

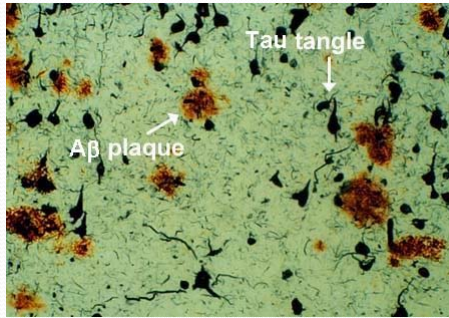
# Relationship Between Cognitive Dysfunction, Alzheimer's Disease and OSA

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## Outline of Lecture

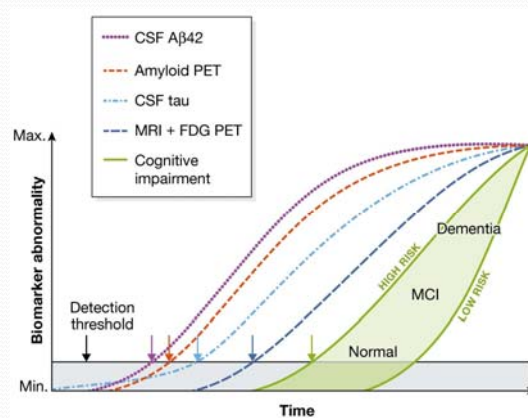
- Pathogenesis of Alzheimer's disorder – role of sleep
- Why should OSA affect Alzheimer's disease?
- What is evidence that OSA plays a role in Alzheimer's disease?
- Is the amyloid hypothesis – the whole story – role of tau?
- Where are we going?

## Pathogenesis of Alzheimer's Disease



Both proteins are involved in pathogenesis.  
Major focus has been on A $\beta$

## Time Course of Amyloid in Alzheimer's disease – Can Be Assessed by PET

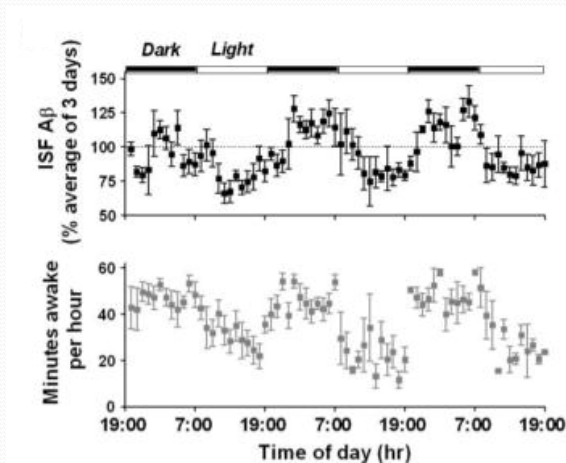


**AMYLOID CHANGES OCCUR YEARS BEFORE SYMPTOMS EMERGE.  
CAN WE INTERVENE BEFORE SYMPTOMS DEVELOP?**

## Why Do We Think Sleep May be Involved?

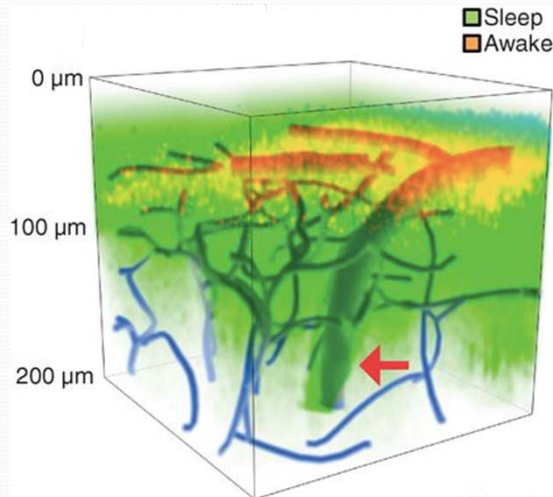
- Reduced production of A $\beta$  in sleep
  - A $\beta$  is produced with neuronal activity
  - A $\beta$  levels are higher in wakefulness than sleep
- Increased clearance (removal) during sleep

## A $\beta$ Levels in Brain Are Higher During Wakefulness and Decline During Sleep (Kang JE, et al, Science 326:1005, 2009)



## Sleep Also Markedly Increases Fluid Flow Out of the Brain

(Xie L, et al, Science 343:373, 2013)



Distribution of CSF tracers injected in a sleeping mouse and then again after the mouse was awakened.

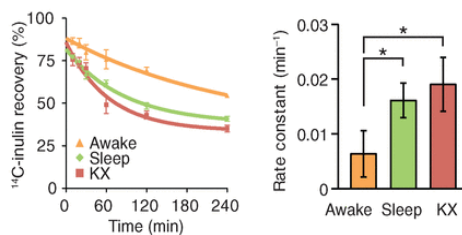
**Blue: blood vessels**  
Arrow: penetrating arteries.

**Green: sleeping mouse**

**Red: awake mouse**

## Sleep Enhances Clearance of Beta-Amyloid (Built Up in Alzheimer's)

(Xie L, et al, Science 343:373, 2013)



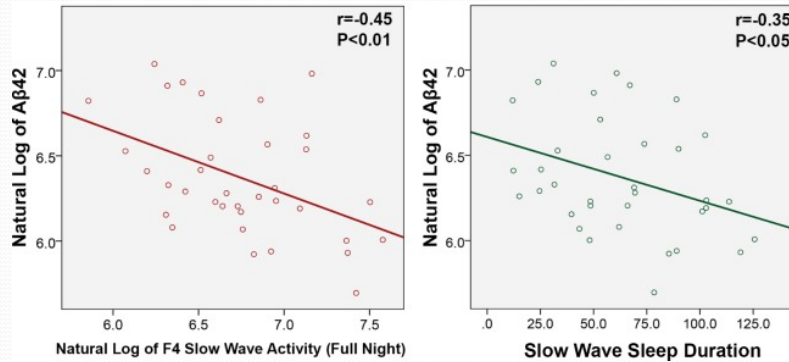
KX = ketamine/xylazine anesthesia



Trash Trucks for Brain Arrive During Sleep

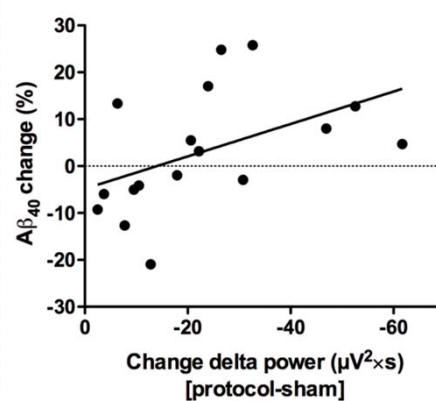
## Relationship Between Reductions in Slow-Wave Sleep and Increases in CSF A $\beta$ 42 in Normal Elderly

(Varga AW, et al, Sleep 39:2041, 2016)



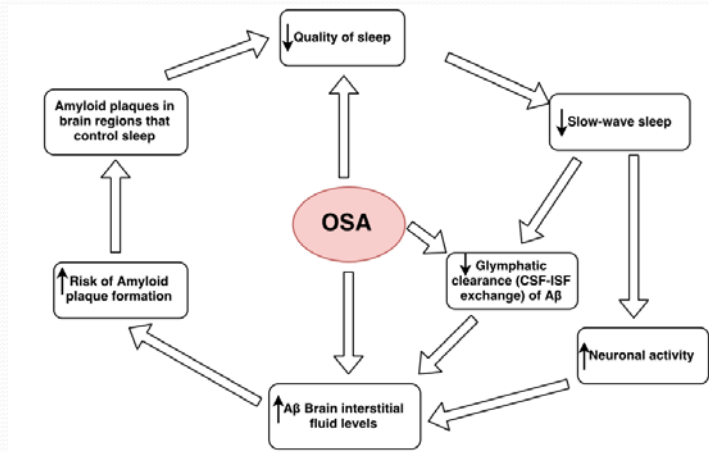
## Disruption of Slow Wave is Associated with Increased in Amyloid $\beta_{40}$ in CSF

(Ju YS, et al, Brain 140:2104, 2017)



## Possible Role of OSA in Amyloid Plaque Formation

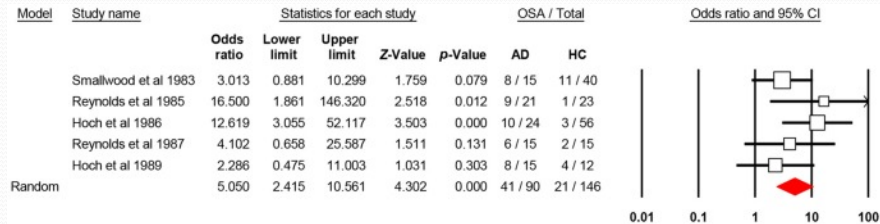
(Sharma RA, AJRCCM 2017, doi: 10.1164/rccm.201704-0704OC)



What About Clinical Information  
in Patients with  
Obstructive Sleep Apnea?

## Sleep Apnea is More Common In Patients with Alzheimer’s Disease – A Meta-analysis

(Emamian F, et al, Front Aging Neurosci 8:78, 2016)



## Presence of Moderate OSA Increases Risk of Future Mild Cognitive Impairment or Dementia

(Yaffe K, et al, JAMA 306:613, 2011)

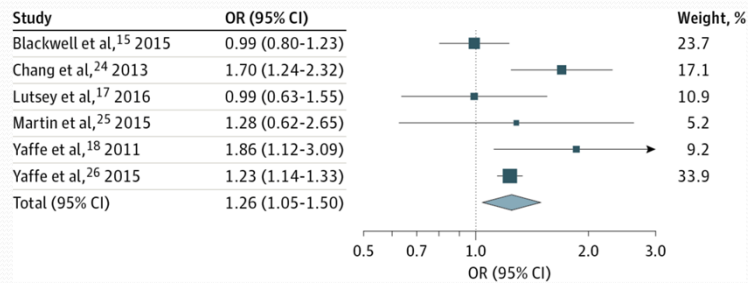
### Oxygen desaturation index

	No (% developed MCI/dementia)	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)
<15 events/hour	46 (43.4%)	1.0	1.0
≥15 events/hour	60 (56.6%)	1.67	1.17 (1.04-2.88)

Associations are with hypoxic measures, not arousals.

\*Adjusted for age, BMI, smoking, hypertension, diabetes, medication use.

## Meta-analysis of Prospective Studies of Association Between Sleep-Disordered Breathing and Risk of Cognitive Impairment (Leng Y, et al, JAMA Neurol 74:1237, 2017)

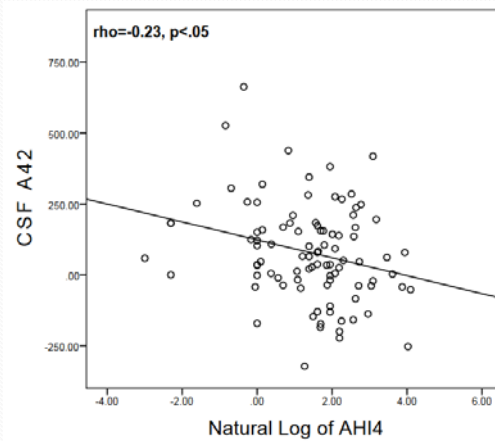


**OSA INCREASES RISK FOR COGNITIVE IMPAIRMENT**

## CSF Biomarker Studies Also Support A Relationship with OSA

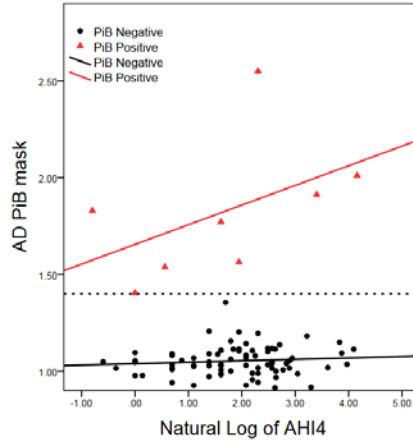
Changes in CSF AB42 Over 2 Years in Cognitively Normal Older Adults (Relationship to baseline AHI)

(Sharma RA, AJRCCM 2017, doi: 10.1164/rccm.201704-0704OC)





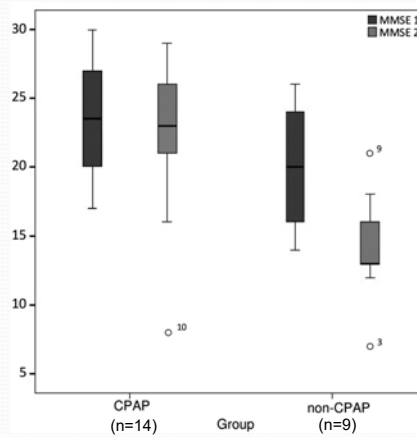
Relationship Between Amyloid Burden by PET Scans and Log AHI in Those with Positive and Negative Studies)  
 (Sharma RA, AJRCCM 2017, doi: 10.1164/rccm.201704-0704OC)



No relationship between change in amyloid load over 2 years by PET and AHI—but sample size small

CPAP Reduces Cognitive Decline in Patients with OSA and Mild to Moderate AD

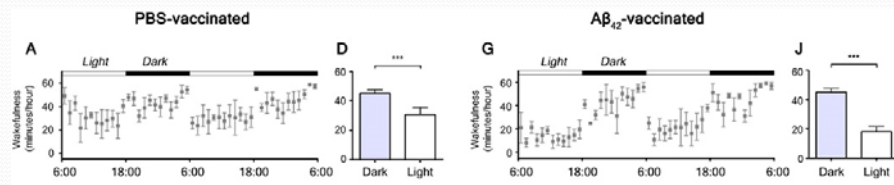
(Troussiere A, et al, J Neurol Neurosurg Psychiatry 85:1405, 2014)



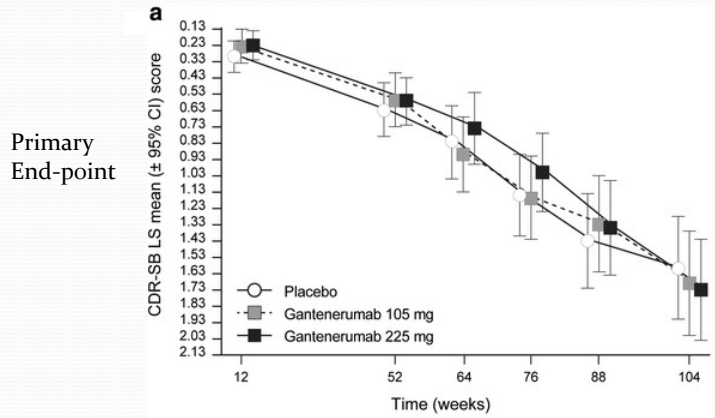
A SMALL, NON-RANDOMIZED, STUDY (3 YEARS)

Targeting  $A\beta$  produces major improvements in mouse models but not yet in humans

Sleep-Wake Abnormalities in Mouse Model of Alzheimer's Disease Are Prevented by  $A\beta_{42}$  Vaccination  
(Roh JH, et al, Sci Transl Med 4:150rs122, 2012)



Studies with Monoclonal Antibody that Binds Aggregated Amyloid Beta in Humans with Prodromal AD Are Negative to Date  
(Ostrowitzki S, et al, Alzheimer's Res Ther 9:95, 2017)



Some trends in biomarker results - ?need for higher doses

Dementia field is paying more attention to role of tau

Tau not well studied in framework of OSA

See Sleep in Alzheimer's Disease—Beyond Amyloid (Holth J, et al, Neurobiol Sleep Circadian Rhythms 2:4, 2017)

## Where Are We Going From Here?

- Clinically
  - Question: Do we have enough data to suggest “screening” for OSA in patients being evaluated for Alzheimer’s disease?
  - Answer: I believe yes given high prevalence of OSA and suggestive (although not conclusive) evidence that OSA is involved in disease progression

## Where Are We Going From Here?

- Research
  - Question: What is most important question to answer?
  - Answer: Trial with propensity score matching of role of CPAP in affecting disease progression in patients with prodromal AD and with at least moderate OSA

Multi-center study in progress (PI: Dr. N. Gooneratne, Penn)

## An Area of Major Public Health Significance

- Can treatment of OSA in individuals with pre-symptomatic disease slow rate of progression of disease?