)

Sleep Disorders

- Sleep apnea (Yaffe et al., 2011)
- Periodic leg movements (Leng et al., 2016)

NYU Langone Health

Sleep and AD: Bidirectional Relationship



Musiek, Holtzman, 2016.

Langone Health

Circadian dysfunction and Risk of AD

TABLE 3: Associations Between Circadian Activity Rhythm Quartiles and Dementia and MCI*

	MCI (n = 302)	Dementia (n = 195)	MCI + Dementia (n = 497)
Amplitude (counts/minute)			
≥4194	1.00 (ref)	1.00 (ref)	1.00 (ref)
3588–4193	1.20 (0.80–1.81)	1.25 (0.77–2.02)	1.26 (0.89–1.78)
2984–3587	1.50 (1.00–2.25)	0.88 (0.53–1.45)	1.30 (0.91–1.85)
<2984	1.57 (1.02–2.42)	1.30 (0.80–2.12)	1.57 (1.09–2.25)
p value for continuous predictor	0.046	0.26	0.020
Mesor (counts/minute)			
≥2437	1.00 (ref)	1.00 (ref)	1.00 (ref)
2149–2436	1.08 (0.72–1.61)	1.01 (0.62–1.65)	1.05 (0.74–1.49)
1861–2148	1.43 (0.95–2.15)	1.14 (0.70–1.86)	1.39 (0.98–1.98)
<1861	1.51 (0.99–2.28)	1.14 (0.70–1.85)	1.42 (0.99 – 2.02)
p value for continuous predictor	0.08	0.94	0.11
Robustness (pseudo F-statistic)			
≥1152	1.00 (ref)	1.00 (ref)	1.00 (ref)
851–1151	1.20 (0.80–1.79)	1.70 (1.03–2.78)	1.39 (0.98–1.97)
595–850	1.31 (0.87–1.96)	1.27 (0.76–2.11)	1.32 (0.93–1.89)
<595	1.45 (0.96–2.20)	1.50 (0.90–2.48)	1.57 (1.10–2.26)
p-value for continuous predictor	0.30	0.32	0.13
Acrophase (hours)			
<1:34 PM	1.29 (0.87–1.94)	1.37 (0.86–2.19)	1.37 (0.97–1.93)
1:34 PM to 3:51 PM	1.00 (ref)	1.00 (ref)	1.00 (ref)
>3:51 PM	1.73 (1.15–2.60)	1.67 (1.07–2.61)	1.83 (1.29–2.61)

*Adjusted for age, clinic site, race, education, depression, body mass index, self-reported walking for exercise, number of IADL impairments, benzodiazepine use, antidepressant use, sleep medication use, alcohol use, caffeine intake, smoking, self-reported health status, hypertension, and history of medical conditions. Participants classified as having dementia are not included in models with MCI as the outcome. Odds ratios represent comparison of cognitively normal to MCI/dementia.
IADL = instrumental activities of daily living; MCI = mild cognitive impairment.

N=1282 older women
Cognitively normal
4.9 year f/u

Tranah GJ, et al., 2011

Fragmented 24 -hour activity rhythm may precede Aβ deposition (Nguyen Ho et al., *JAMA Neurol*, 2024)

Fragmented 24 -hour activity rhythms seem to disproportionately impact marginalized groups (Smagula et al., Sleep Health, 2024; Sauers et al., *SLEEP*, 2024)

Fragmented 24 -hour activity rhythms are associated with an increased risk of AD and cognitive decline (Winer et al., *Alzheimers Res Ther*, 2024)

Fragmented 24 -hour activity rhythms are associated with CSF and plasma biomarkers of AD in at -risk individuals (Baril et al., *Alzheimer Dement*, 2024)

Diurnal variation of plasma p -tau217 (Della Monica et al., *Transl Psychiatry*, 2024)

For p-tau217, the lowest levels were observed in the morning upon waking and the highest values in the afternoon/ early evening.

The magnitude of the diurnal variation for p-tau217 was similar to the reported increase in p-tau217 over one year in amyloid-β-positive mild cognitively impaired people.

- *Fragmented RAR may serve as a preclinical biomarker of early neurodegenerative processes and may be especially effective for marginalized groups*
- *A need to understand why relationships were stronger in APOE4 carriers*

JOURNAL ARTICLE

The role of actigraphy in detecting and characterizing the early phases of Alzheimer's disease

Joseph R Winer

Sleep, Volume 47, Issue 5, May 2024, zsae076, https://doi.org/10.1093/sleep/zsae076

Published: 18 March 2024 **Article history**

PDF Split View Cite Permissions Share

NYU Langone Health

OSA and Future Risk of Cognitive Impairment

Table 3. Mild Cognitive Impairment or Dementia Among Older Women According to Hypoxia, Sleep Fragmentation, or Sleep Duration Measures

	Mild Cognitive Impairment or Dementia, No. (%) (n = 107)	OR (95% CI) Unadjusted	Adjusted[a]
Hypoxia and Disordered Breathing Measures			
Oxygen desaturation index, events/h			
<15	46 (43.0)	1 [Reference]	1 [Reference]
≥15	60 (56.1)	1.67 (1.03-2.69)	1.71 (1.04-2.83)
Oxygen saturation <90%			
<1% of sleep time	64 (59.8)	1 [Reference]	1 [Reference]
≥1% of sleep time	43 (40.2)	0.87 (0.54-1.41)	0.83 (0.51-1.38)
Sleep time in apnea or hypopnea, %			
Low (median: 0.9 [range, 0-2.2])	31 (29.0)	1 [Reference]	1 [Reference]
Mid (median: 4.4 [range, 2.3-7.0])	31 (29.0)	1.00 (0.55-1.82)	1.16 (0.61-2.20)
High (median: 16.4 [range, 7.0-66.8])	45 (42.1)	1.79 (1.01-3.20)	2.04 (1.10-3.78)
Sleep Fragmentation Measures			
Arousal index, arousals/h			
Low (median: 10.1 [range, 2.4-14.5])	44 (41.1)	1 [Reference]	1 [Reference]
Mid (median: 18.2 [range, 14.6-22.6])	30 (28.0)	0.52 (0.29-0.94)	0.54 (0.29-0.98)
High (median: 33.1 [range, 22.6-66.4])	32 (29.9)	0.59 (0.34-1.06)	0.58 (0.32-1.07)
Wake after sleep onset, min			
Low (median: 40.7 [range, 2.0-61.0])	31 (29.0)	1 [Reference]	1 [Reference]
Mid (median: 82.0 [range, 62.0-105.0])	32 (29.9)	1.06 (0.58-1.94)	1.17 (0.63-2.19)
High (median: 170.6 [range, 108.0-336.0])	44 (41.1)	1.69 (0.95-3.02)	1.79 (0.97-3.29)
Sleep Duration Measure			
Total sleep time, min			
Low (median: 269.9 [range, 128.0-330.0])	41 (38.3)	1 [Reference]	1 [Reference]
Mid (median: 358.2 [range, 331.0-385.0])	29 (27.1)	0.56 (0.31-1.01)	0.58 (0.31-1.09)
High (median: 425.5 [range, 386.0-630.0])	37 (34.6)	0.83 (0.47-1.47)	0.83 (0.46-1.51)

Abbreviations: CI, confidence interval; OR, odds ratio.
[a] Adjusted for age, race, body mass index (calculated as weight in kilograms divided by height in meters squared), education level, smoking status, presence of diabetes, presence of hypertension, antidepressant use, benzodiazepine use, and use of nonbenzodiazepine anxiolytics.

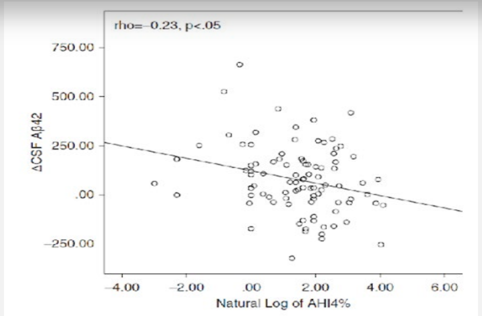
Initial N=298 older women
Cognitively normal
4 year f/u

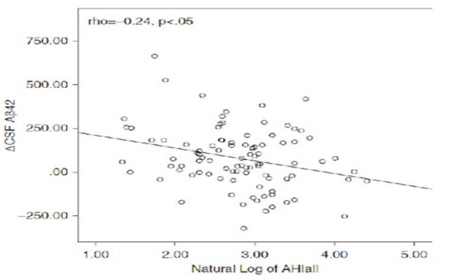
Yaffe K, et al., JAMA, 2011

Obstructive Sleep Apnea as a physiologic marker of AD pathology

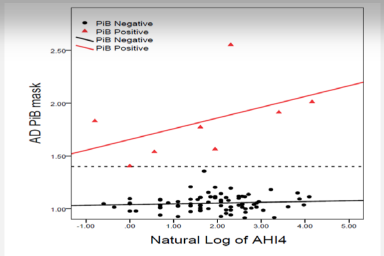
Obstructive Sleep Apnea Severity Affects Amyloid Burden in Cognitively Normal Elderly: A Longitudinal Study.

Relationship between longitudinal change in cerebrospinal (CSF) Aβ42 and the natural log of apnea hypopnea indices (AHIs) at baseline

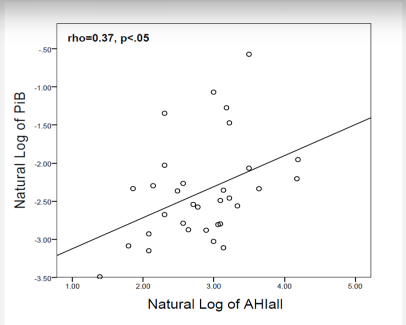




At cross-section, severity of OSA is associated with greater brain Aβ deposition in PB positive participants



Relationship between longitudinal change in AD PiB-mask and the apnea hypopnea indices (AHIs) at baseline.



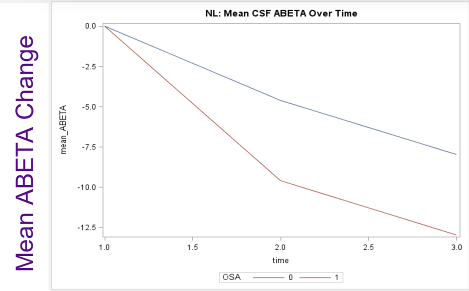
Sharma, Varga, **Bubu ….Osorio** 2017

NYU Langone Health

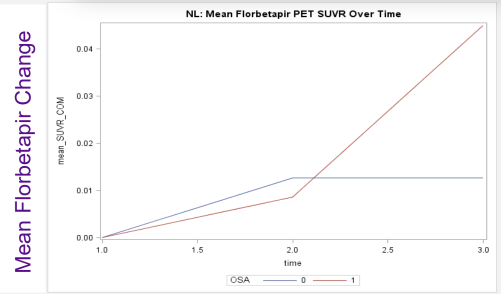
Obstructive Sleep Apnea and Longitudinal Alzheimer's Disease Biomarker Changes

Cognitively Normal (NL) OSA+ subjects had a faster rate of longitudinal decreases in CSF Aβ42 levels

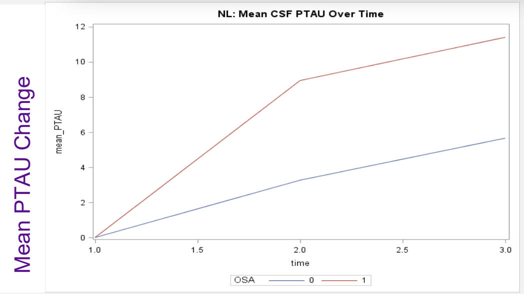
NL: Mean CSF ABETA Over Time



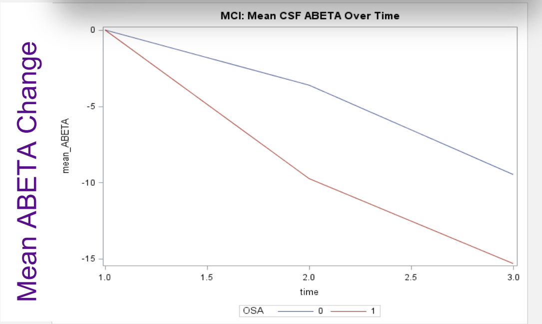
Cognitively Normal (NL) OSA+ subjects had a faster rate of longitudinal increases in florbetapir PET uptake



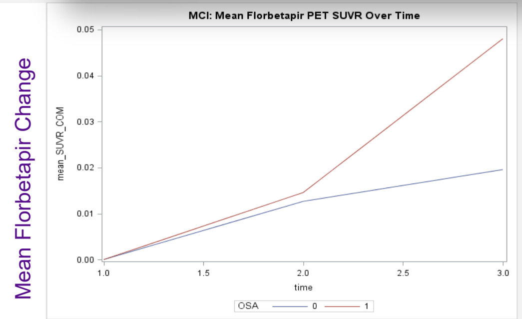
Cognitively Normal (NL) OSA+ subjects had a faster rate of longitudinal increases in CSF P-tau



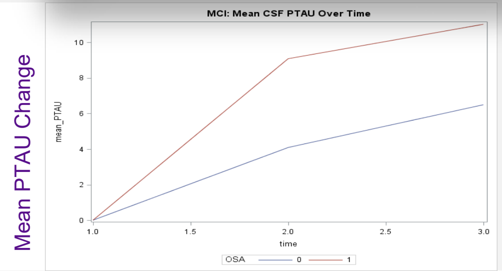
Mild Cognitive Impaired(MCI) OSA+ subjects had a faster rate of longitudinal decreases in CSF Aβ42 levels



Mild Cognitive Impaired(MCI) OSA+ subjects had a faster rate of longitudinal increases in florbetapir PET uptake



Mild Cognitive Impaired (MCI) OSA+ subjects had a faster rate of longitudinal increases in CSF P-tau



Bubu et al SLEEP 2019

NYU School of Medicine
NYU LANGONE MEDICAL CENTER

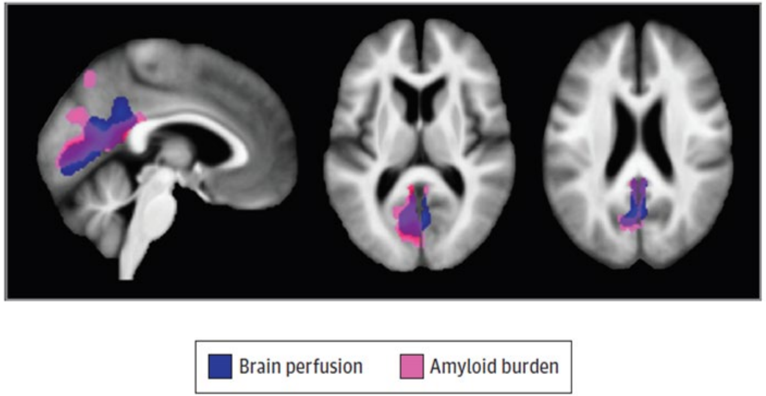
JAMA Neurology | Original Investigation

Association of Sleep-Disordered Breathing With Alzheimer Disease Biomarkers in Community-Dwelling Older Adults

A Secondary Analysis of a Randomized Clinical Trial

Claire André, PhD; Stéphane Rehel, MSc; Elizabeth Kuhn, MSc; Brigitte Landeau, MSc; Inès Moulinet, MSc;
Edelweiss Touron, MSc; Valentin Ourry, MSc; Gwendoline Le Du, MSc; Florence Mézenge, BA;
Clémence Tomadesso, PhD; Robin de Flores, PhD; Alexandre Bejanin, PhD; Siya Sherif, PhD; Nicolas Delcroix, PhD;
Alain Manrique, MD, PhD; Ahmed Abbas, PharmD; Natalie L. Marchant, PhD; Antoine Lutz, PhD;
Olga M. Klimecki, PhD; Fabienne Collette, PhD; Eider M. Arenaza-Urquijo, PhD; Géraldine Poisnel, PhD;
Denis Vivien, PhD; Françoise Bertran, MD; Vincent de la Sayette, MD; Gaël Chételat, PhD; Géraldine Rauchs, PhD;
for the Medit-Ageing Research Group

Figure 3. Overlap of Sleep-Disordered Breathing–Associated Brain Changes Across Neuroimaging Modalities

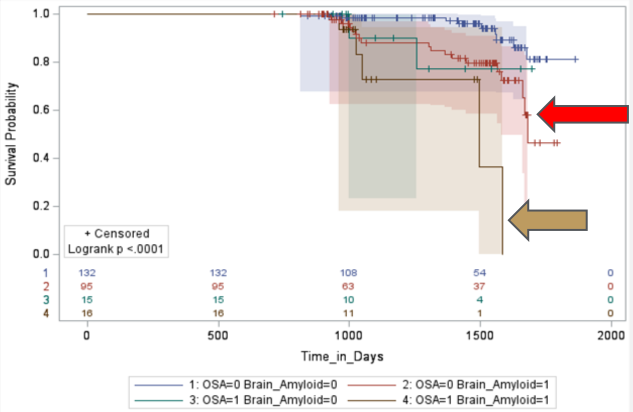


- Participants with SDB showed greater amyloid burden, gray matter volume, perfusion and metabolism overlapping mainly over the posterior cingulate cortex and precuneus.

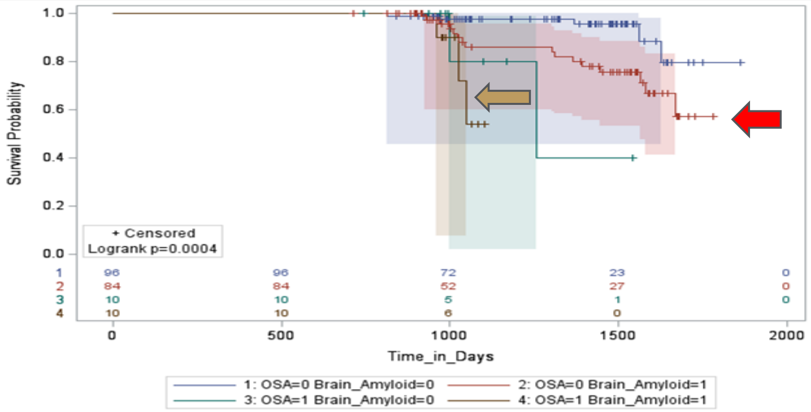
Obstructive Sleep Apnea as a modifier of AD risk

Bubu et al Alzheimer's & Dementia 2019

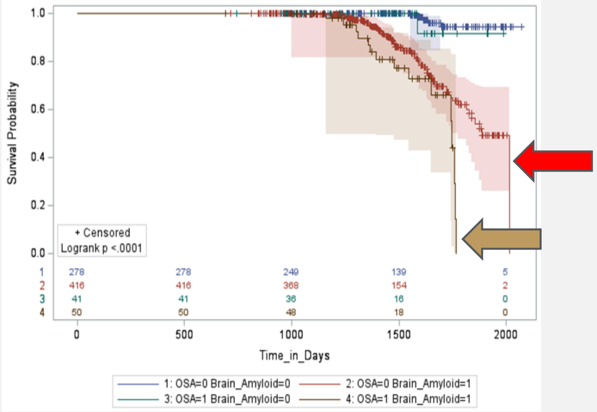
Kaplan–Meier Product Limit Survival Estimates and time-to-progression from NL to MCI (OSA & Aβ load PARTICIPANTS)



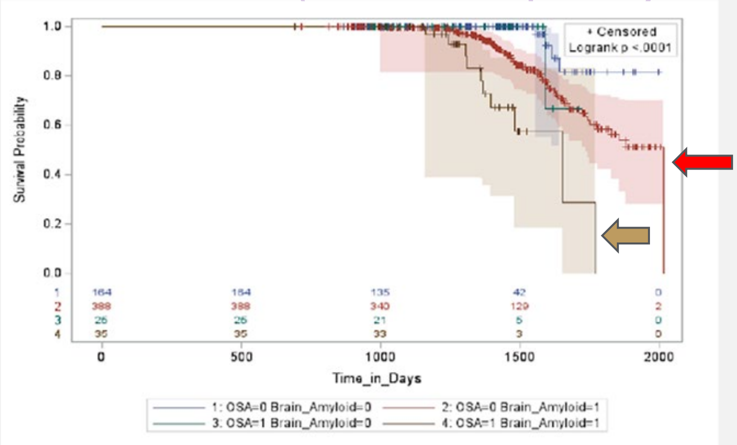
Kaplan–Meier Product Limit Survival Estimates and time-to-progression from NL to MCI (All TN+ Participants by OSA & Aβ load)



Kaplan–Meier Product Limit Survival Estimates and time-to-progression from MCI to AD (OSA & Aβ load PARTICIPANTS)

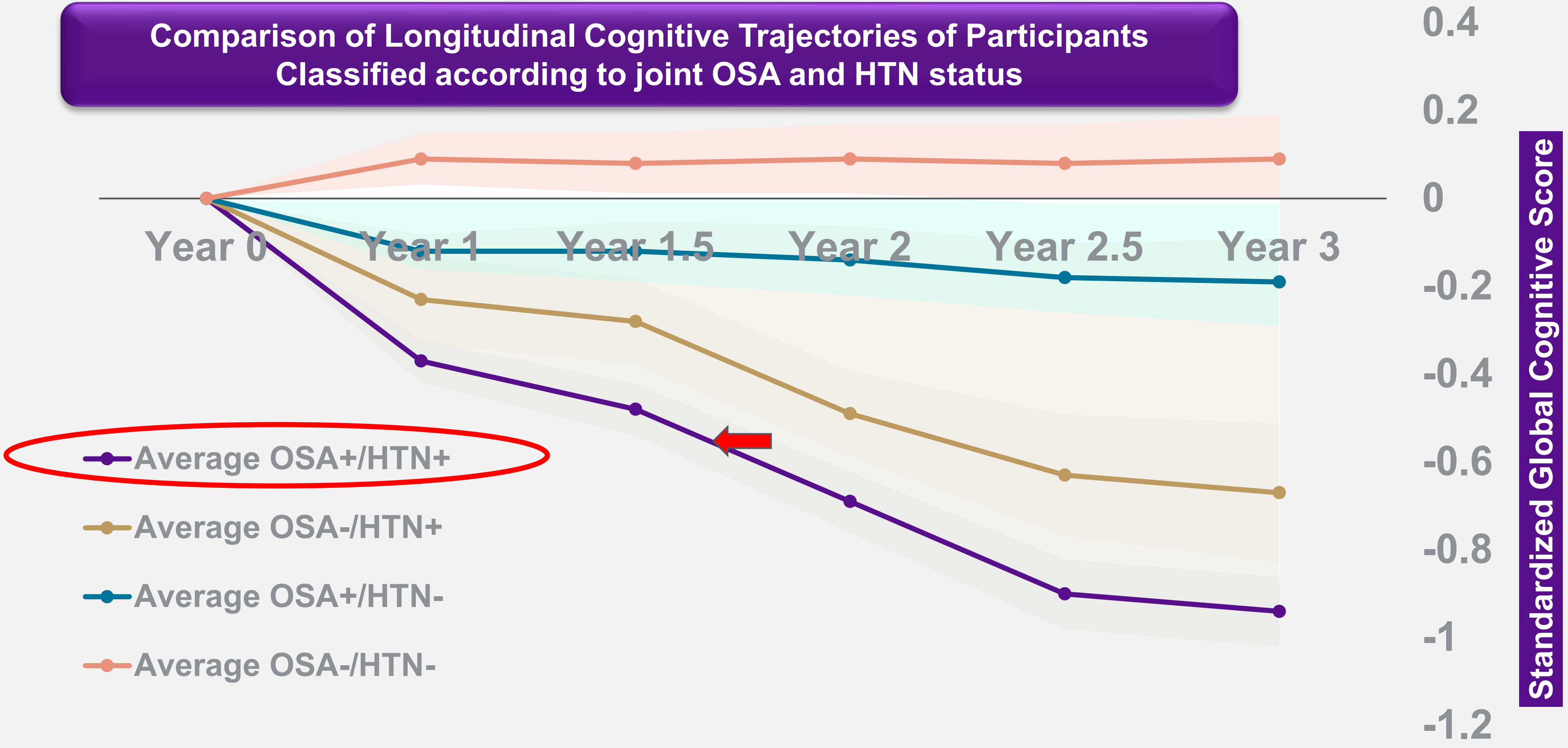


Kaplan–Meier Product Limit Survival Estimates and time-to-progression from MCI to AD (All TN+ Participants by OSA & Aβ load)



Bubu et al Am J Respir Crit Care Med. 2022

Comparison of Longitudinal Cognitive Trajectories of Participants Classified according to joint OSA and HTN status



NYU Langone Health

Interventions

Selective Orexin 2 Receptor Blockade Alleviates Cognitive Impairments and the Pathological Progression of Alzheimer's Disease in 3xTg-AD

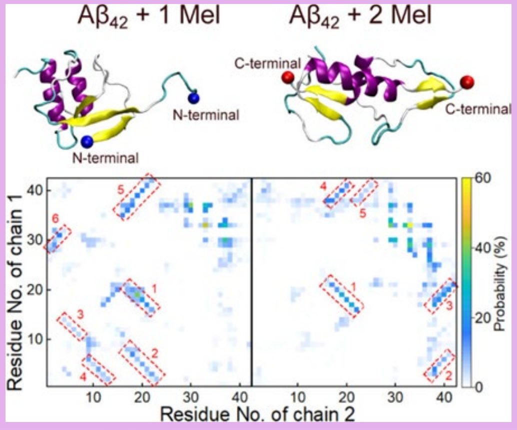
(Hu et al., J Gerontol A Biol Sci Med Sci, 2024)

- Suvorexant (DORA) improved cognitive deficits in APP/PS1 mice by reducing Aβ deposition, but DORA-22 showed no effect on working memory or Aβ plaque density in 5xFAD mice.
- DORAs may be inconsistent due to dual OX1R and OX2R blockade.
- Chronic OX1R blockade worsened cognitive function and synaptic plasticity in 3xTg-AD mice, increasing soluble Aβ oligomers and p-tau levels.
- **HERE**: Exogenous 2-SORA MK-1064 improved cognition, synaptic plasticity, and anxiety/ depression-like behaviors in 3xTg-AD mice.
- MK-1064 reduced Aβ/tau pathology and neuroinflammation, partly by restoring circadian rhythms, promoting sleep, and reducing wakefulness.

Structural Insight into Melatonin's Influence on the Conformation of Aβ42 Dimer Studied by Molecular Dynamics Simulation

(Kang et al., J Phys Chem B, 2024)

- Used computational simulations, found that conformation of Aβ42 dimer is dependent on melatonin levels.
- Oligomers with parallel β-sheets exhibit slower rates of fibril formation compared to the oligomers with antiparallel β-sheets
- In simulation with two melatonin molecules present, that the Aβ42 dimer adopts parallel β-sheet is expected to have slower rates of fibril formation.



Randomized-Controlled Trial Targeting Cognition in Early Alzheimer's Disease by Improving Sleep with Trazodone (REST)

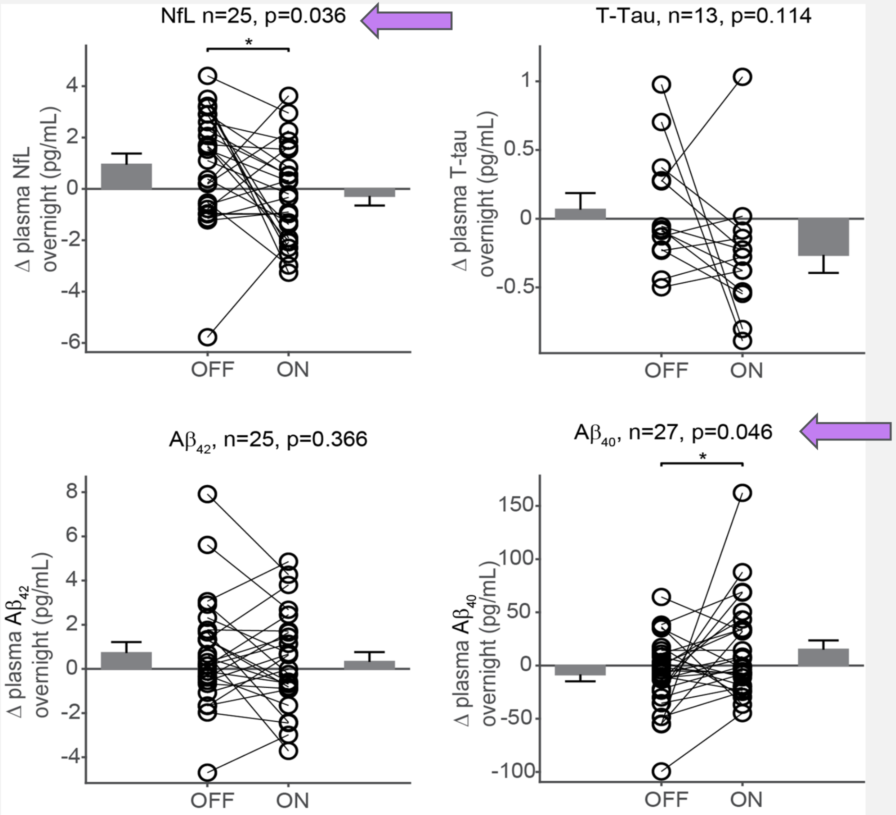
(Eyob et al., J Alzheimers Dis, 2024)

- Trazodone: safe and widely used among older adults
- Serotonin receptor antagonists and reuptake inhibitors (SARIs); not a true member of SSRIs class of antidepressants, but does share many properties of the SSRIs.
- Has shown promise in inducing slow wave sleep in older adults
- Trial to understand its effects on sleep and cognition in the prodromal stages of AD (100 older adults with amnestic MCI and sleep complaints)

NYU Langone Health

Acute OSA induction resulted in an evening-to-morning increase in plasma NfL and decrease in Aβ40.

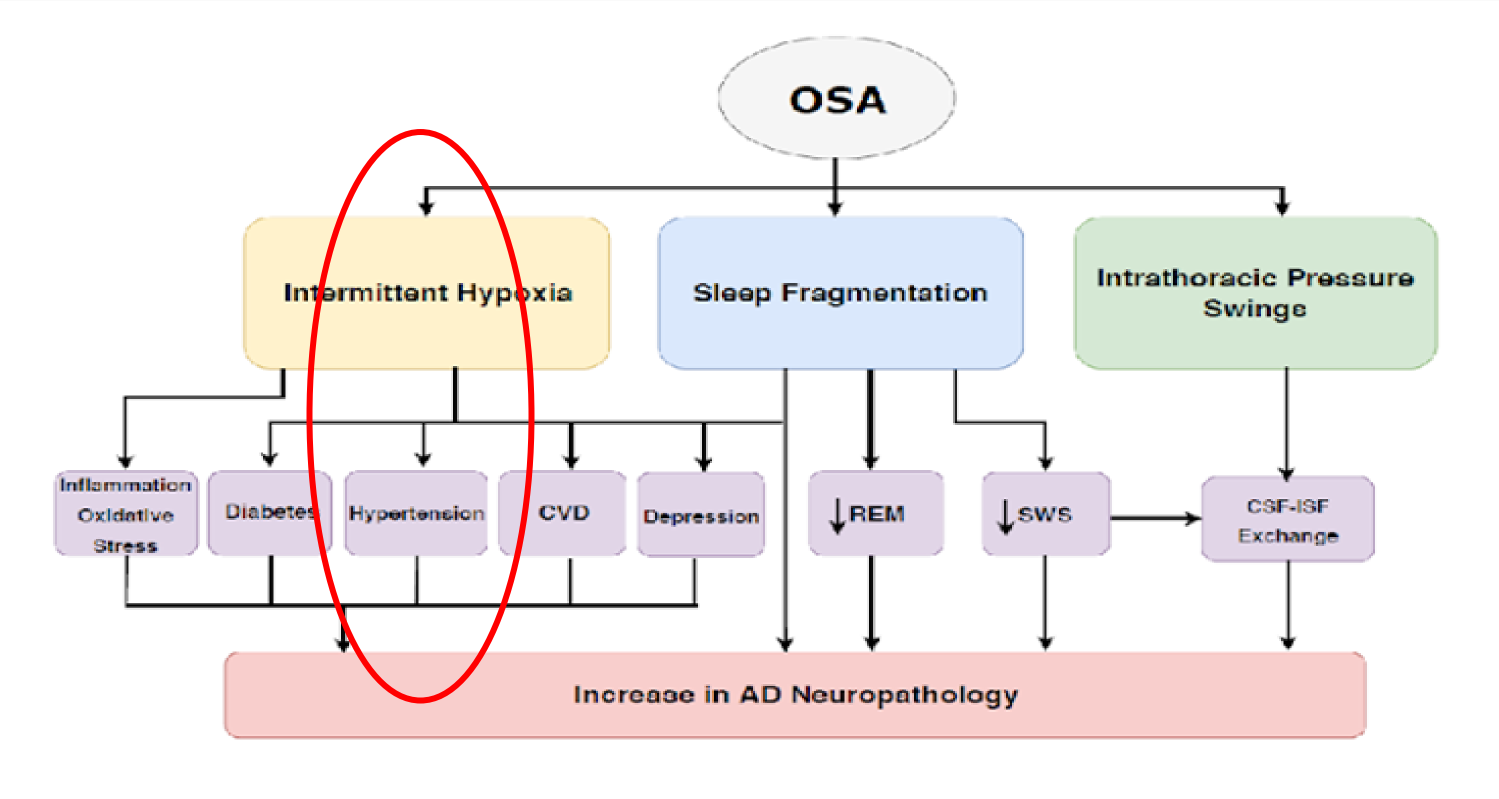
- We analyzed blood collected in the evening (10:40 pm) and next morning (6:40 am) across a night of NPSG recorded sleep
- 30 individuals with severe OSA during conditions of therapeutic PAP or the third consecutive night off PAP (acute withdrawal) in a counterbalanced fashion.
- Participants were 51.5 years old (95% CI, 47.3-55.6), 27% women, and 67% non-Hispanic white.



Kam, Jun, Parekh, Bubu et al Am J Respir Crit Care Med. 2022

NYU Langone Health

Figure : Proposed Mechanisms Linking OSA with Amyloid Deposition in Late-life



Andrade, Bubu et al JAD 2019

NYU Langone Health

Acknowledgements

Author Block:

- Bubu OM
- Mbah AK
- Debure L
- Williams NJ
- de Leon M
- Jean-Louis G
- Osario RS

Funding:

- NIH/NIA 1K23 AG068534
- NIH/NIA 1P30AG066512-01 Developmental Grant
- NIH/NIA CIRAD P30- AG059303 PILOT GRANT
- NIH/NHLBI R25HL105444 Small Research Project
- NIH/NIA R01AG056031
- NIH/NIA1R01AG056531
- NIH/NHLBI R01HL118624
- NIH/NIA K07AG052685
- AASM Foundation #231-BS-20

NYU Langone Health

NYU School of Medicine

Icahn School of Medicine at Mount Sinai

Acknowledgements

Ricardo S. Osorio
MD MS

Olugbenga Ogedegbe
MD MPH

Indu Ayappa
PhD

NYU Sleep Health
Disparity Team

Girardin Jean-Louis
PhD

David Rapoport
MD

Mony de Leon
PhD

Andrew Varga
MD PhD

NYU Langone Health

THANK YOU

FOR YOUR ATTENTION