Sleep Clues to Alzheimer's Disease

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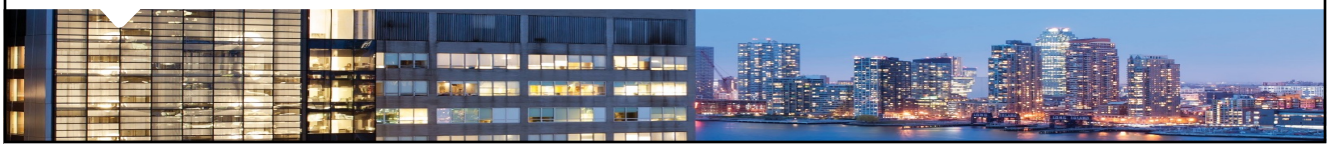

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- Consultant: None
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- Additional disclosure: None

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Objectives

- Providing an update on putative mechanisms that underlie the association between disrupted sleep-wake rhythms and risk of developing Alzheimer's disease (AD), both from a mechanistic (primarily preclinical/genetic) as well as a clinical/epidemiological perspective.
- This presentation will include evidence implicating obstructive sleep apnea (OSA) as a risk factor for AD.
- Evidence showing OSA's independent and synergistic effects with Aβ and/or tau, as well as vascular risk (hypertension), that can combine to significantly increase AD pathology and progression risk will be presented

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Overview

- Brief Definition of Sleep
- Sleep Physiology Primer
- Sleep in Normal Aging
- Sleep disturbances in AD
- AD Primer/Regional Nature of AD & AD related Sleep pathophysiology
- Sleep disruptions worsens AD pathology
- Sleep as a marker of AD pathology
- Obstructive sleep apnea as a risk factor and modifier of AD risk
- Conclusion and Summary

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Brief definition of sleep

- Sleep is a complex physiological state characterized by reduced or absent consciousness, relatively suspended sensory activity, and inactivity of nearly all voluntary muscles
- Two types of sleep exist, non-rapid eye movement (NREM) sleep which is divided into stages 1, 2, and 3/4, representing a continuum of relative depth, and rapid eye movement (REM) sleep
- NREM and REM sleep both have unique characteristics including variations in brain wave patterns, eye movements, and muscle tone
- Sleep architecture (i.e. basic structural organization of normal sleep) and Sleep efficiency (i.e. how sleep is initiated and maintained), varies continuously and considerably with age

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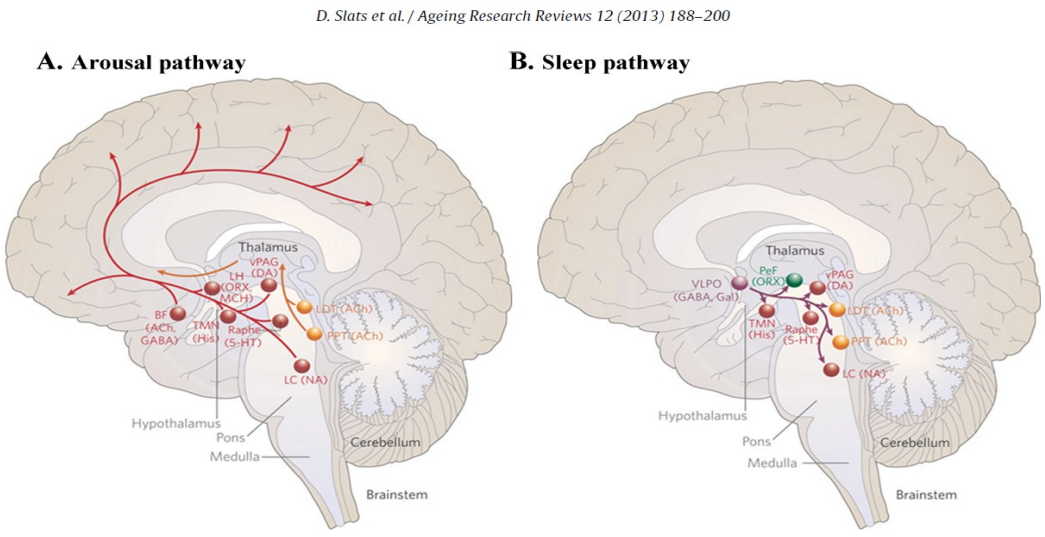
Sleep Physiology



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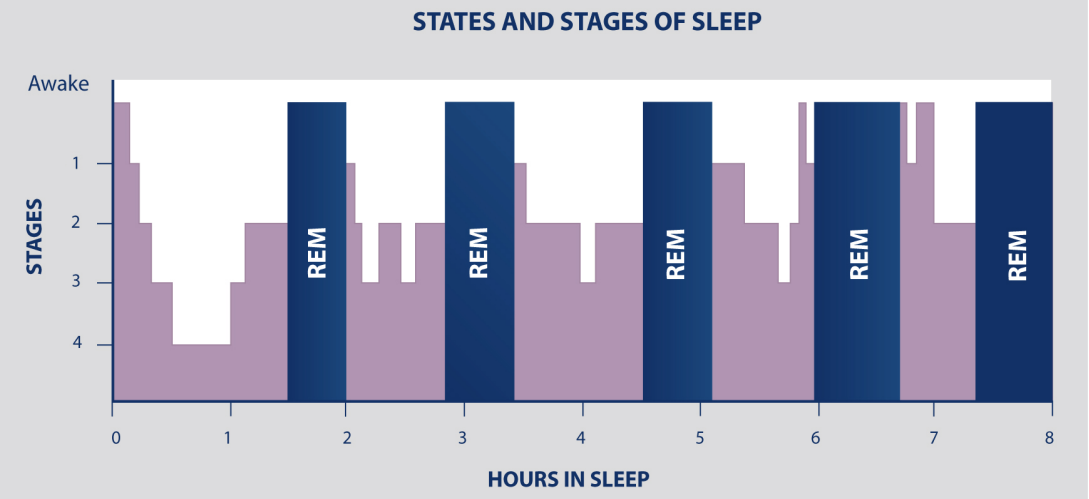
The Sleep Cycle in Adults:



Healthy Brain Aging

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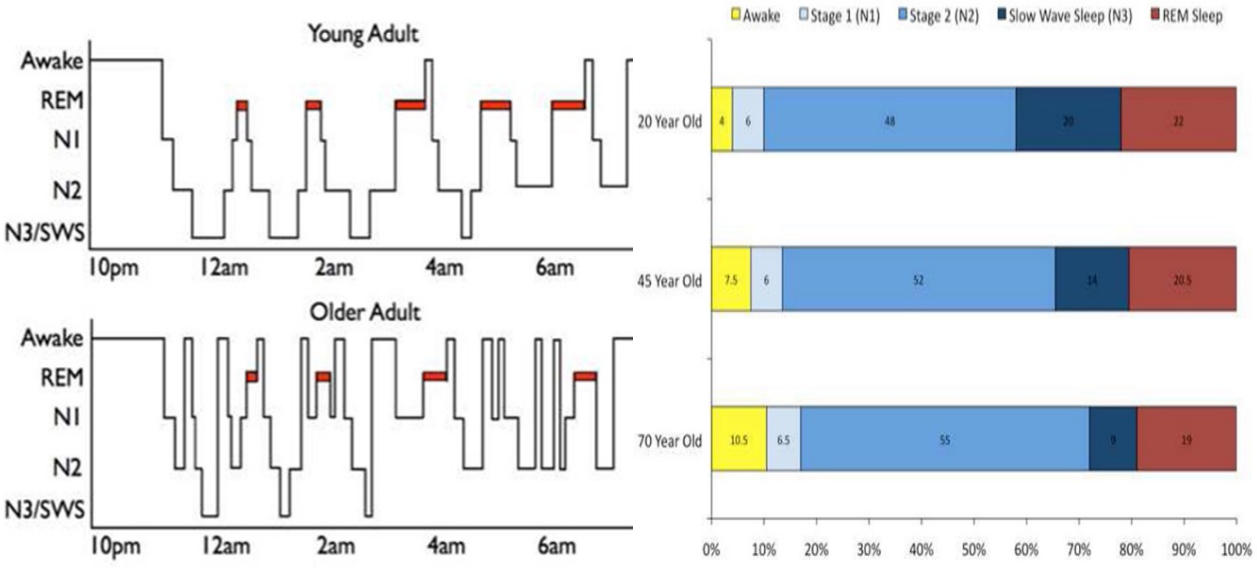
Age related changes in sleep



Scullin MK. Perspect Psychol Sci. 2015 Jan; 10(1): 97–137

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Impaired Sleep Physiology in & Sleep disturbances associated with AD

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Impaired Sleep Physiology in AD

- Several anatomical elements of the AAS are affected in AD, including the nucleus basalis of Meynert in the basal forebrain, the thalamus, and several nuclei in the brainstem; the locus coeruleus, the upper raphe nuclei, and the tegmentopontine reticular nuclei.
- The thalamus itself, which is thought to be involved in arousal, is severely affected in AD as well; neurofibrillary changes occur in the anteroventral nucleus of the thalamus
- The impairments in the locus coeruleus, the tegmentopontine reticular nuclei, and regions of superior and dorsal brainstem may lead to failing motor inhibition during REM, causing REM Behavior Disorder (RBD)
- Post-mortem hypothalami of AD patients and controls demonstrated a significant decrease in the number of hypocretin-1 immunoreactive neurons
- Total melatonin levels decrease during aging but patients with AD show more profound reductions

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Sleep disturbances associated with AD

- Sleep architecture alterations
- Sleep-wake cycle alteration

Sleep disorders & AD

- Sleep-related breathing disorders
- Circadian rhythm disturbances in AD
- Restless legs syndrome
- Other primary sleep disorders

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AD pathophysiology & 3 AD-related sleep deficits are local or regional

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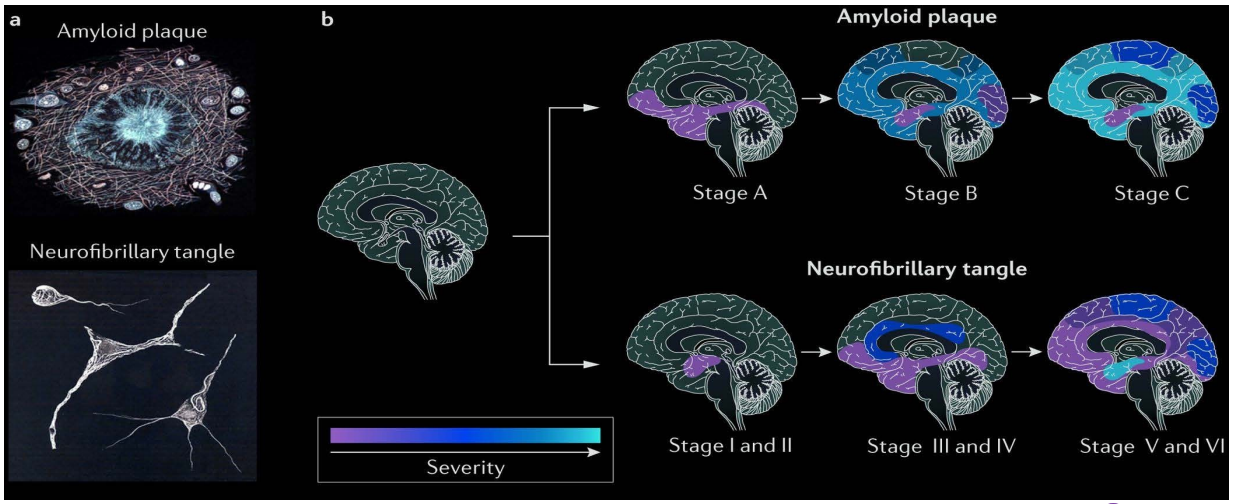
AD pathophysiology is regional

Defining AD pathologies | **Regional deposition changes with disease severity**



Masters et al, 2015

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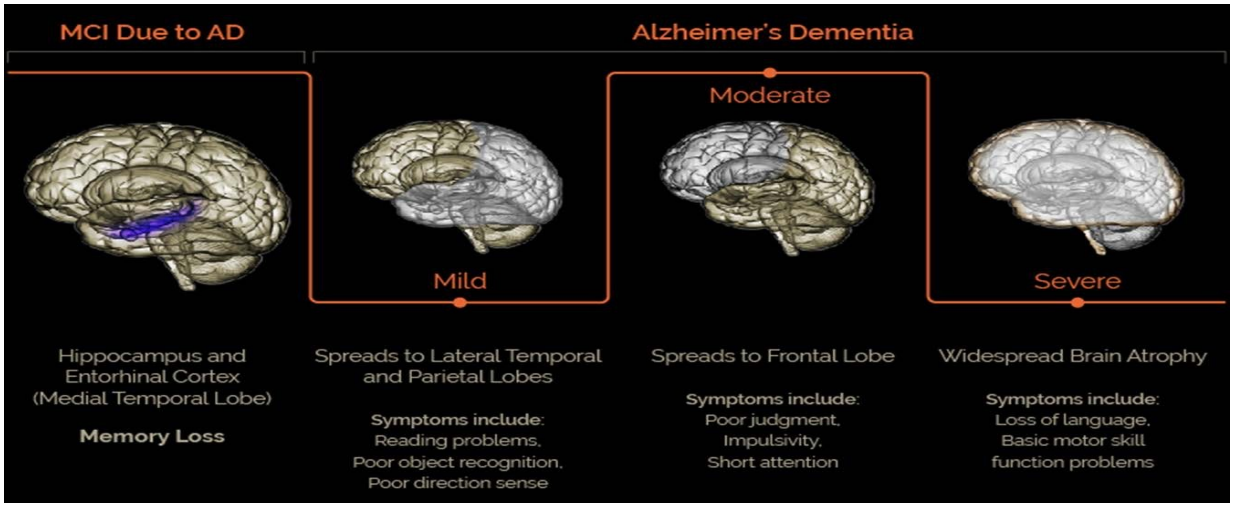
AD pathophysiology is regional



Aβ and tau deposition triggers regionally-specific trajectory of neurodegeneration that predicts the trajectory of cognitive decline

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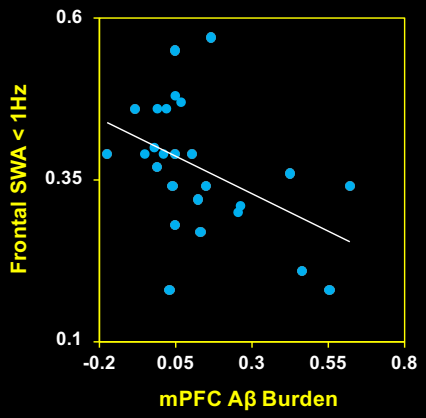
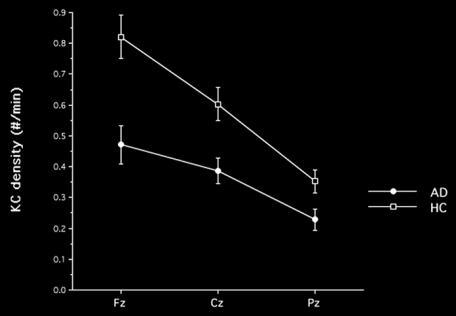
3 AD-related sleep deficits are local, too

1) Frontal Slow waves/K-complexes

Healthy Older Adult Controls



AD patients vs Healthy Controls



Mander et al, 2015;
De Gennaro et al, 2017

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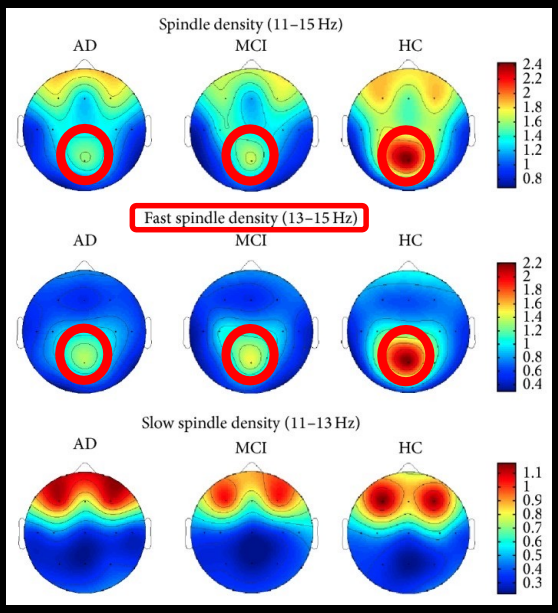
3 AD-related sleep deficits are local, too

2) Posterior fast sleep spindles



AD & MCI patients: fewer parietal fast sleep spindles (13-15Hz)

Gorgoni et al, 2016

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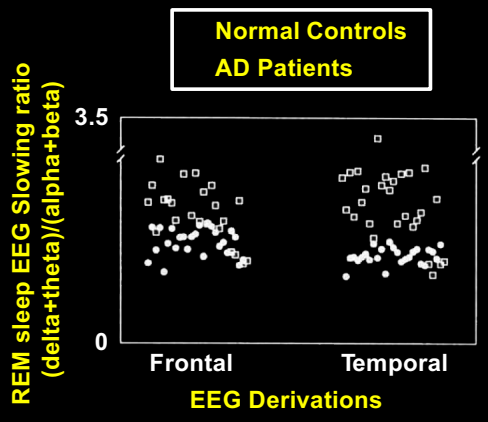
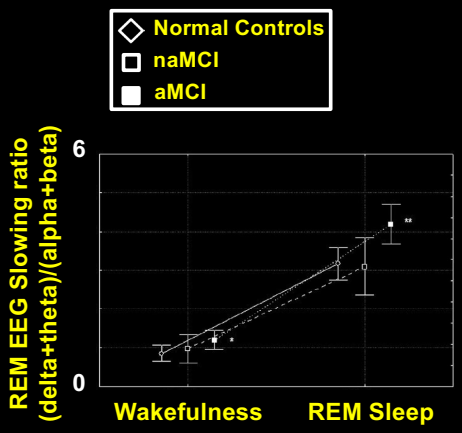
3 AD-related sleep deficits are local, too

3) Frontal-Temporal REM sleep EEG desynchrony





Discrimination Analysis
Accuracy: 90.4%
Sensitivity: 81.5%
Specificity: 100%

Hassainia et al, 1997;
Brayet et al, 2015

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Sleep problems and disorders as a risk factor for AD

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Sleep and Alzheimer's Disease Risk

- 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)
    - Short sleep duration (Winer et al., 2021, Sabia et al., 2021)
  - 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; Varga et al.; 2016; Lucey et al., 2019)
  - Sleep disorders
    - Sleep apnea (Yaffe et al., 2011; Ju et al. 2019; Sharma et al; 2018; Bubu et al., 2019, 2020, 2022)
    - Periodic leg movements (Leng et al., 2016)

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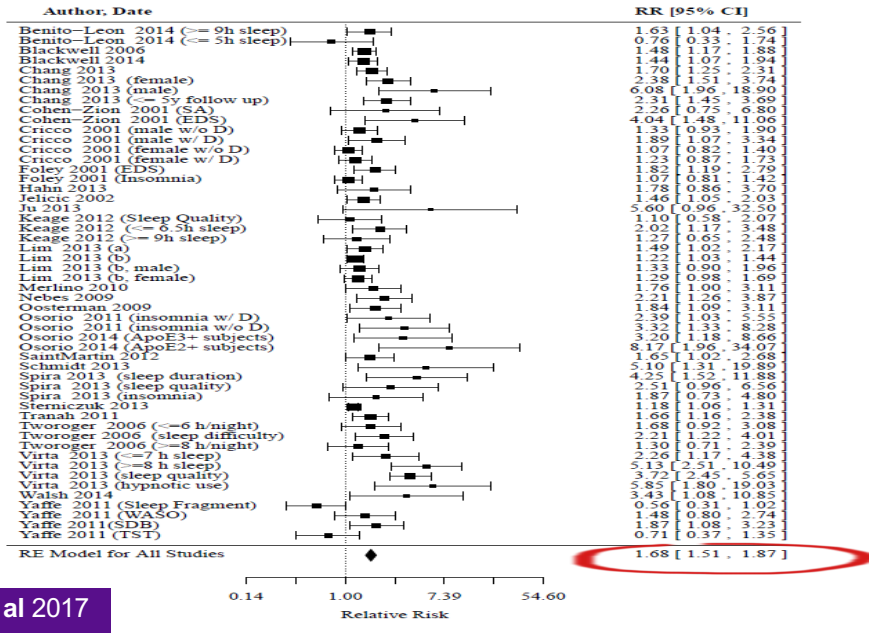
Figure : Forest plot presenting overall meta-analysis based on risk estimates for the effect of sleep on cognitive decline and/or Alzheimer's disease



Bubu et al 2017

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Obstructive Sleep Apnea (OSA) and Incident Alzheimer's Disease Risk (Avg. Follow-up 8.3 years)

	Model 1		Model 2		Model 3	
	HR	95% CI	HR	95% CI	HR	95% CI
OSA positive versus OSA negative (Cohort I)	2.23	1.73-2.84	2.18	1.47 - 3.02	2.22	1.66 - 2.91
AHI > 5 - ≤ 14.9 events/h of sleep	1.67	1.13-2.24	1.63	1.17 - 2.27	1.66	1.13 - 2.34
AHI > 15 - ≤ 29.9 events/h of sleep	1.81	1.62-2.74	1.72	1.31 - 2.93	1.78	1.42 - 2.75
AHI ≥ 30 events/h of sleep	2.63	1.86-2.92	2.59	1.36 - 3.0	2.63	1.84 - 2.93
OSA positive versus OSA negative (Cohort II)	2.37	1.82-3.04	2.33	1.52-3.06	2.41	1.71-3.33
AHI > 5 - ≤ 14.9 events/h of sleep	1.83	1.34-2.64	1.81	1.41-3.04	1.83	1.32-2.65
AHI > 15 - ≤ 29.9 events/h of sleep	2.02	1.42-2.44	1.97	1.22-2.84	2.01	1.22-2.48
AHI ≥ 30 events/h of sleep	2.62	1.62-3.09	2.55	1.32-3.07	2.59	1.34-3.07
Demography						
Sex						
Female	2.28	1.41 - 3.56	2.21	1.27 - 3.61	2.38	1.31 - 3.47
Male	1.42	1.13 - 2.33	1.38	1.09 - 2.38	1.37	1.14 - 2.41
Race/Ethnicity n (%)						
Non-Hispanic White	1.87	1.29 - 3.48	1.75	1.19 - 3.41	1.83	1.21 - 3.37
Black/African American	2.56	1.45 - 2.73	2.48	1.36 - 3.01	2.24	1.24 - 2.71
Hispanic	1.81	1.42 - 3.56	1.76	1.23 - 3.67	1.73	1.38 - 3.51
Others	1.13	0.54 - 1.87	1.03	0.56 - 1.86	1.01	0.48 - 1.66
Socioeconomic status						
Educational level n (%)						
High school or less	2.73	1.22 - 3.37	2.54	1.13 - 3.46	2.62	1.18 - 3.06
At least some college or technical school	1.82	1.47 - 2.83	1.77	1.25 - 2.76	1.78	1.36 - 2.91
Graduate or professional school	1.31	1.05 - 2.46	1.18	1.02 -2.53	1.29	1.04 - 2.47

Bubu et al Manuscript in Preparation

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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

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Sleep disturbance Worsens (with) AD Pathology

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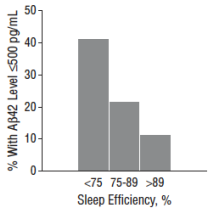
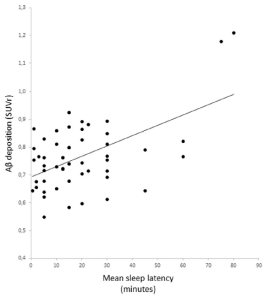
Sleep disturbance Worsens with AD Pathology

- Aβ deposition associated with decreased sleep efficiency (actigraphy) and increased daytime napping (Ju et al., 2013).



- Longer sleep latency (PSQI) associated with higher levels of brain Aβ (Brown et al., 2016).
- Increased Aβ deposition correlated with longer self-reported mean sleep latency (Branger et al., 2016).



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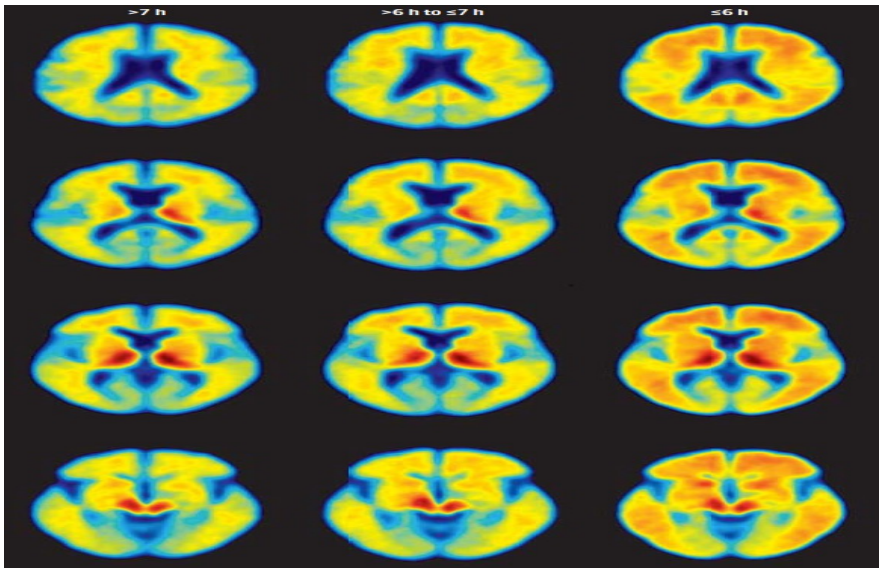
Increased amyloid with decreased self-reported sleep time and poorer sleep quality



Spira et al., 2013

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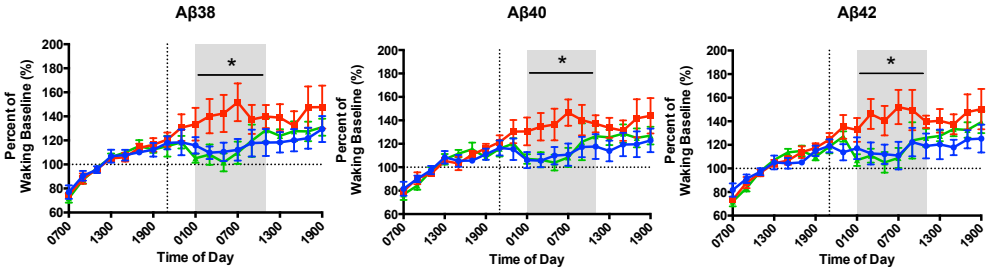
Sleep Deprivation Increases Overnight Aβ



Blue=Control; Red=Sleep-deprived; Green=Drug
Horizontal line: 100% of waking baseline
Vertical line: 21:00, start of intervention and ^{13}C-leucine infusion
Shaded: Overnight period 0100-1100
*p<0.0001

Lucey et al., 2018

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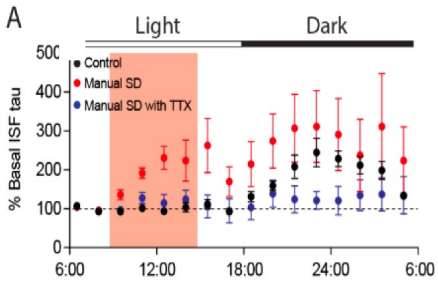
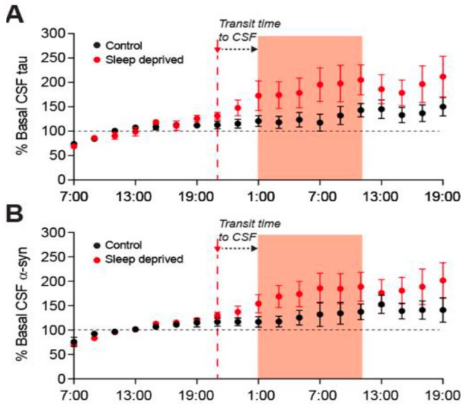
Tau, Alpha-Synuclein, and Sleep-Wake Activity

Mice



Holth et al., 2019

Humans



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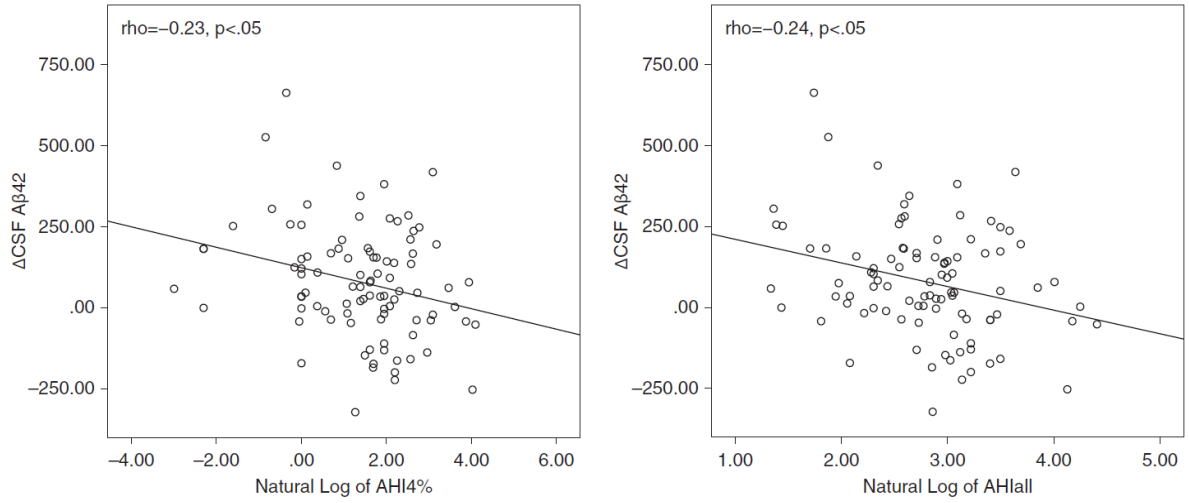
Relationship between longitudinal change in cerebrospinal (CSF) Aβ42 and the natural log of apnea hypopnea indices (AHIs) at baseline.



Sharma, Varga, **Bubu et al** 2017

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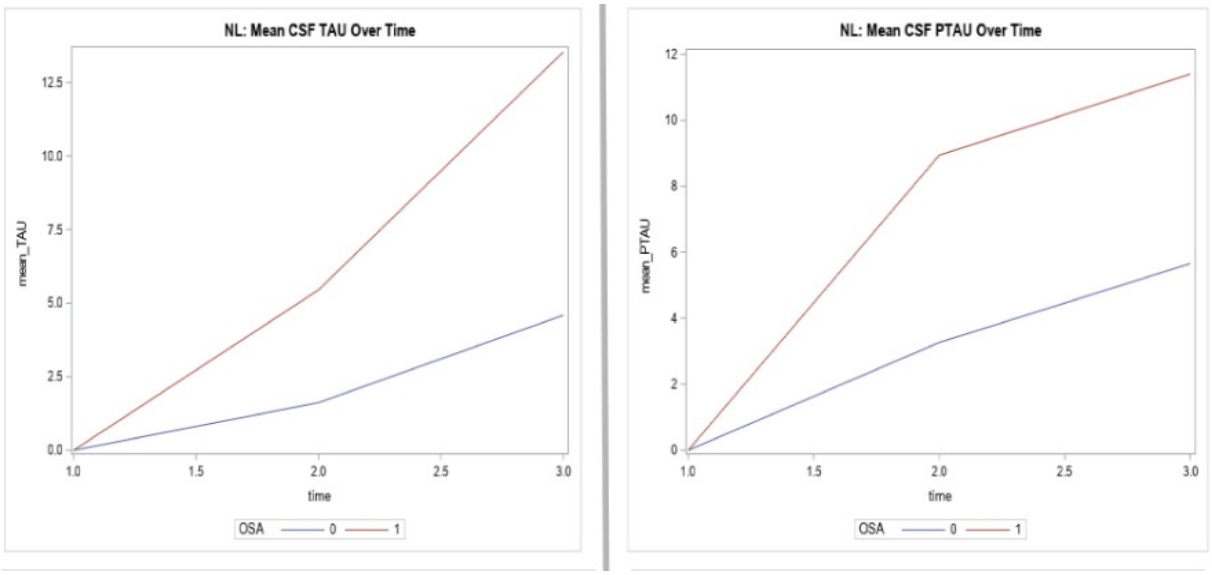
OSA is associated with faster annual increase in CSF-Tau & CSF-PTau



Bubu et al SLEEP 2019

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Sleep as a marker for AD pathology

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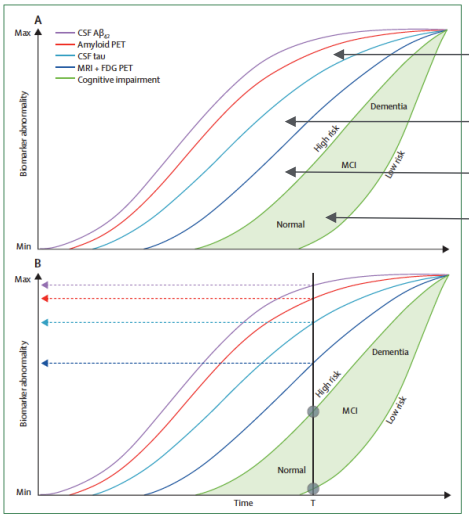
Sleep as a marker for AD pathology



ΔSleep?

ΔSleep?

ΔSleep?

ΔSleep?

What changes with sleep and AD pathology?

- Sleep marker?
  - TST, SE, SWA?
- Circadian marker?
  - Amplitude?

Jack CR, et al., Lancet Neurol., 2013; 12(2): 2007-16

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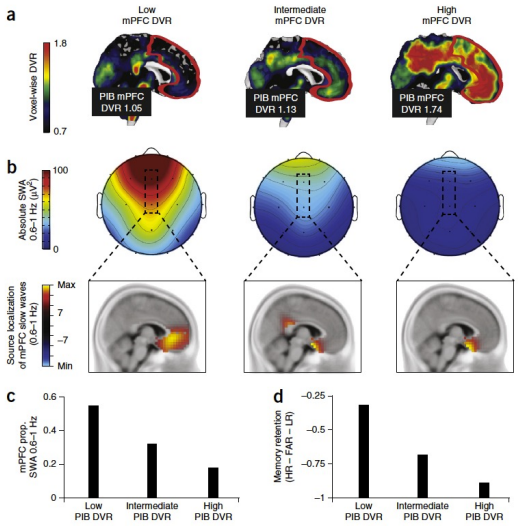
Aβ and NREM Slow Wave Activity



N=26
Cognitively normal

Mander et al., 2015

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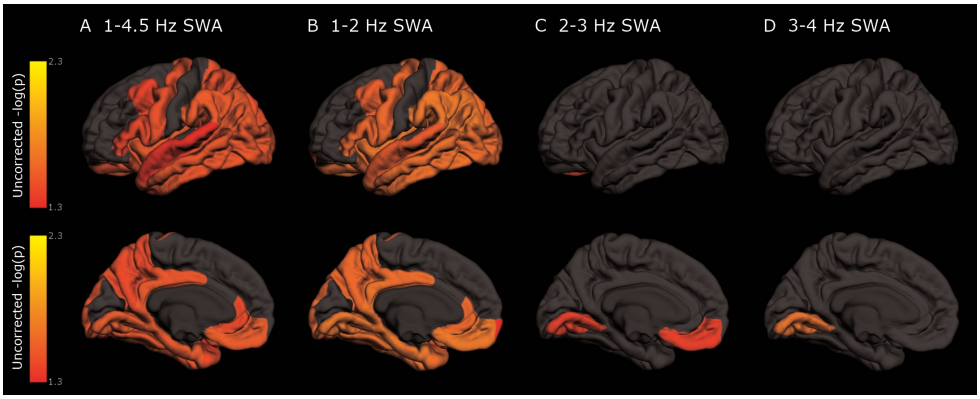
Regional Differences Between NREM SWA and Tau PET



Corrected for multiple comparisons

Lucey et al., 2019

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Sleep problems/disorders as a modifier of AD risk

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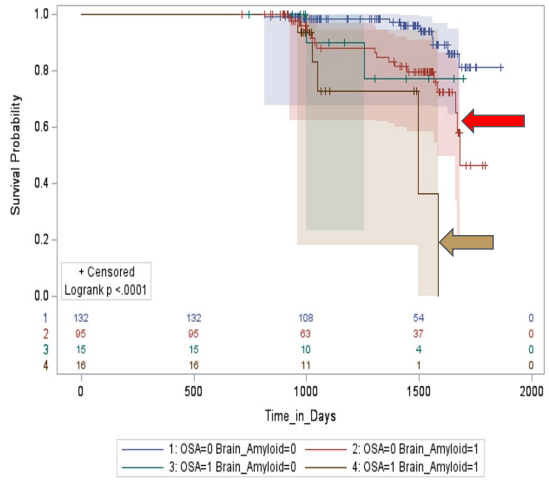
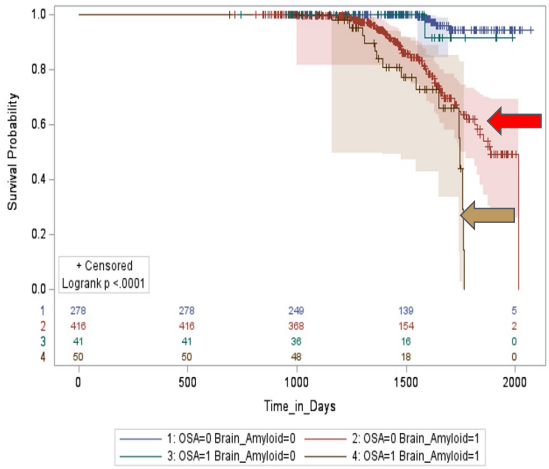
Bubu et al Alzheimer's & Dementia 2019

Kaplan–Meier Product Limit Survival Estimates and time-to-progression (ALL NL PARTICIPANTS COMPARED BY OSA & BRAIN AMYLOID STATUS)



Kaplan–Meier Product Limit Survival Estimates and time-to-progression (ALL MCI PARTICIPANTS COMPARED BY OSA & BRAIN AMYLOID STATUS)



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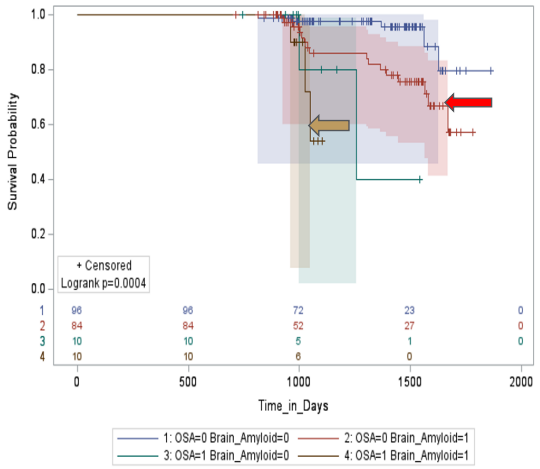
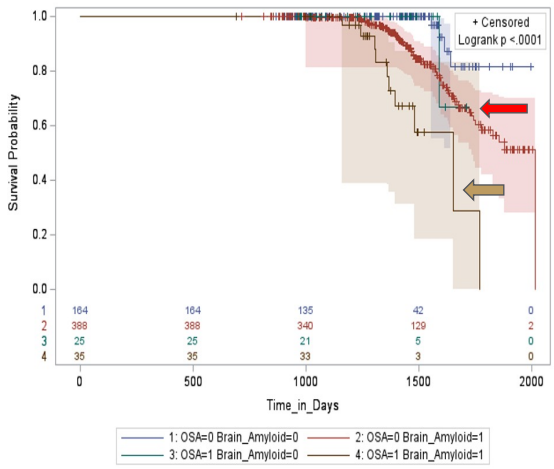
Kaplan–Meier Product Limit Survival Estimates and time-to-progression (ALL TN+ NL PARTICIPANTS COMPARED BY OSA & BRAIN AMYLOID STATUS)



Kaplan–Meier Product Limit Survival Estimates and time-to-progression (ALL TN+ MCI PARTICIPANTS COMPARED BY OSA & BRAIN AMYLOID STATUS)



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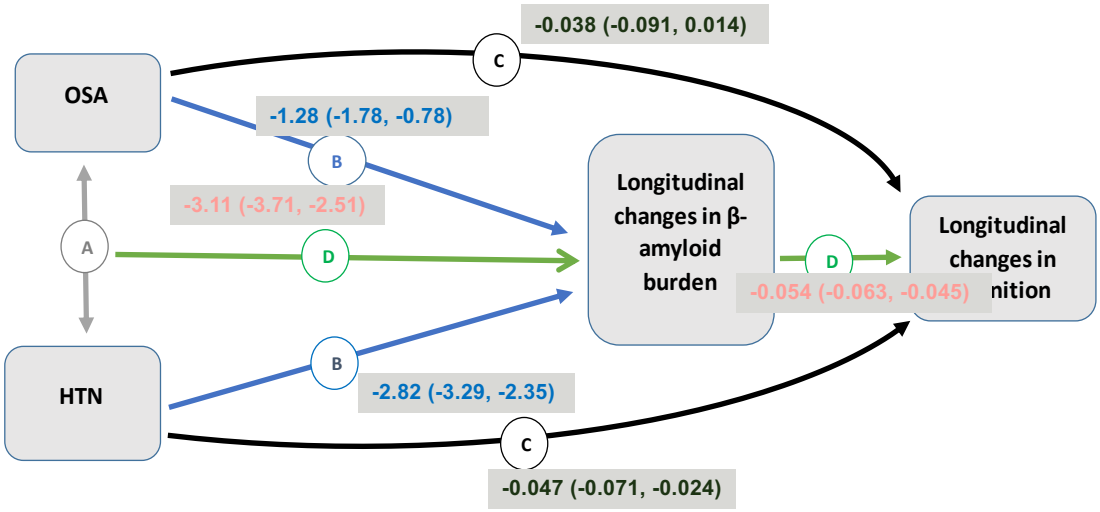
Bubu et al Am J Respir Crit Care Med. 2022

Co-occurrence of OSA and hypertension interact synergistically to promote β-Amyloid burden and cognitive decline in clinically normal older adults



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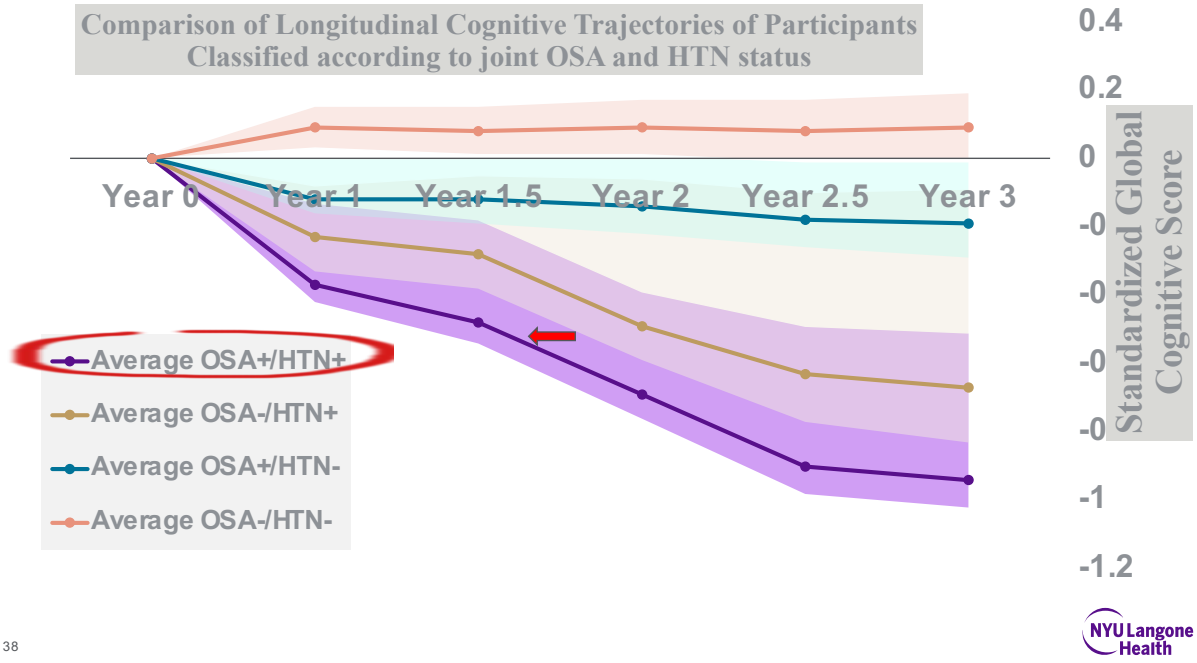
Bubu et al Am J Respir Crit Care Med. 2022



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Bubu et al Frontiers Aging Neuroscience. 2021

Interactive associations of NPI-Q assessed sleep disturbance (SD) and vascular risk with an MCI (aMCI plus non-amnestic MCI) diagnosis during follow-up in clinically normal older adults, NACC UDS data.

Outcome	*Model 1 Term	**aOR (95% CI)	***Pvalue
Conversion Risk from CN to MCI	SD*time	1.37 (1.10–1.67)	< 0.007
	FHS-CVD*time	3.24 (1.72–4.76)	< 0.001
Outcome	***Model 2 Term**	**aOR (95% CI)**	***Pvalue***
Conversion Risk from CN to aMCI	FHS-CVD*SD*time	3.95 (2.18–5.71)	< 0.001
***#Model 2 Term FHS-CVD Stratified Analyses (SD+ vs. SD-)**			
Conversion Risk from CN to aMCI	Highest FHS-CVD tertile	3.87 (2.23–5.51)	< 0.003
	Middle FHS-CVD tertile	2.88 (1.47, 4.29)	< 0.001
	Lowest FHS-CVD tertile	REF	REF
Outcome	***Model 3 Term**	**aOR (95% CI)**	***Pvalue***
Conversion Risk from CN to aMCI	SD*time	1.22 (1.03–1.41)	0.043
	FHS-CVD*time	2.67 (1.22–4.12)	< 0.003
	FHS-CVD*SD*time	2.78 (1.29–4.38)	< 0.001
	CSF-Aβ*time	2.89 (1.43–4.35)	< 0.001
	CSF-Tau*time	4.47 (2.65–6.29)	< 0.001
	CSF-PTau*time	3.01 (1.12–4.91)	< 0.001
	Hippocampal Volume*time	2.52 (1.37–3.67)	< 0.005

*MCI, mild cognitive impairment; FHS-CVD, Framingham heart study cardiovascular disease; NACC UDS, National Alzheimer's Coordinating Center Uniform Dataset; SD, sleep disturbance; 95%CI, 95% confidence interval; *Model term assessed, **Model Adjusted for age, sex, BMI, education, ApoE4 status, clinical history of diabetes, hypertension, smoking, marital status, living arrangement, NPI-Q assessed co-morbidity and informant characteristicsand center-ID; *#Model 2 Term FHS-CVD Stratified Analyses (SD+ vs. SD-). The FHS-CVD Stratified Analyses (SD+ vs. SD- corresponds to Model 2 where we investigated the FHS-CVD*SD*time interaction term. Since SD is a categorical variable, using data driven techniques we split the FHS-CVD risk score into tertiles within the SD groups. This was done for stratified analyses and for visualization purposes to generate strata specific estimates. **aOR: adjusted odds ratios obtained for logistic mixed effect model beta estimates. ***P-value = 0.05/3 ≤0.017 controlling for family wise error.*

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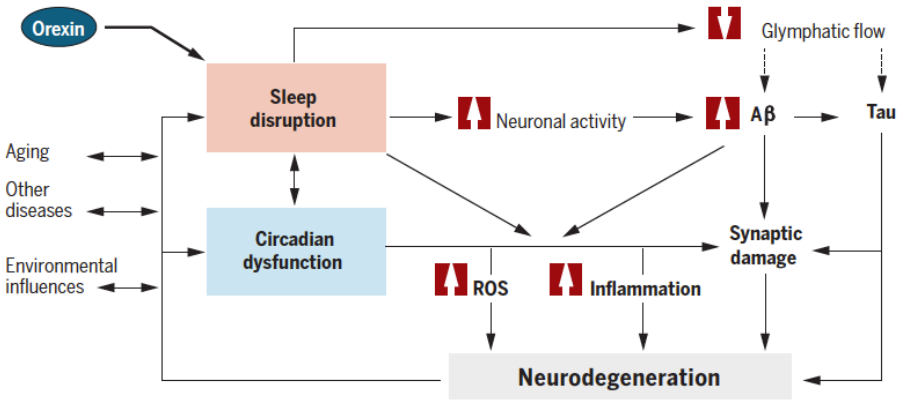
Sleep and AD: Bidirectional Relationship



Musiek, Holtzman, 2016.

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Conclusions

1) Sleep disturbance worsens AD pathology

- Overnight concentrations of all Aβ isoforms and tau increase ~30-50% above the waking baseline in the sleep-deprived group compared to control and drug groups
- Future Directions:
  - Intervention studies needed

2) Sleep disturbance and disorders (i.e. OSA) modifies AD risk

- a contributory role of an OSA-Aβ synergism related to cognitive decline that can be independent of tau as well as synergistic with tau deposition
- A possible contributory role of sleep problems and/or OSA and other commonly co-occurring vascular risk factors on biomarkers of AD pathology
- Future Directions:
  - Intervention studies needed

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Conclusions

3) Sleep as an AD biomarker

- Multiple sleep and circadian disturbances associated with AD pathology (even in cognitively normal individuals) and future risk of cognitive impairment
- Future Directions:
  - What is the best sleep/circadian parameter to monitor? Which one(s) is closest to transition/change point from cognitively normal to impaired
    - NREM SWA may be a marker of neurodegeneration and cognitively decline at the earliest stages of AD
  - Longitudinal studies needed

4) Sleep and AD bidirectional relationship

- Sleep disturbances are associated with increased AD risk/
- AD patients have increased sleep disturbances
- Sleep disturbances are associated with markers of AD pathology
- Two intersect: when to intervene?

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