

# Obstructive Sleep Apnea (OSA), MCI and AD: **Is There a Direct Link?**

Ricardo Osorio, MD

[ricardo.osorio@nyumc.org](mailto:ricardo.osorio@nyumc.org)

# Disclosures

## ✓ Financial

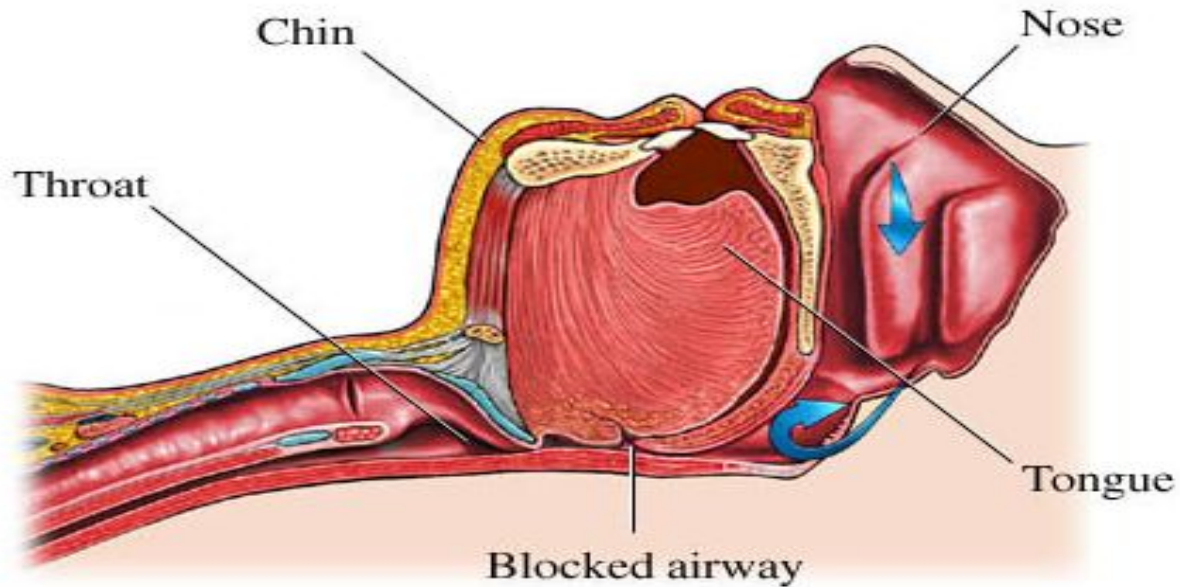
- I have no financial conflicts of interest to declare

## ✓ Off Label Use

- I will not discuss off-label therapies

# Obstructive Sleep Apnea Syndrome

- ✓ Intermittent functional obstruction of the upper airway that occurs primarily or only during sleep
- ✓ Pathophysiology - Complex interaction of:
  - Anatomy of the airway structures
  - Collapsibility of the airway soft tissues
  - Neural control of the airway and breathing
  - Intrinsic sleep mechanisms
- ✓ **OBSTRUCTIVE SLEEP APNEA (OSA) SYNDROME** – repetitive obstructive events combined with consequences (sleepiness and other daytime or long term events)

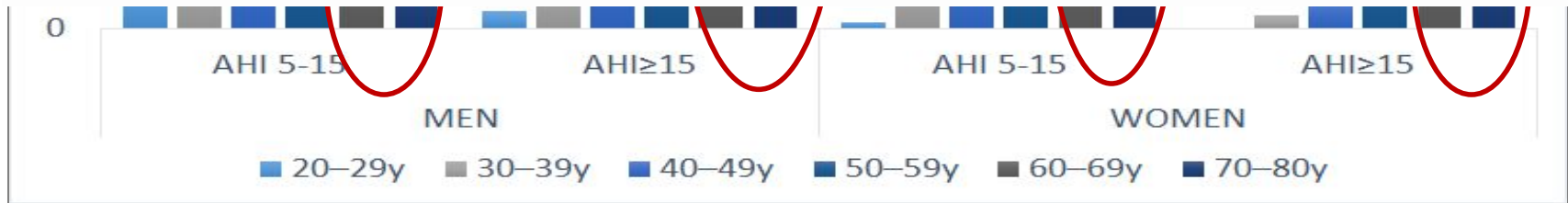


**Apnea Hypopnea Index (AHI) =  $\frac{\text{\# of apneas} + \text{\# of hypopneas}}{\text{Total Sleep Time}}$**

**Intermittent Hypoxia, Arousals from Sleep, Autonomic Activation**

# OSA prevalence increases with age

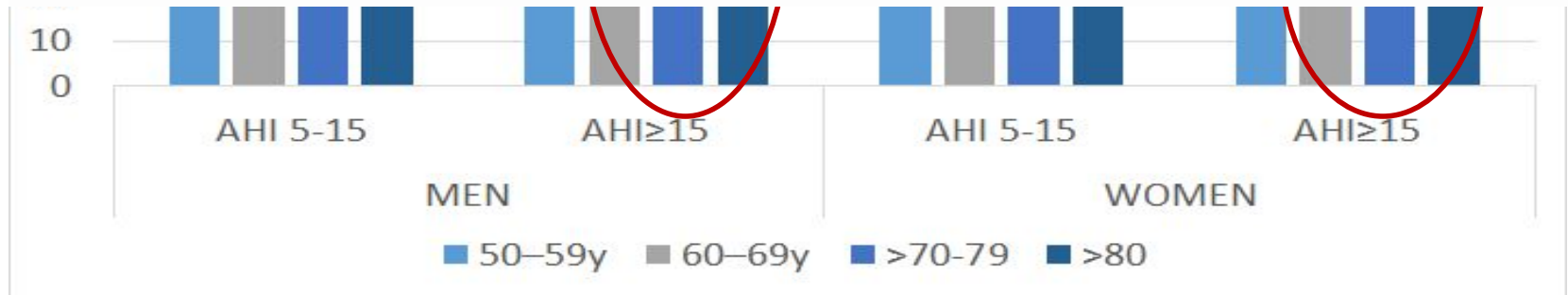
- ✓ Prevalence of any OSA 9-38% in the general adult population
- ✓ 13-33% in adult men, 6-19% in adult women
- ✓ If sleepiness is included, 12.5% in men and 5.9% in women
- ✓ As high as 84% overall in the elderly and 90% in elderly men
- ✓ At  $\geq 15$  events/h AHI, 6-17% adults,  $>49\%$  in elderly



# OSA in the NYU cohort

## Elderly:

- ✓ At  $\geq 15$  events/h AHI, 71% men, 58% of women
- ✓ At  $\geq 30$  events/h AHI, 27% of men, 20% women



# Is it clinically relevant?

- ✓ Excess mortality:
  - Males <50 yrs. with moderate-severe OSA (Lavie P, 2005)
  - Males age 40-70 with moderate-severe OSA (Punjabi NM, 2009)
- ✓ Hypertension:
  - Males and females < 60 yrs. (Haas DC, 2005)
  - No association in the elderly (Sawatari H, 2016)
- ✓ Coronary heart disease: Middle-aged men (30-70 yrs.) (Sánchez-de-la-Torre M, 2013)
- ✓ Excessive Daytime Sleepiness
- ✓ Stroke: **Increased Risk (Muñoz R, 2006; Stone KL, 20016)**
- ✓ Impaired Cognition:
  - Impaired memory in small case-control studies (Ju G, 2012).
  - No association in large cohorts (Sforza E, 2010).

# NYU Cohort

n=231	Normal AHI4% <5)	Mild AHI4% 5-14.9	Moderate-Severe AHI4% ≥15
Age	65.6±8.6	68.2±7.2	70.3±7.5*
% female	73.3%	59.8%	52.6%*
BMI	25.3±4.8	27.2±4.9	28.9±6.7*
ApoE4%	29.2%	31.7%	33.3%*
Hypertension	36.9%	39.8%	57.1%†
Diabetes	4.8%	6.0%	8.6%
Cardiovascular disease	2.4	9.5	2.9
Reported total sleep time	7.2±1.0	7.2±1.0	7.4±1.2
Epworth Sleepiness	5.1±3.5	6.1±3.3	6.4±3.9†

\*p<0.05, †<0.1

No cognitive impairment at cross-section



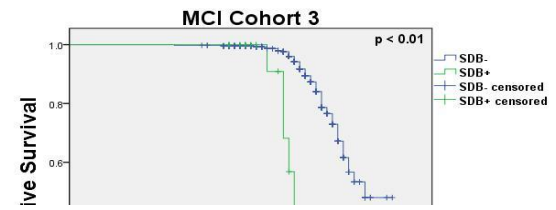
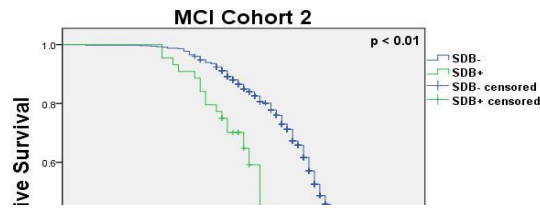
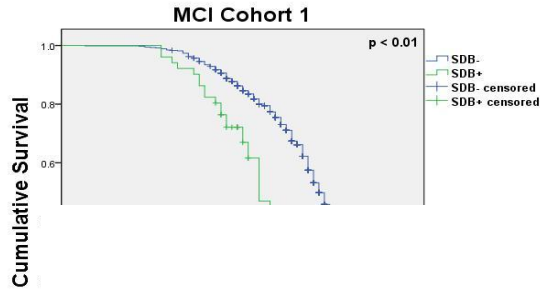
# Relevance in MCI and AD...

- ✓ AD patients have 5 times higher chance of OSA than matched controls (Emamian F, 2016)
- ✓ Severity of OSA correlates with severity of cognitive impairment (Ancoli-Israel S, 1991)
- ✓ CPAP is partially effective in improving cognition (Ancoli-Israel S, 2008)
- ✓ CPAP slows cognitive deterioration in MCI (Osorio RS, 2015) and AD (Cooke JR, 2009; Troussière AC, 2014)
- ✓ OSA as a potential cause of 'reversible dementia' or 'reversible MCI syndrome'

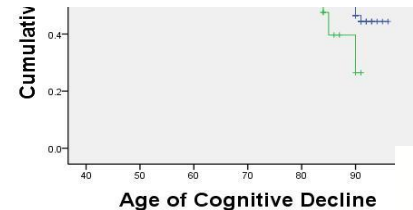
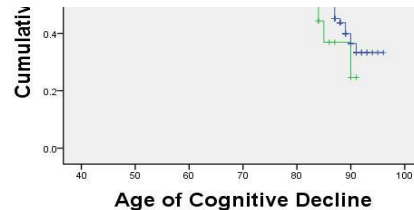
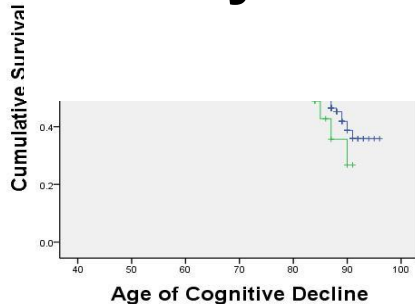
# A risk factor for cognitive decline?

- ✓ Small changes in attention at the 8 yr f.u. **PROOF Study** (Martin MS, 2015).
- ✓ No changes in cognition at the 15 yr f.u. **ARIC Study** (Lutsey PL, 2016)
- ✓ Women with OSA more likely to develop MCI or dementia at the 5 yr f.u. **SOF Study** (Yaffe K, 2011)
- ✓ Increased risk of developing dementia within 5 years of diagnosis (> in men than in women) (Chang WP, 2013)
- ✓ Earlier age of cognitive decline to MCI and AD **ADNI Study** (Osorio RS, 2014)

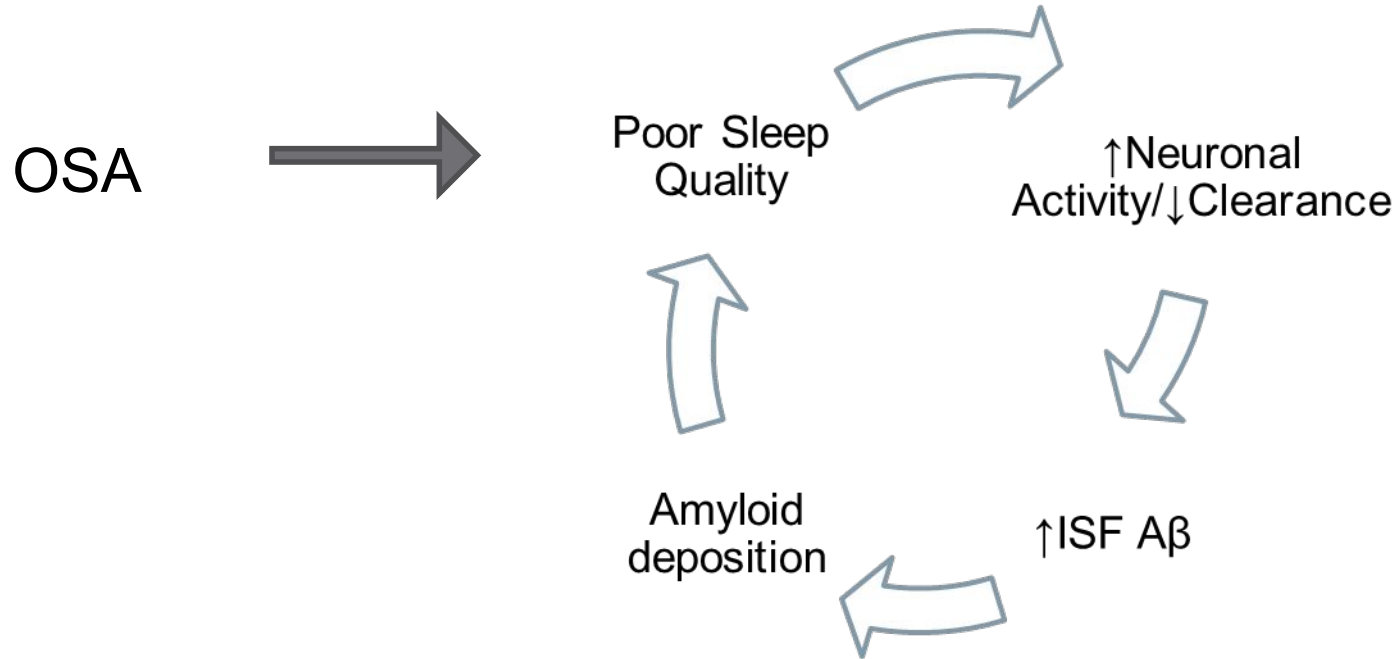
# OSA Advances Cognitive Decline



**Reported OSA patients had an MCI and AD onset 12 and 5 yrs earlier than controls**



# OSA Increases Amyloid Deposition



Modified from Ju et al, 2014

In 95 cognitively normal (CN) elderly

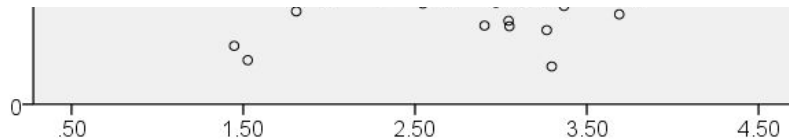
- In ApoE3+ OSA was associated with increases in CSF Tau
- In ApoE4+ OSA was associated with a trend towards lower CSF A $\beta$ 42

(Osorio RS, 2014)

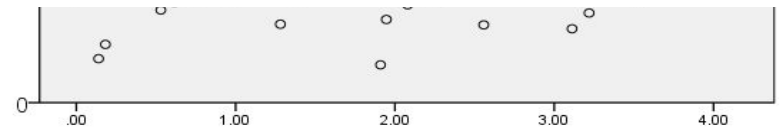


**At cross-section with an n=178 CN (mean age 69.1 $\pm$ 7.3)**

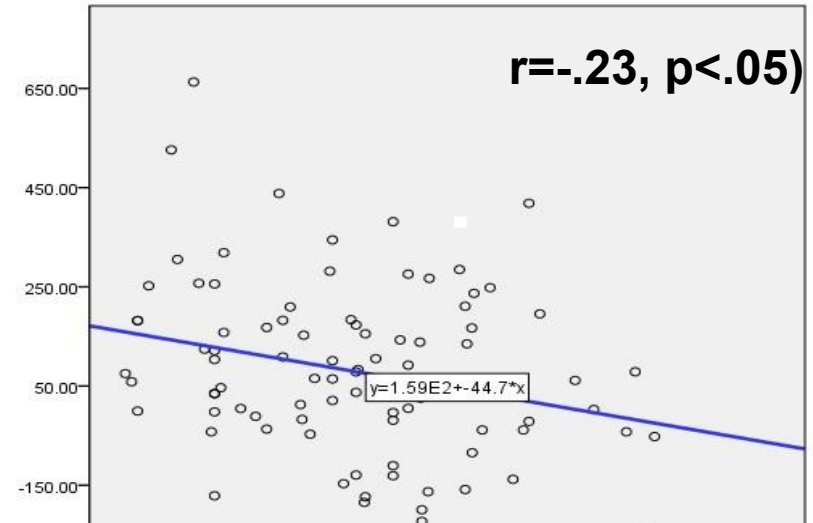
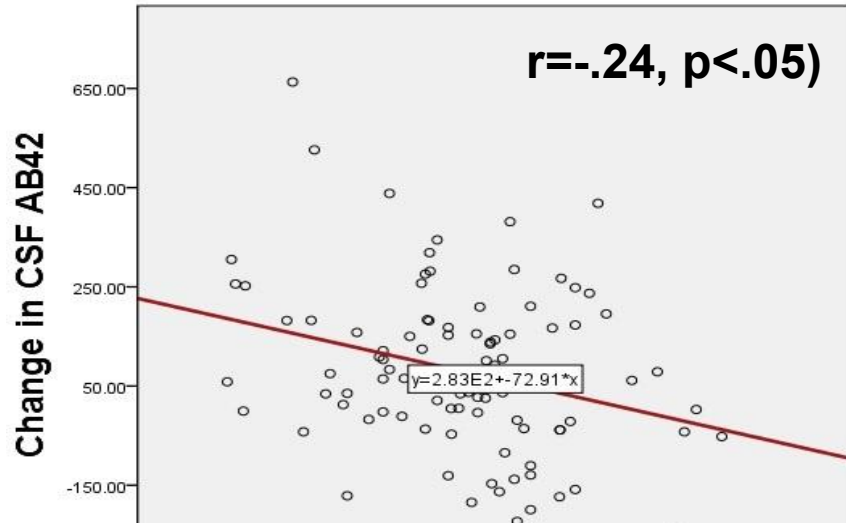
**NO EFFECTS**



LnAHIall



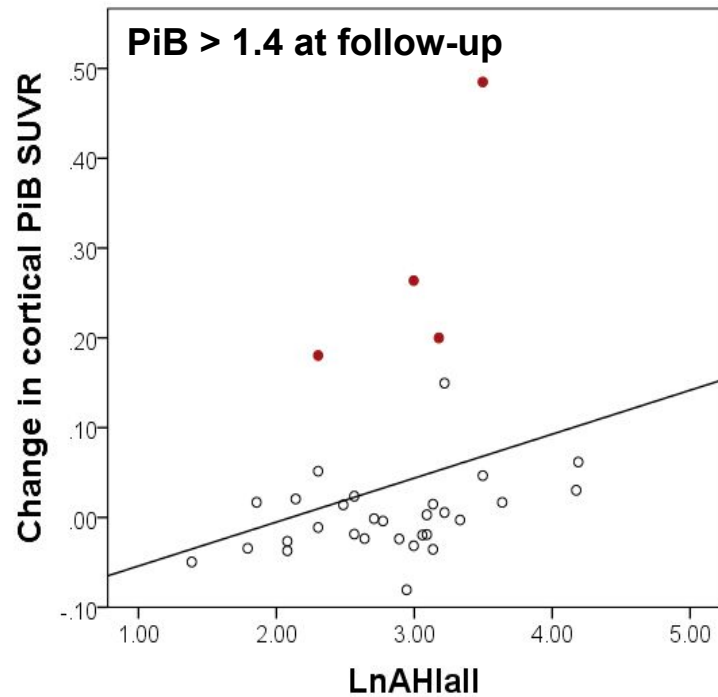
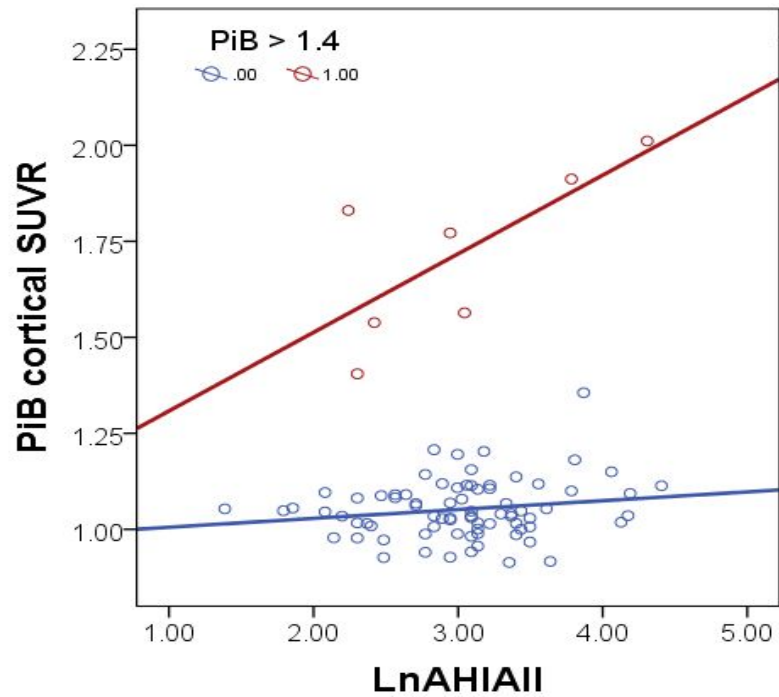
LnAHI4%

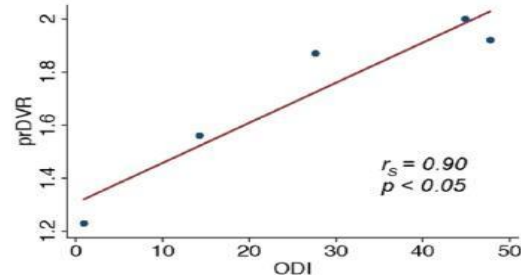
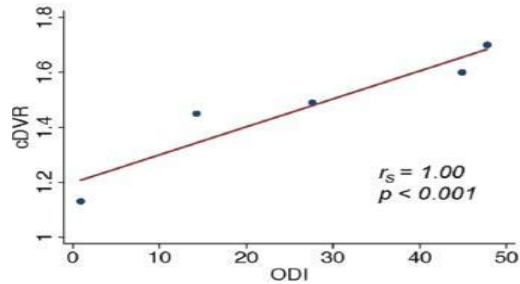
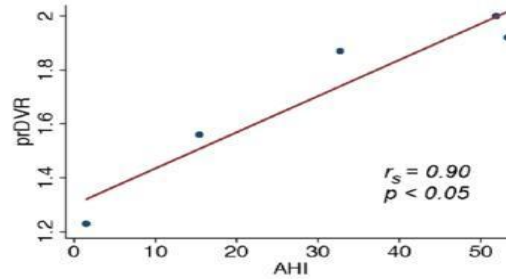
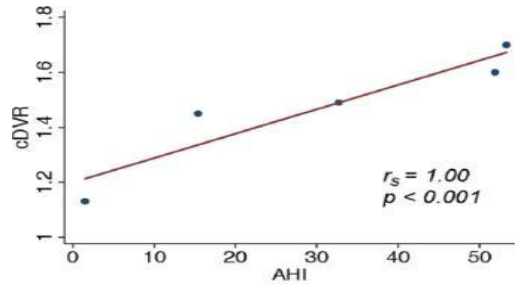


Within subjects, **Rep. Measures ANOVA**

LnAHIall **F=9,7, p<0.01** adjusting for ApoE4+/time LPs

LnAHI4% **F=7.9, p<0.01** adjusting for ApoE4+/time LPs



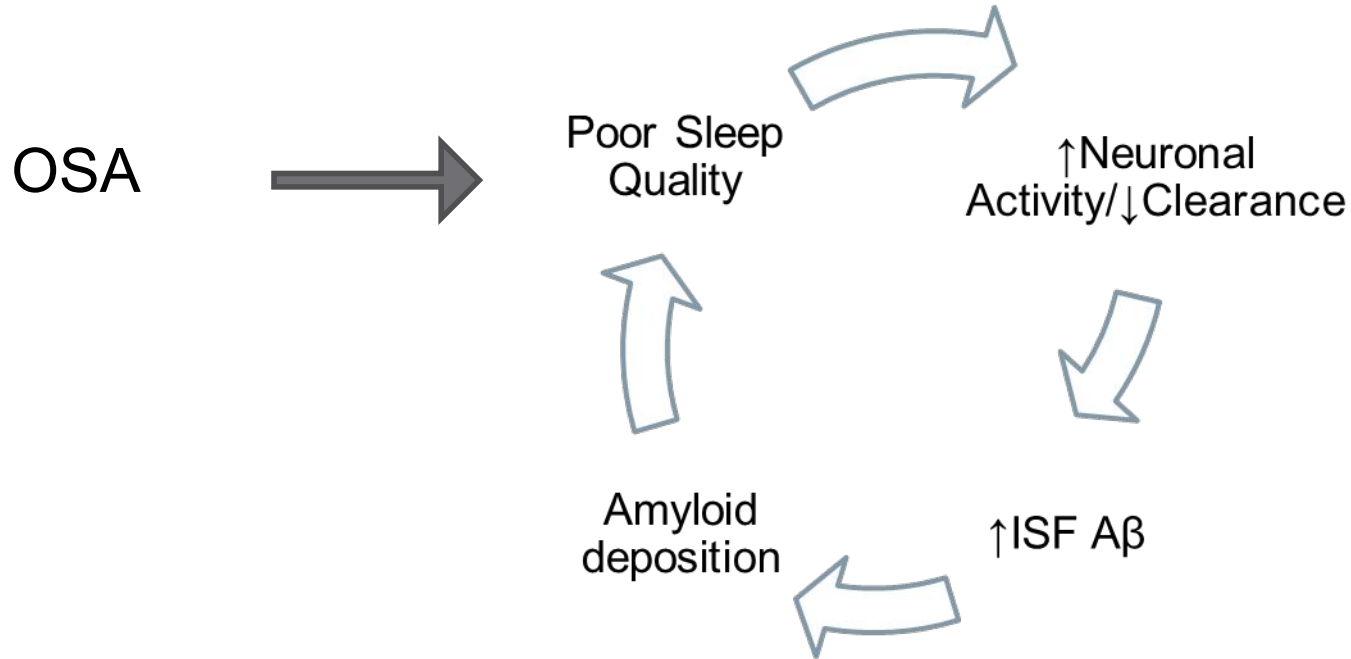


(Spira AP, 2014)

*'Among participants with MCI, AHI and ODI were associated with greater A $\beta$  deposition globally and regionally in the precuneus'*



# OSA Increases Amyloid Deposition



Modified from Ju et al, 2014

# A direct link?

- ✓ Both sleep disruption and intermittent hypoxia facilitate protein aggregation in animal and cellular models
- ✓ OSA increases oxidative stress and pro-inflammatory cytokines
- ✓ Sleep disruption is associated with decreased transport function of the BBB microvessels (He J, 2014)
- ✓ OSA may increase intracranial pressure and disrupt CSF-ISF exchange (Ju YE, 2016)
- ✓ OSA may decrease clearance of subarachnoid CSF directly into dural lymphatic channels (increase venous pressure) (Ju YE, 2016)

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