Sleep in Older Age & in People with Dementia

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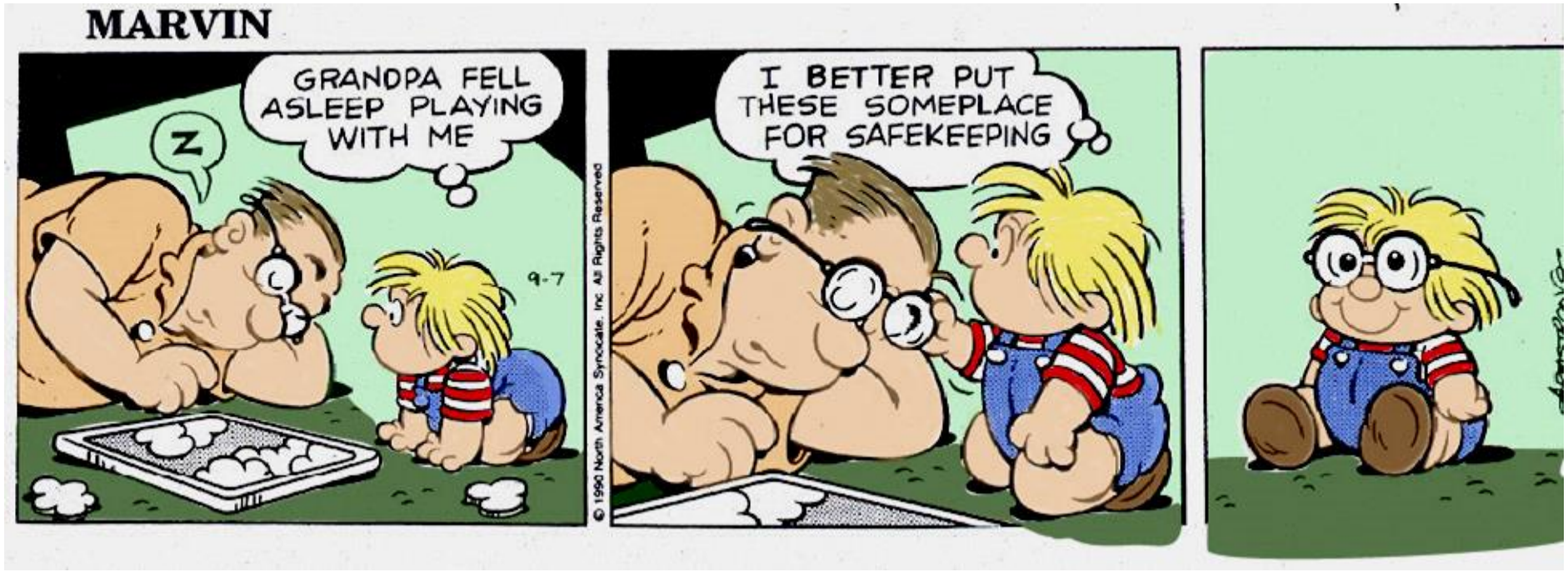
Conflict of Interest Disclosures for Speakers

Sonia Ancoli-Israel, PhD has no financial relationships to disclose

Learning Objectives

- After this session, you will be able to:
  1. Identify changes in sleep architecture with age
  2. Understand consequences of poor sleep in older adults
  3. Identify co-morbidities often associated with poor sleep in older adults
  4. Identify primary sleep disorders common in older adults and their treatment
  5. Learn about the association between OSA and cognition/dementia
  6. Learn about the association between sleep/circadian rhythms and cognition/dementia


MARVIN
GRANDPA FELL ASLEEP PLAYING WITH ME
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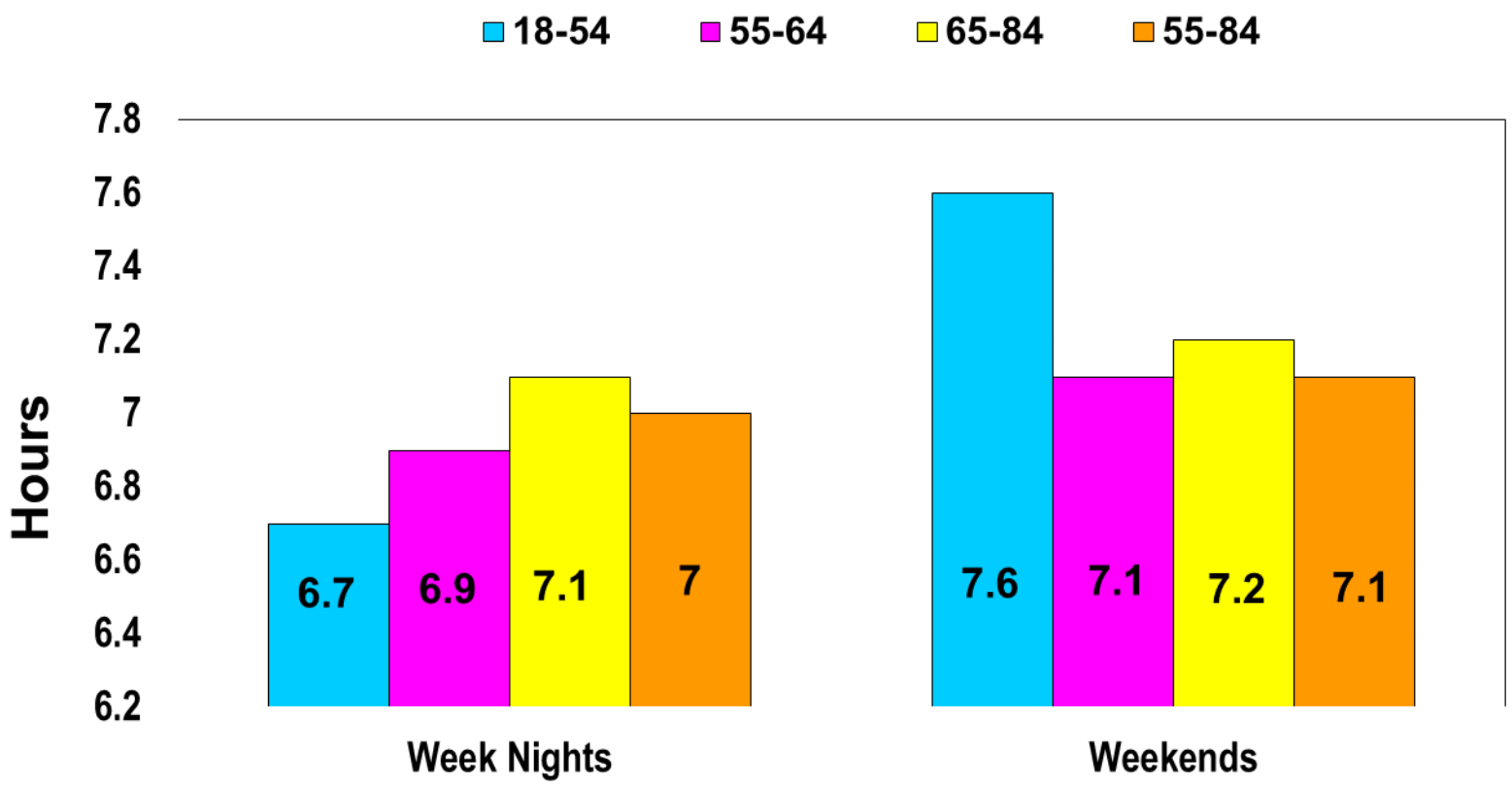
I BETTER PUT THESE SOMEPLACE FOR SAFEKEEPING

Reported Hours Slept
Older vs. Younger American Adults



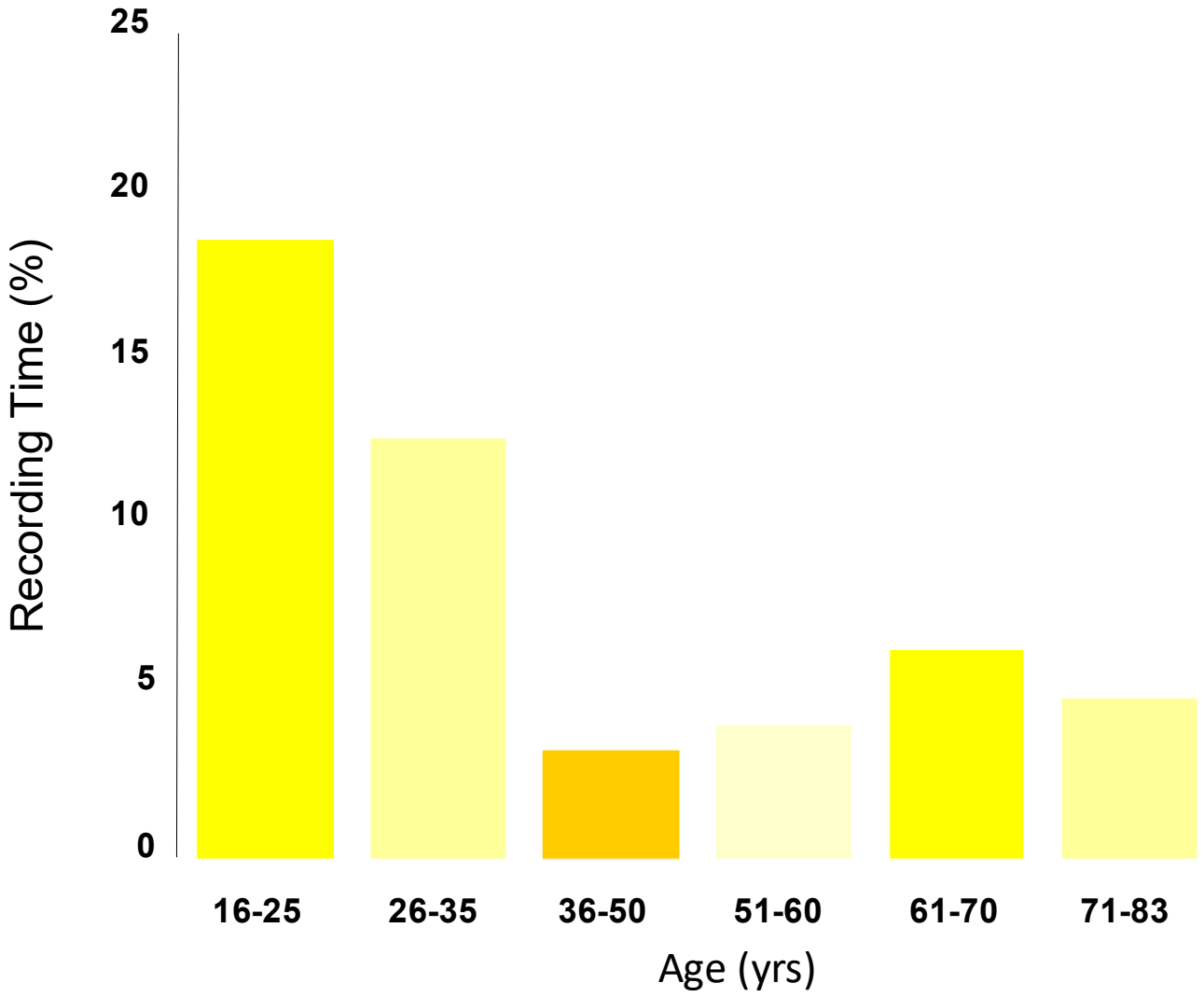
2003 NSF Sleep in America Poll

Changes in Sleep with Age

- Meta-analytic review of 65 sleep studies in healthy persons
  - 3557 total subjects aged 5-102 years
- Most age-related sleep changes occur in early and mid-years of human life span
- In healthy older adults:
  - Sleep remains relatively constant from age 60 to mid-90s
    - Except for SE which decreases

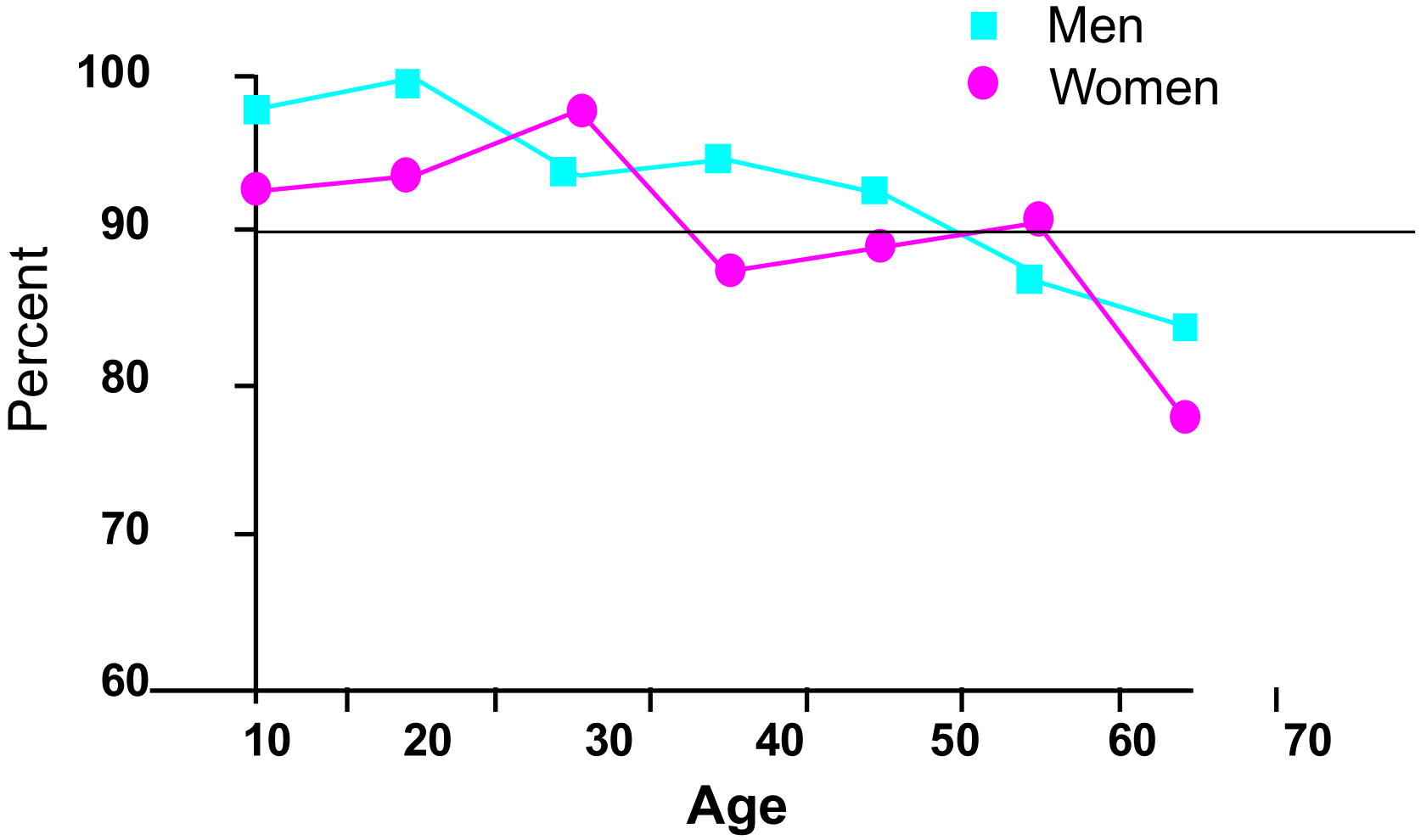
Ohayon MM et al. *Sleep.* 2004, 27:1255-1273.

Slow Wave Sleep



Van Cauter E et al. *JAMA*. 2000;284:861-868

Changes with Age: Sleep Efficiency



Modified from Ohayon et al. Sleep 2004, 27:1255-1273

Sleep disturbance and depression in older men (MrOS sleep study; n=3051)

Depressive symptoms have a strong, graded association with subjective sleep disturbances and are moderately associated with objectively measured prolonged sleep latency

	Normal) (n=2310)	Depressive symptoms (n=537)	Depression (n=204)	P-value
Subjective (PSQI)				
Pittsburgh Sleep Quality Index >5	1.0 (referent)	2.06 (95% CI 1.67-2.55)	3.68 (95% CI 2.54-5.33)	<0.001
Objective (5-days actigraphy)				
Sleep latency ≥1 hour	1.0 (referent)	1.40 (1.03-1.90)	1.68 (1.08-2.61)	0.006

All analyses adjusted for age, clinic site, race, body mass index, living alone, alcohol intake, smoking status, cognitive impairment, physical activity, certain medical conditions, education, self-reported health status, IADL impairments, and use of antidepressants, benzodiazepines and non-benzodiazepine anxiolytic/hypnotics.

Paudel et al, J Am Geriatr Soc. 2008 Jul;56(7):1228-35

Sleep disturbance and physical function in older men (MrOS sleep study; n= 2,862, >67y/o)

- Lighter and more fragmented sleep were associated with poorer performance
  - In age adjusted models, shorter TST, SE<80%, WASO ≥ 90 min, were associated with lower grip strength, slower walking speed, inability to stand from a chair without assistance, and inability to complete a narrow walk course

	Inability to Perform Chair Stand	Inability to Perform Narrow Walk	P-value
SE<80%	1.72 (95% CI 1.19, 2.49)	1.34 (95% CI 1.08, 1.66)	<0.05
WASO>90 min	1.73 (95% CI 1.20, 2.49)	1.33 (95% CI 1.07, 1.64)	<0.05

All analyses adjusted for age, BMI, clinic site, antidepressant use, hypertension, comorbid disease (history of at least one medical condition including cardiovascular disease, osteoarthritis, diabetes, COPD and Parkinson's disease), Physical Activity Scale for the Elderly, and smoking

Dam, Ewing, Ancoli-Israel et al, JAGS, 2008 56(9):1665-73

Summary of Study of Osteoporotic Fractures (SOF) Study Results (n= 3,022)

- A 30-40% increased risk of subsequent falls associated in older women with
  - TST< 7 hours / night
  - SE $\leq$ 65%
- An increased mortality risk in older women with
  - TST< 5 hours / night
  - SE $\leq$ 65%
  - >2 hour naps

After adjusting for race, age, BMI, medical conditions, depression, cognitive function, exercise, IADL, use of anti-depressant or benzodiazepine

Stone,K.L., Ewing,S.K., Lui,L.Y., Ensrud,K.E., Ancoli-Israel,S.,et al. JAGS 54:1177-1183, 2006; Stone,K.L., Ancoli-Israel,S., Blackwell,T., et al. *Arch. Intern. Med.* :168(16):1768-1775:2008

Consequences of Disturbed Sleep

- Difficulty sustaining attention
- Slowed response time
- Difficulty with memory
- Decreased performance

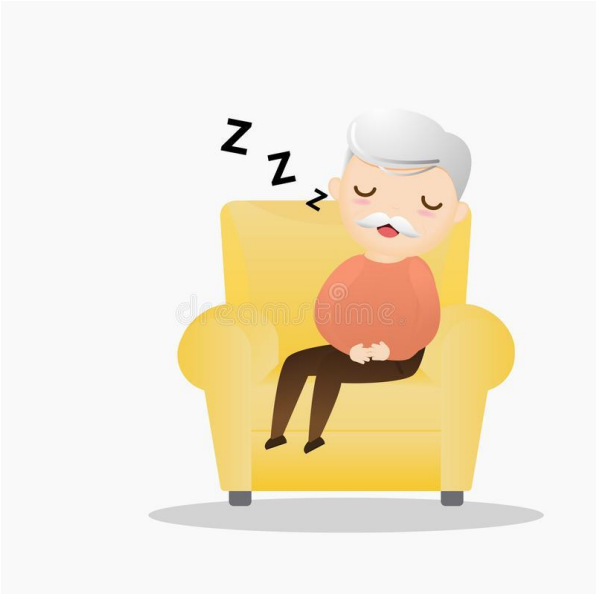
- Higher risk of
  - depression
  - poor physical function
  - cognitive impairment
  - falls
  - mortality

May all be misinterpreted as dementia

Ancoli-Israel S, Roth T. *Sleep*. 1999;22(suppl 2):S347-S353; Ancoli-Israel, 2000, Sleep, 23 (suppl), S23 - S30; Blackwell, Yaffe, Ancoli-Israel et al, J Gerontol: MED SCI, 2006, 61A(4):405–410; Dam, Ewing, Ancoli-Israel et al, JAGS, 2008 56(9):1665-73; Paudel et al, J Am Geriatr Soc. 2008 Jul;56(7):1228-35; Stone,K.L., Ewing,S.K., Lui,L.Y., Ensrud,K.E., Ancoli-Israel,S.,et al. JAGS 54:1177-1183, 2006; Stone,K.L., Ancoli-Israel,S., Blackwell,T., et al. *Arch. Intern. Med.* :168(16):1768-1775:2008

Why does sleep deteriorate as we get older?

- Is it aging?
- NO
- Age per se does NOT cause sleep problems
- BUT, all the things that go along with aging, do

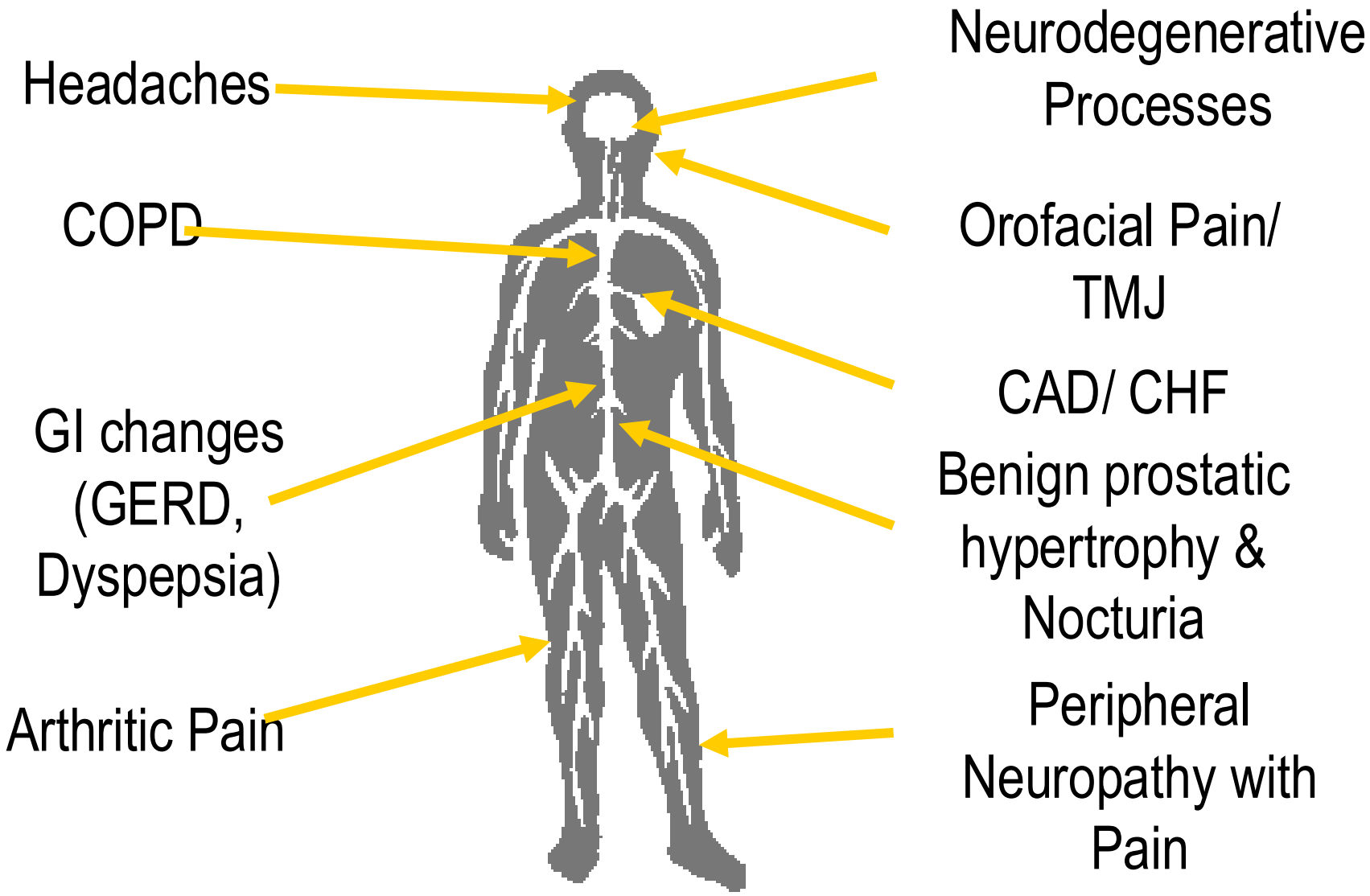


Factors Affecting Ability to Sleep in the Elderly

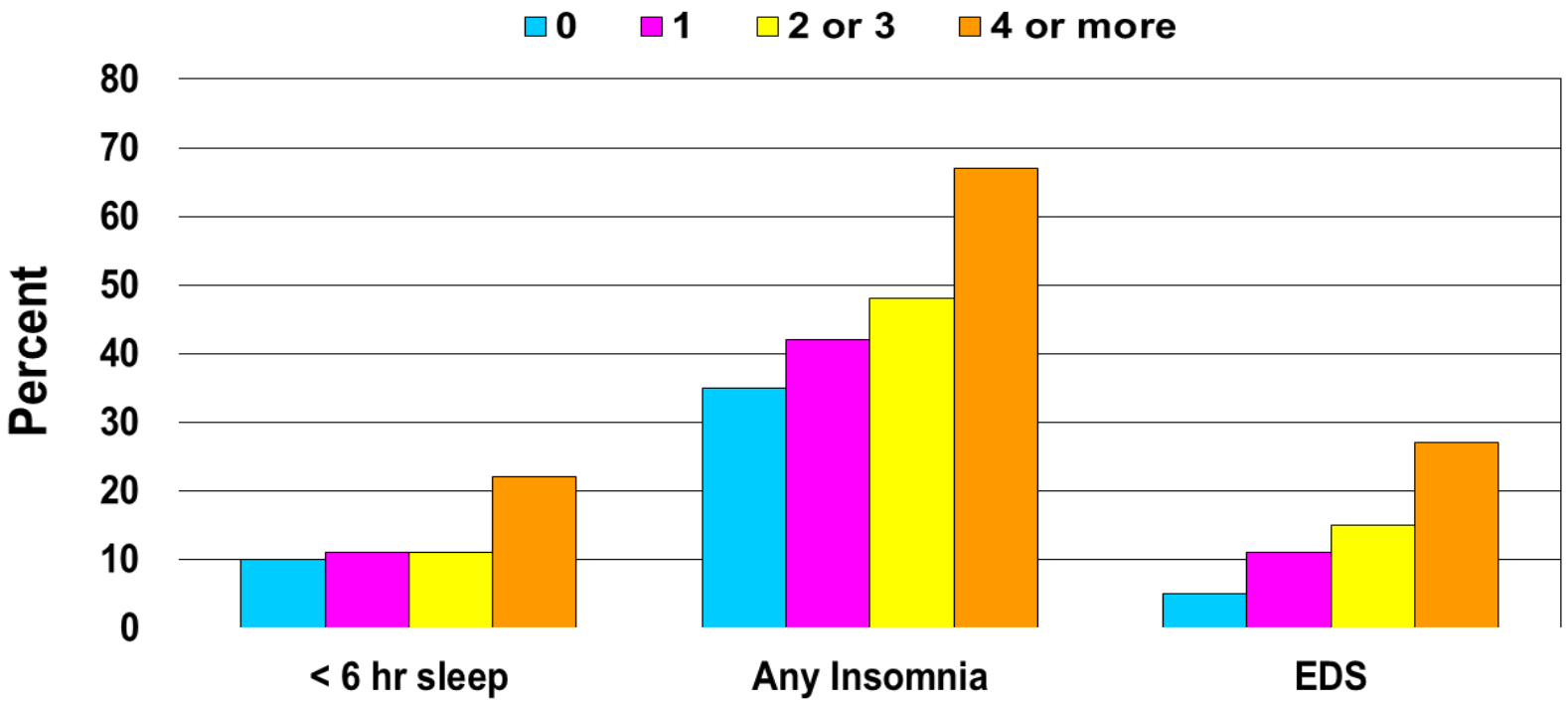
- Medical/psychiatric illness
- Medications/polypharmacy
- Circadian rhythm disturbances
- Primary sleep disorders
  - **Insomnia**
  - **Sleep apnea**
  - REM Behavior Disorder
  - Restless Legs Syndrome/Periodic Limb Movements in Sleep

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision. Washington, DC: American Psychiatric Association; 2000:597-661.

Many Medical Conditions are Co-Morbid with Disturbed Sleep



Sleep Problems and Multiple Medical Conditions



Foley, Ancoli-Israel, Bitz, Walsh, J Psychosom Res. 2004, 56(5):497-502.

Polypharmacy

Medications and Substances Associated with Insomnia

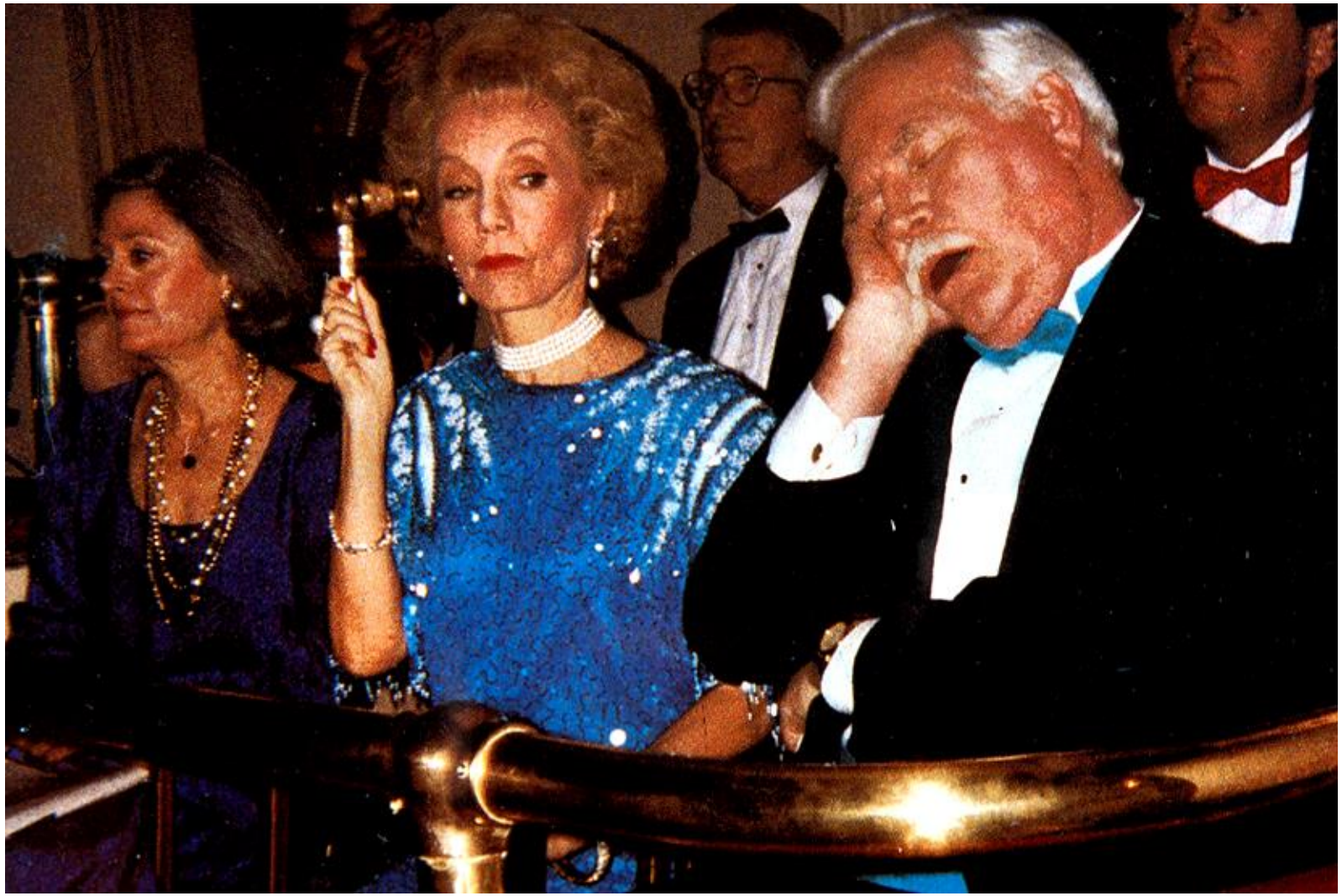
- Alcohol
  - Acute use
  - Withdrawal
- Caffeine
- Nicotine
- Antidepressants
  - SSRI
  - SNRI, atypical
- Corticosteroids
- Decongestants
  - Phenylpropanolamine
  - Pseudoephedrine
- β agonists, theophylline derivatives
- β antagonists
- Statins
- Stimulants
- Dopamine agonists

Any drug that crosses the blood brain barrier and affects a neurotransmitter system may be associated with insomnia

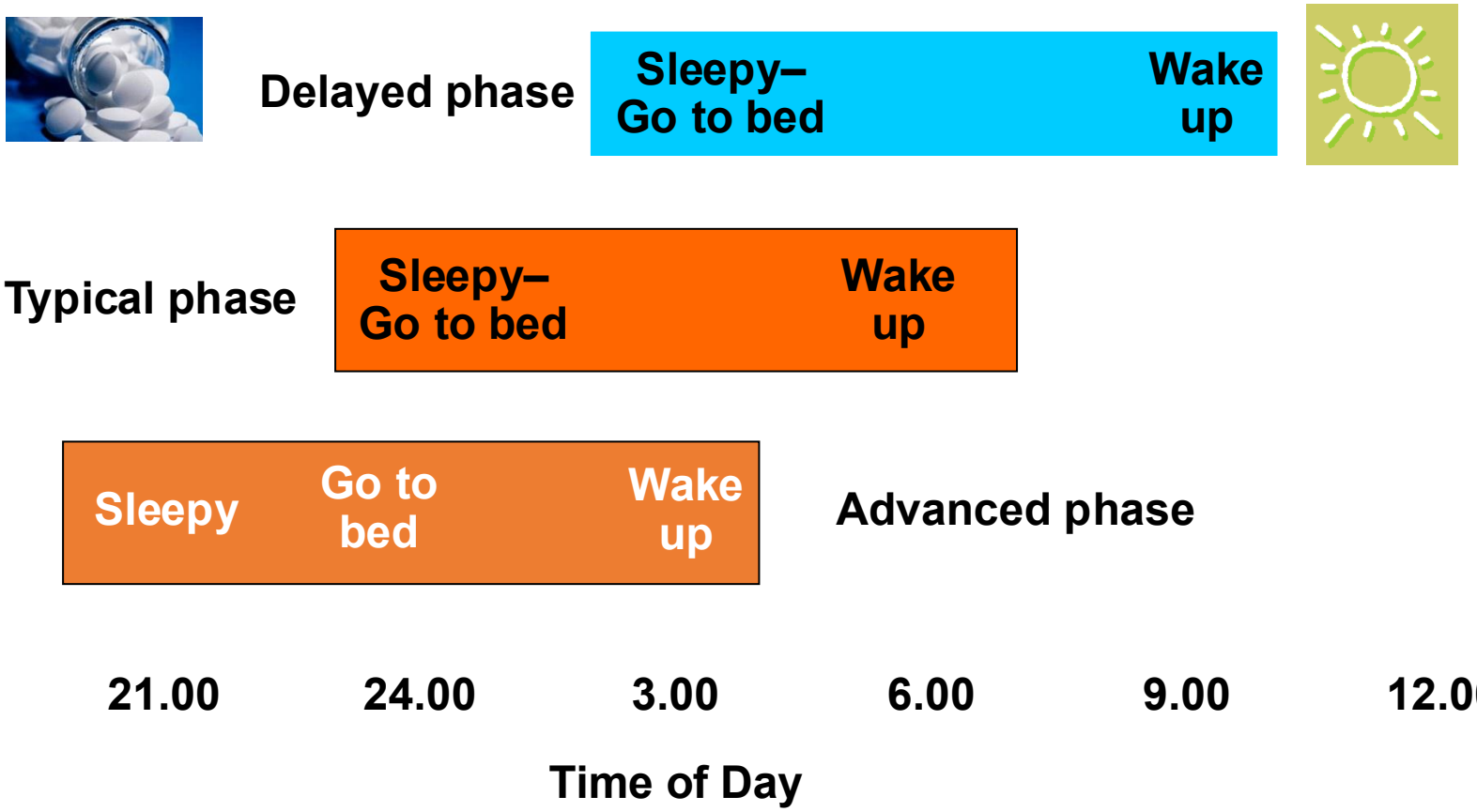
SSRI = Selective Serotonin Reuptake Inhibitor; SNRI = Serotonin and Norepinephrine Reuptake Inhibitor; Schweitzer, PPSM.

Hauri PJ. Insomnia. *Clin Chest Med*. 1998;19:157-168. *A Special Report: Sleep Disturbance*. Boston, MA: Harvard Medical School Health Publications Group; 1999.

Circadian Rhythm Disturbance: "Early to bed, early to rise…"

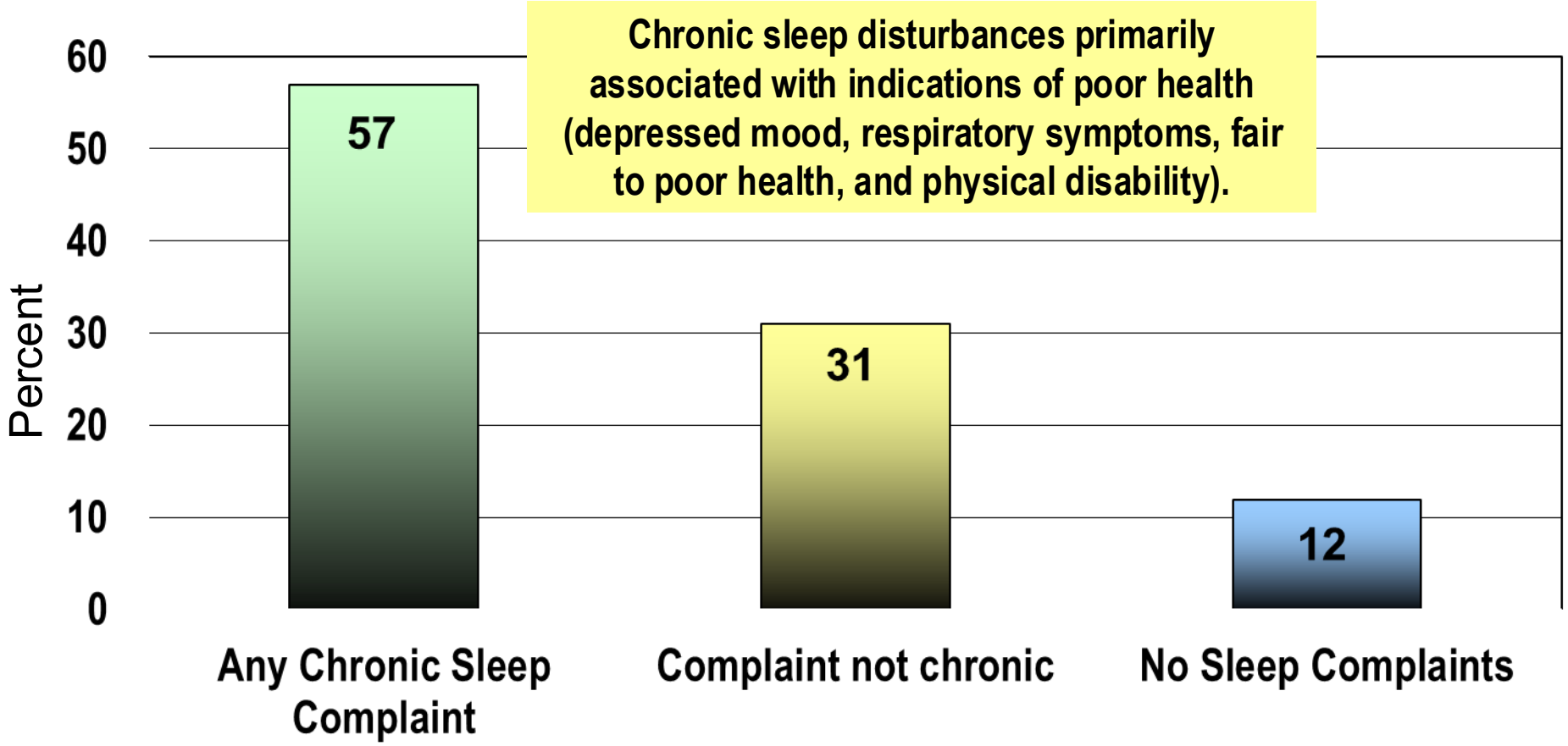


Circadian Sleep Phases



Modified from Ancoli-Israel, All I Want is a Good Night's Sleep, 1996

Insomnia Complaints
Prevalence Within Elderly (n=9282)



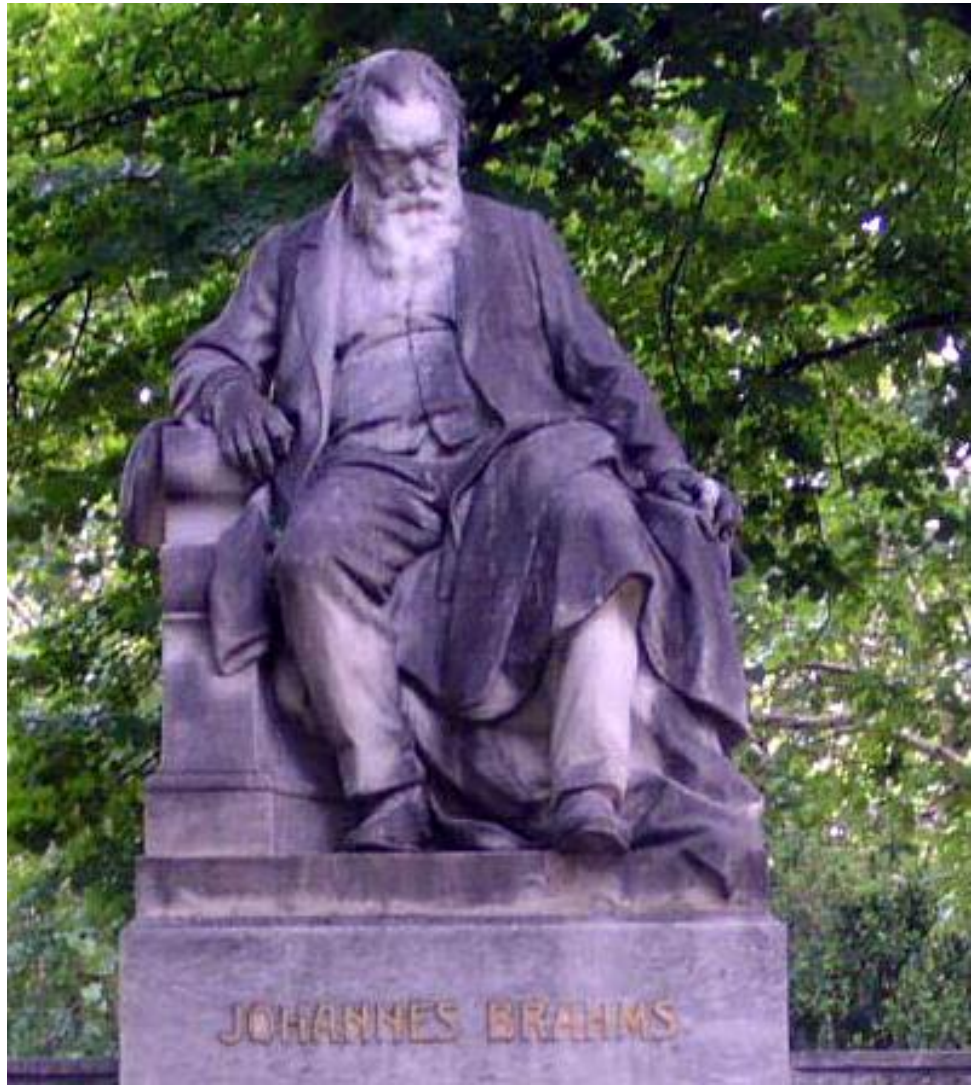
Foley, et al., Sleep, 1995, 18:425-432

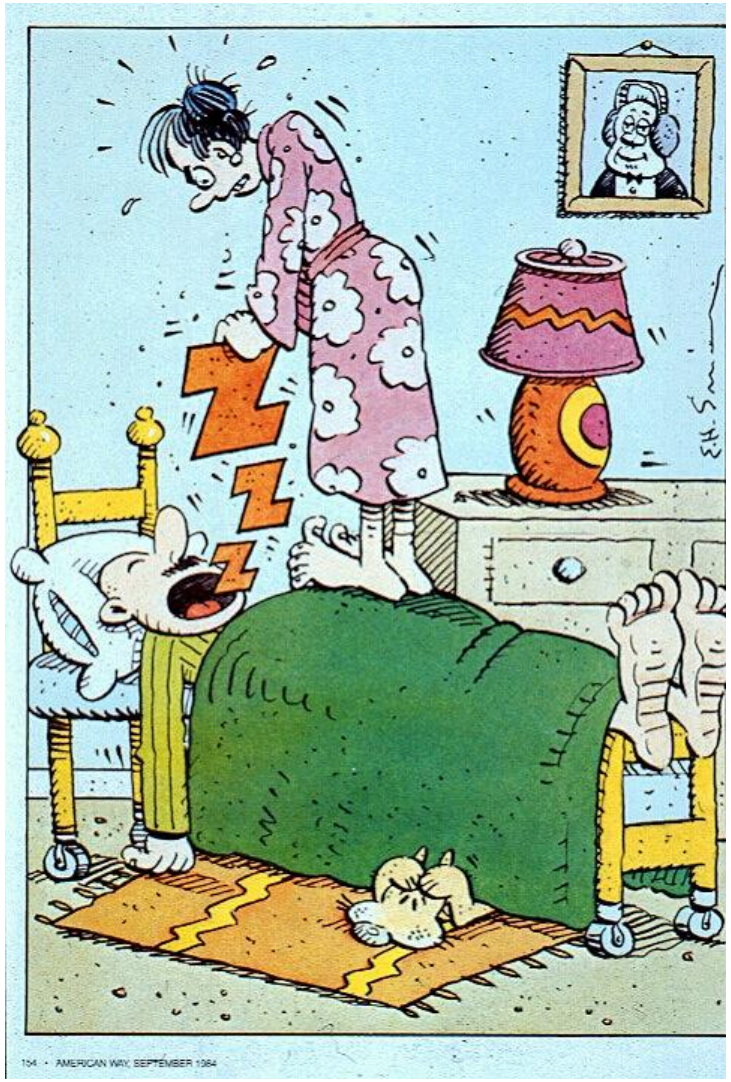
Incidence of Insomnia in the Elderly

- Of the 2000 survivors with chronic insomnia at baseline, about 50% had no symptoms at follow-up
  - Improved self-perceived health associated with discontinuation of insomnia symptoms
- Foley et al concluded:
  - "…these data do not support a model of incident insomnia caused by the aging process *per se*."

Foley D et al. *Sleep*. 1999;22:S366-372.

Sleep Disordered Breathing





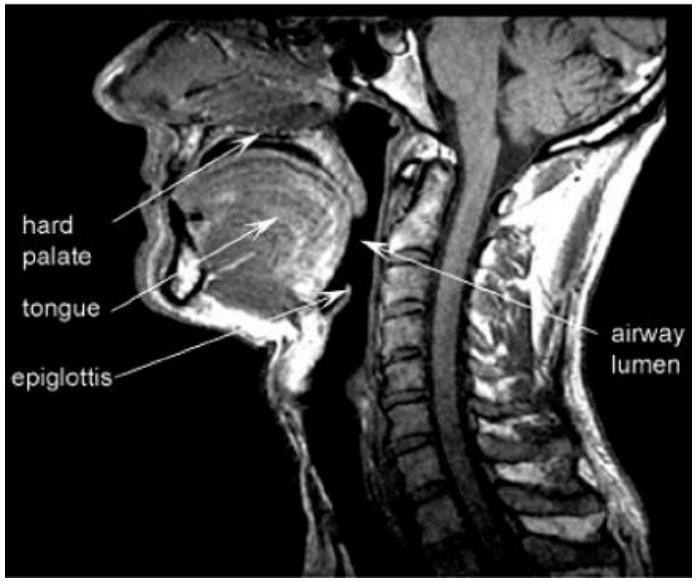
Prevalence of OSA in Older Adults

- One of the earliest studies to examine OSA in older adults (n=427; >65y/o) found a prevalence of 62% at RDI>10
- A much larger study of older men (MrOs; n=2911; age 76y) found that
  - 26.4% had RDI≥15; 60% had RDI≥5
    - The prevalence of RDI>15 increased with increasing age quartile (p=0.005)
    - The prevalence of RDI>5 did not increase with increasing age quartile (p=0.68)
- A more recent large study of community-recruited adults found that
  - for those aged 60-85 years (n=902), 48.7% had an RDI≥15 (64.7% in men, 35.2% in women)
    - significantly higher than in younger adults

Ancoli-Israel S et al Sleep, 1991, 14(6):486-495; Mehra R et al. JAGS 55:1356–1364, 2007;
Heinzer, R et al Lancet Respir Med. 2015; 3(4): 310–318

Changes in airway anatomy with age - MRI findings

- Soft palate gets longer
- Pharyngeal fat pads increase in size
- Shape of bony structures around pharyngeal airway change
- Response of genioglosus muscle to negative pressure stimulation diminishes



Midsagittal magnetic resonance image illustrating anatomic structures of interest

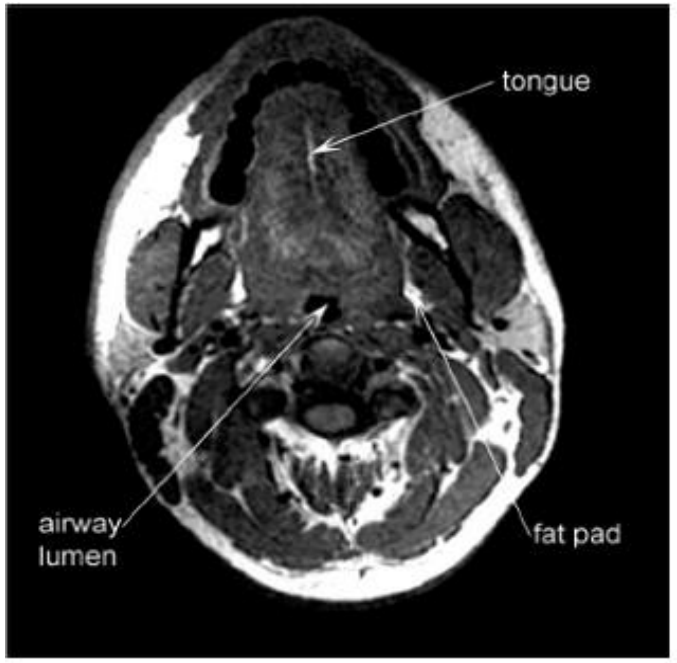


Figure 2 Axial magnetic resonance image illustrating structures relevant to pharyngeal collapse.

Malhotra et al. *Am J. Med,* 2006. 119:72.e9-e14

Is OSA pathological in elderly?

- ??? Most studies suggest that OSA does not increase the risk of mortality in the older adult
- Most studies DO suggest that older adults with SDB are
  - excessively sleepy
  - that OSA may contribute to
    - decreased quality of life
    - greater risk of nocturia, hypertension and cardiovascular disease
    - decreased cognitive function

Launois SH, et al. Sleep apnea in the elderly: a specific entity? Sleep Med Rev 2007; 11(2).

Association with OSA: Cognition
SOF (n = 400; age 82.8y)

- Cross sectional study of older women
- OSA associated with cognitive impairment (MMSE)
  - AHI≥15
    - OR 1.4, 95% CI 1.03-1.9
  - AHI≥30
    - OR 3.4, 95% CI 1.4-8.1
  - SaO2 nadir<80%
    - OR 2.7, 95% CI 1.1- 6.6].14
- Each standard deviation increase in AHI was associated with 70% greater odds of cognitive impairment.

Spira AP et al Sleep-disordered breathing and cognition in older women. J Am Geriatr Soc 2008;56:45-50.

Older women with OSA have an increased risk of developing cognitive impairment – Prospective Study

- Compared women
  - with OSA (n=105; 35.2%)
  - without OSA (n=193)
- At 5-year follow-up, those with OSA were more likely to develop MCI or dementia
    - 31.1% [n=60] vs 44.8% [n=47]; adjusted OR, 1.85; 95% CI, 1.11-3.08
- Elevated SaO_2 (>15 events/hour) and high % of TST (>7%) with apnea or hypopnea were associated with risk of developing
  - MCI (AOR, 1.71 [95% CI, 1.04-2.83])
  - dementia (AOR, 2.04 [95% CI, 1.10-3.78])
- Measures of sleep fragmentation (arousal index and wake after sleep onset) or sleep duration (total sleep time) were not associated with risk of cognitive impairment

Yaffe, K et al. JAMA. 2011;306(6):613-619

Studies of OSA and AD Biomarkers

Research reviewed involving OSA and AD biomarkers.

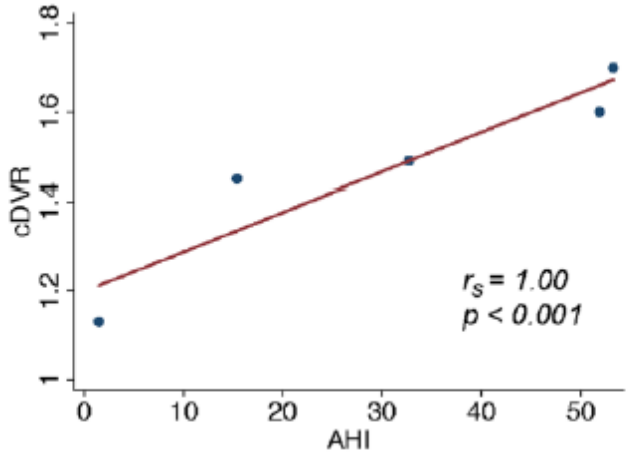
Authors	Study design and recruitment	Population	Age (years)	Sex (% female)	AD Biomarkers
Spira et al. 2014	Cross-sectional, community volunteers	5 MCI, 8 controls	MCI 75±11, controls 69±6	MCI 20%, controls 62.5%	Aβ deposition (PET-PiB)
Bu et al. 2015	Cross-sectional, sleep center	45 OSAS, 49 controls	OSAS 44±10, controls 43±10,	OSAS 27%, controls 31%	Serum $A\beta_{40}/A\beta_{42}$
Ju et al. 2016	Cross-sectional, community volunteers	10 OSA, 31 controls	OSA 56±4, control 53±6	OSA 30%, controls 48%	CSF $A\beta_{40}$, $A\beta_{42}$, tau, P-tau181
Liguori et al. 2017	Cross-sectional, sleep center	25 OSA, 10 OSA-CPAP, 15 controls	OSA 68±8, OSA-CPAP 67±7, controls 66±9	OSA 32%, OSA-CPAP 30%, controls 40%	CSF $A\beta_{42}$, P-tau, T-tau
Yun et al. 2017	Cross-sectional, community volunteers	19 OSA, 19 controls	OSA 57±4, controls 57±4	OSA 53%, controls 53%	Aβ deposition (PET-PiB)
Elias et al. 2018	Cross-sectional, war veterans	42 OSA, 77 non-OSA	OSA 68±5, non-OSA 68±4	No females	Aβ deposition (PET 18F-florbetaben, 18F-AV1451)
Motamedi et al. 2018	Cross-sectional, military personnel	28 mod-severe OSA, 22 mild OSA, 24 controls	Mod-severe OSA 36±8, mild OSA 34±8, controls 31±8	Mod-severe OSA 0%, mild OSA 4% controls 8%	Serum $A\beta_{40}$, $A\beta_{42}$, Tau
Sharma et al. 2018	Longitudinal, community volunteers	35 mod-severe OSA, 76 mild OSA, 97 controls	Mod-severe OSA 71±8, mild OSA 69±7, controls 68±7	Mod-severe OSA 51%, mild OSA 58%, controls 69%	CSF $A\beta_{42}$, P-tau181, T-tau, Aβ deposition (PET-PiB)
Liguori et al. 2019	Cross-sectional, community volunteers	20 OSA, 20 AD, 15 controls	OSA 59±4, AD 66±4, controls 64±8	OSA 30%, AD 65%, controls 47%	CSF $A\beta_{40}$, $A\beta_{42}$, P-tau, T-tau,
Handa et al. 2019	Cross-sectional, tertiary hospital	14 OSA	65±10	29%	Aβ deposition (PET-PiB)
Bubu et al. 2019	Longitudinal, community volunteers	798 (103 OSA+) MCI, 325 (22 OSA+) AD, 516 (29 OSA+) cognitively normal	MCI 74(68,79) AD 76(71,80) cognitively normal 74(71,78)	MCI 40% (25% OSA+), AD 37% (27% OSA+), cognitively normal 49% (27% OSA+)	CSF $A\beta_{42}$, P-tau181, T-tau, Florbetapir PET uptake
Ju et al. 2019	Interventional, community volunteers	18 (14) OSA-CPAP	57±8	23%	CSF $A\beta_{40}$, $A\beta_{42}$, T-tau
Carvalho et al. 2020	Cross-sectional, population based	292 cognitively unimpaired (43 with "witnessed apneas")	WA+ 73 (range 69-80), WA- 75 (range 69-82)	WA+ 23% WA- 75 38%	AV-1451 Tau-PET, Aβ deposition (PET-PiB)
André et al. 2020	Cross-sectional, community volunteers	96 SDB+, 31 SDB-	SDB+ 69±4, SDB- 69±4	SDB+ 58%, SDB- 77%	Florbetapir PET uptake

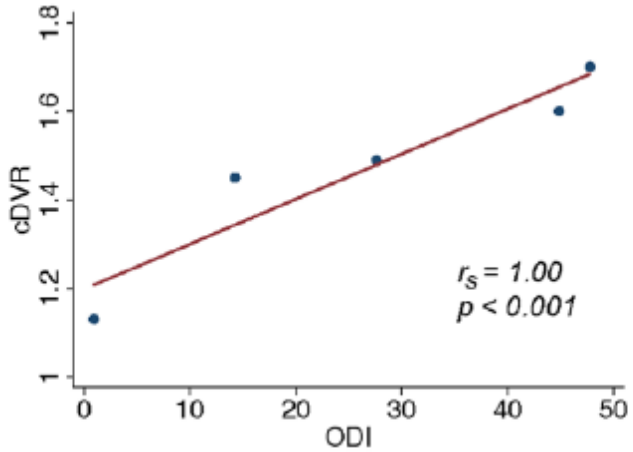
Aβ; amyloid-β; AD: Alzheimer's disease; CPAP: continuous positive airway pressure; CSF: cerebrospinal fluid; OSA: obstructive sleep apnea; OSAS: obstructive sleep apnea syndrome; PET: positron emission tomography; WA: witnessed apnea. Median (SEM), Median [IQR]. Ages and percentages values are rounded from the source manuscript. **Studies involving CPAP are highlighted in green.**

Mullins A et al
Neurobiology of Disease
145 (2020) 105054

OSA and β-amyloid Burden in Older Adults

- Baltimore Longitudinal Study of Aging, neuroimaging substudy; Pilot study
  - 13 older adults (8 with normal cognition and 5 with mild cognitive impairment)
  - neuropsychological testing, PSG, Aβ imaging
- Results: Among participants with MCI, higher AHI and oxygen desaturation index were associated with greater Aβ deposition
  - There were no significant associations between OSA and Aβ deposition among cognitively normal participants.
  - There were no significant associations between sleep duration or sleep fragmentation and Aβ deposition
- **Conclusion:** These preliminary results suggest that among older adults with mild cognitive impairment, greater OSA severity is associated with greater Aβ deposition.

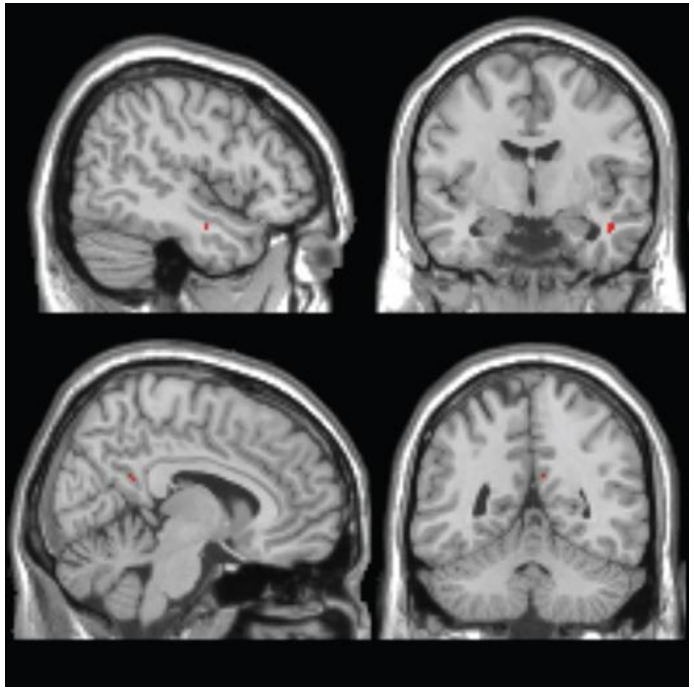




Spira A et al. SAGE Open Med. 2014 Aug 12;2. doi: 10.1177/2050312114546520

OSA associated with increased Aβ pathology

- PET from cognitively-normal adults with (n=19) and without OSA (n=19).
  - age 50-65 years
- Conclusion: OSA accelerates amyloid deposition and may contribute to the development or progression of Alzheimer's disease



Yun CH et al. J Alzheimer's Dis. 2017;59(1):21-29

Sleep Apnea and Dementia (n=92)

- 90% of the patients had AHI ≥5
  - Mean AHI = 32.0; SD = 26.1
- 63% of the patients had AHI ≥15
  - Mean AHI = 40.6; SD = 26.7
- 50% of the patients had AHI ≥20
  - Mean AHI = 46.9; SD = 26.6
- Those with more severe AD have more severe OSA (p=0.03)
- Those with more severe OSA have more severe dementia (p=0.004)

Gehrman, Ancoli-Israel, et al. *J Am Geriatric Psychiatry.* 2003;11:426-433;
Ancoli-Israel et al., JAGS, 1991, 39:258-263

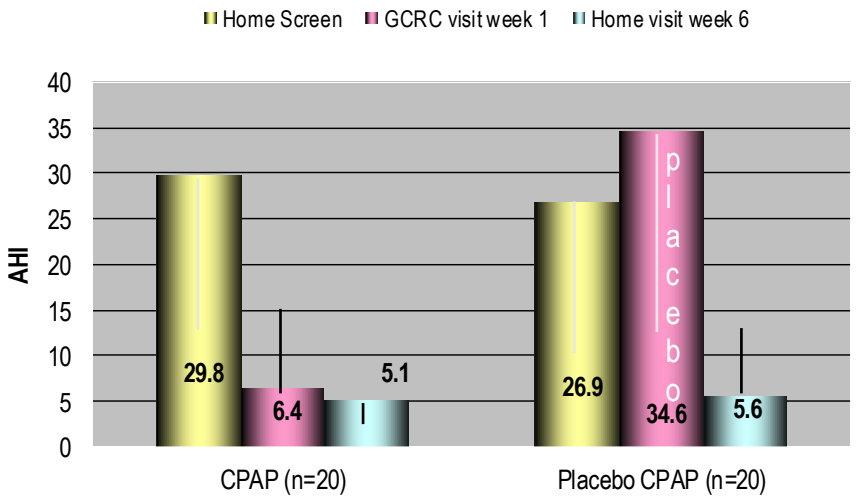
Does treating sleep apnea *in the older adult* lead to improvements?

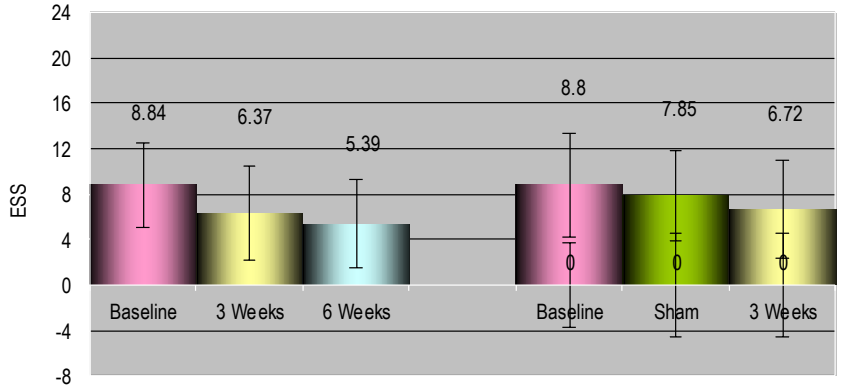
- In a review of the literature, Weaver and Chasen concluded that data suggest that in the elderly, CPAP
  - Reduces or eliminates apneas and hypopneas
  - Improves sleep architecture
  - Improves daytime sleepiness
  - Improves self-reported symptoms (snoring and gasping)
  - Improves motor speed and nonverbal learning and memory
  - Improves vascular resistance, platelet coagulability and other factors affecting cardiac function
  - Has a positive effect on nocturia, reducing the number of voids per night.

Weaver TE, Chasens ER. Continuous positive airway pressure treatment for sleep apnea in older adults. Sleep Med Rev 2007; 11(2)

Effect of CPAP in Alzheimer's Disease

- 3-weeks of CPAP in AD results in improvement in
  - AHI levels and ↓SpO_2
  - Epworth Sleepiness scores
  - Deeper Sleep
    - ↓N1, ↑N2,REM; ↓WASO, ↓ArI, Improved cognitive functioning
    - Longer use slowed dementia progression





Ayalon et al. AJGP 2006 14(2):176-80; Chong et al JAGS 2006 54(5):777-81; Cooke, JR. et al. Sleep Med. 2009;10(10):1101-6; Ancoli-Israel,S., et al *JAGS.* :2008, 56:2076-81

Studies effect of CPAP on Cognition

- “CPAP may be effective in improving cognition, particularly in the presence of sleepiness and given good treatment adherence.
- CPAP treatment also shows promise for delaying further cognitive decline in those with MCI and AD
  - more cognitive assessments where encoding and recall are separated by a period of sleep are needed to understand OSA-related impaired cognition within individuals.”

Research reviewed involved OSA and cognition.

Authors	Study design and recruitment	Population	Age (years)	Sex (% female)	Cognitive domain or task
Yesavage et al. 1985	Cross sectional, sleep clinic	41 OSA	70±7	No females	Attention, executive function, memory
Berry et al. 1990	Cross sectional, sleep clinic	8 OSAS, 12 controls	OSAS 69±5, controls 68±2	No females	Memory
Bedard et al. 1991	Cross sectional, sleep clinic	20 mod-severe OSAS	52±9	Not reported	Reaction time, vigilance
Heyward et al. 1992	Cross sectional, retirement village	55 non-demented elderly	78±4	22%	Attention, executive function, memory
Phillips et al. 1992	Cross sectional, community volunteer	93 healthy adults	66±9	52%	Attention, executive function, memory
Naëgelé et al. 1995	Cross sectional, clinic & community volunteers	17 OSA, 17 controls	OSA 46±3, controls 48±3	No females	Attention, memory
Boland et al. 2002	Cross sectional, population based	1700 SHHS cohort	62 (range 52-75)	54%	Attention, executive function, memory
Salerio et al. 2002	Cross sectional, clinic & community volunteers	28 OSA, 26 controls	OSA 44±8, controls 46±5	OSA 39%, controls 42%	Memory, executive function
Foley et al. 2003	Cross sectional, community volunteer	718 OSA	Range 79-97	No females	Attention, executive function, memory
Ferini-Strambi et al. 2003	RCT, sleep clinic	23 OSA (CPAP+ 15 days), 23 controls	OSA 57±6, controls 56±5	OSA 9%, controls 17%	Processing speed, executive function
Aloia et al. 2005	RCT, sleep clinic	12 OSA (6 CPAP+)	65±8	Not reported	Attention, executive function, memory
Quan et al. 2006	Cross sectional, population based	67 OSA, 74 controls	OSA 58±9, controls 57±9	OSA 33%, controls 47%	Attention, vigilance, executive function, memory
Naëgelé et al. 2006	Cross sectional, clinic & community volunteers	55 OSA, 55 controls	OSA 46±11, controls 48±8	OSA 31%, controls 27%	Memory
Chong et al. 2006	RCT, clinic	40 with OSA: 19 (CPAP+ 3 weeks), 20 (Sham CPAP)	78±7	CPAP 76%, Sham 75%	Sleepiness
Kim et al. 2007	Cross sectional, population based	611 Wisconsin cohort	53±8	43%	Vigilance
Mathieu et al. 2008	Cross sectional, sleep clinic	14 young & 14 older OSAS, 12 young & 18 older controls	Young 38±2 & older 62±2 OSAS, young 30±2 & older 63±2 controls	Young 7% & older 7% OSAS, young 17% & older 11% controls	Attention, executive function, memory
Sohre et al. 2008	Cross sectional, community volunteer	57 OSA, 391 controls	OSA 84±6, controls 83±3	100%	Executive function
Akhunetin et al. 2008	Cross sectional, sleep clinic	58 OSAS, 41 controls	OSA 68 (range 32-93), controls 69 (range 33-83)	Not reported	Attention/alertness
Kloepfer et al. 2009	Cross sectional, clinic & community volunteers	15 OSA, 20 controls	OSA 46±6, controls 47±6	OSA 33%, controls 40%	Memory
Sharma et al. 2010	Cross sectional, clinic & community volunteers	50 severe OSA, 25 controls	OSA 43±8, controls 46±6	OSA 18%, controls 16%	Alertness, memory executive function
Slavia et al. 2010	Cross sectional, community volunteer	405 OSA, 582 controls	68±2	OSA 49%, controls 59%	Attention, executive function, memory
Saaresranta et al. 2012	RCT, sleep clinic	20 OSA, 17 controls	OSA 50 (range 27-65), controls 64 (range 30-69)	No females	Memory, verbal fluency
Bowden et al. 2011	Cross sectional, clinic & community volunteers	17 OSA, 20 controls	OSA 41±13, controls 38±9	Not reported	Attention, memory executive function
Blackwell et al. 2011	Cross sectional, population based	2909 older men	78±6	No females	Executive function
Artiti et al. 2011	Cross sectional, sleep clinic	174 mod-severe OSA	50±12	25%	Sleepiness
Frubos-Strom et al. 2013	Cross sectional, community volunteer	208 mod-severe OSA	48±11	44%	Memory, executive function
Ju et al. 2012	Cross sectional, sleep clinic	42 OSA, 21 controls	OSA 68±4, controls 69±6	OSA 38%, controls 48%	Executive function
Kashlla et al. 2012	RCT, sleep clinic	566 OSA (CPAP+ 6 months), 942 OSA (Sham CPAP)	CPAP 52±12, Sham 51±12	CPAP 15%, Sham 14%	Attention, vigilance, memory
Nikodemova et al. 2013	Cross sectional, community volunteer	755 Wisconsin cohort	54 (range 30-61)	38%	Memory, executive function
Landry et al. 2014	Cross sectional, sleep clinic	12 OSA, 12 controls	OSA 53±2, controls 53±3	OSA 25%, controls 25%	Overnight motor memory, sleepiness
Djonlagic et al. 2014	Cross sectional, sleep clinic	38 OSA, 20 controls	OSA 41±1, controls 35±3	Not reported	Overnight motor memory, vigilance
Varga et al. 2014	Interventional, sleep clinic	18 severe OSA (CPAP compliant 2+ months)	54	22%	Overnight spatial memory, vigilance
McMillan et al. 2014	RCT, sleep clinic	219 OSA (148 CPAP+ 3.12 months)	OSA-CPAP 71±5, OSA 71±5	OSA-CPAP 14%, OSA 21%	Sleepiness, global cognition
Troussière et al. 2014	Cross sectional, memory clinic	40 with severe OSA 14 (CPAP+ >3 months), 9 (no CPAP)	CPAP+ 73 (range 68-80) CPAP- 78 (range 75-79)	CPAP+ 73 (range 68-80) CPAP- 78 (range 75-79)	Global cognition
Blackwell et al. 2015	Longitudinal, community volunteers	1132 OSA, 1504 controls	OSA 76±5, controls 78±5	No females	Global cognition
Martin et al. 2015	Longitudinal, population based	599 OSA	67±5	56%	Global cognition
Djonlagic et al. 2015	Cross sectional, sleep clinic	29 OSA (14 CPAP+ 1 night), 15 controls	OSA 43±13, CPAP 44±11, controls 37±11	Not reported	Overnight motor memory, vigilance
Martinez-Garcia et al. 2015	RCT, sleep clinic	115 (CPAP+ 5 months), 109 (no CPAP)	OSA-CPAP 75±4, OSA 76±4	OSA-CPAP 56%, OSA 27%	Sleepiness, executive function
Guimaraes et al. 2015	RCT, sleep clinic	Severe OSA 17 CPAP+ 5 months, 16 no CPAP	OSA-CPAP 71±9, OSA 72±8	OSA-CPAP 59%, OSA 25%	Memory, executive function
Lutsey et al. 2016	Longitudinal, population based	446 OSA, 521 controls	OSA 63±5, controls 65±4	OSA 39%, controls 47%	Global cognition
Landry et al 2016	Cross sectional, sleep clinics	34 OSA, 13 CPAP+ 1 night, 17 CPAP+ >6 weeks, 14 controls	OSA 47±2, CPAP 1night 48±2, CPAP compliant 49±2, Controls 47±3	OSA 17%, CPAP 1night 38%, CPAP compliant 24%, Controls 57%	Overnight motor memory, sleepiness, vigilance
Jackson et al. 2018	Cross sectional, clinic & community volunteers	110 OSA (88 CPAP+ 6 months), 81 controls	OSA 47±1, CPAP 46±1, controls 48±2	OSA 22%, CPAP 18%, controls 28%	Sleepiness, vigilance, executive function
Bhat et al. 2018	Cross sectional, sleep clinic	92 mild-mod & 90 severe OSA (CPAP+ >1 month)	Mild-mod OSA 50±12, severe 53±13	27%	Sleepiness, fatigue, vigilance
Gagnon et al. 2019	Observational, community volunteers	57 OSA, 54 mild/non OSA	OSA 63±6, non OSA 65±7	OSA 55%, non OSA 62%	Subjective and objective cognition
Richards et al. 2019	RCT, clinic & community volunteers	94 MCI with OSA (29 CPAP+ 6.12 months)	OSA-CPAP 67±7, OSA 73±8	OSA-CPAP 31%, OSA 40%	Global cognition, vigilance, memory
Kainulainen et al. 2020	Observational, sleep clinic	794 OSA	57 (IQR 46-67)	41%	Vigilance

Mullins A et al Neurobiology of Disease 145 (2020) 105054

When to Treat Sleep Apnea in the Elderly?

- The bottom line is that if the sleep apnea is associated with clinical symptoms, then it should be treated, regardless of the age of the patient.
  - Excessive daytime sleepiness
  - Hypertension
  - Cognitive dysfunction
  - Nocturia
  - Cardiac disease
  - High levels of sleep-disordered breathing

Ancoli-Israel, Sleep Med Rev. 2007 Apr;11(2):83-5.

PLMS and Cognition/Dementia

- Older men (n=2636) without dementia but with PLMS followed for 3.5 years[1]
  - Results and Conclusions:
    - Higher PLMS frequency was associated with greater decline in cognition over 3-4 years, particularly in executive function
    - Those with a PLMI ≥ 30 were 48% more likely to experience the development of significant cognitive impairment
- Retrospective study based on inpatient medical records of hospitalized middle-aged and elderly patients (n=818)[2]
  - Results and Conclusions:
    - PLMS≥5 was associated with poorer cognitive function
    - REM sleep duration and PLMS-related arousal played a partial mediating role

1. Leng, Y. et al. Periodic limb movements in sleep are associated with greater cognitive decline in older men without dementia. *Sleep* 39, 1807–1810 (2016)
2. Sun S, et al Periodic leg movements and cognitive function in middle-aged and elderly adults with mediating role of REM duration and PLMS-related arousal. Sci Rep. 2025 Jun 3;15(1):19468. doi: 10.1038/s41598-025-04660-7. PMID: 40461718; PMCID: PMC12134141

Sleep and Cognition/Dementia

"Is it that your sleep is disrupted and the Alzheimer's proteins build up -- or are the Alzheimer's proteins being deposited in the brain, disrupting sleep, and that's where the cycle gets initiated?“

Ronald Petersen, MD, Mayo Clinic

Sleep/wake disturbance → Neurodegenerative disease

Association of sleep duration in middle and old age with incidence of dementia (n=7959 participants of the Whitehall II study)

- 25-year follow-up
- Results
  - Higher dementia risk associated with a sleep duration of six hours or less at age 50 and 60, compared with a normal (7 h) sleep duration
  - Persistent short sleep duration at age 50, 60, and 70 compared to persistent normal sleep duration was also associated with a 30% increased dementia risk
    - independently of sociodemographic, behavioral, cardiometabolic, and mental health factors
- Conclusion: Short sleep duration in midlife is associated with an increased risk of late-onset dementia

Sabia, S., Fayosse, A., Dumurgier, J. *et al.* Association of sleep duration in middle and old age with incidence of dementia. *Nat Commun* **12**, 2289 (2021)

Sleep disturbance and cognition in older women (SOF; n=2932 women, mean age 83.5 years)

- Objectively measured (5-days actigraphy) disturbed sleep was consistently related to poorer cognition

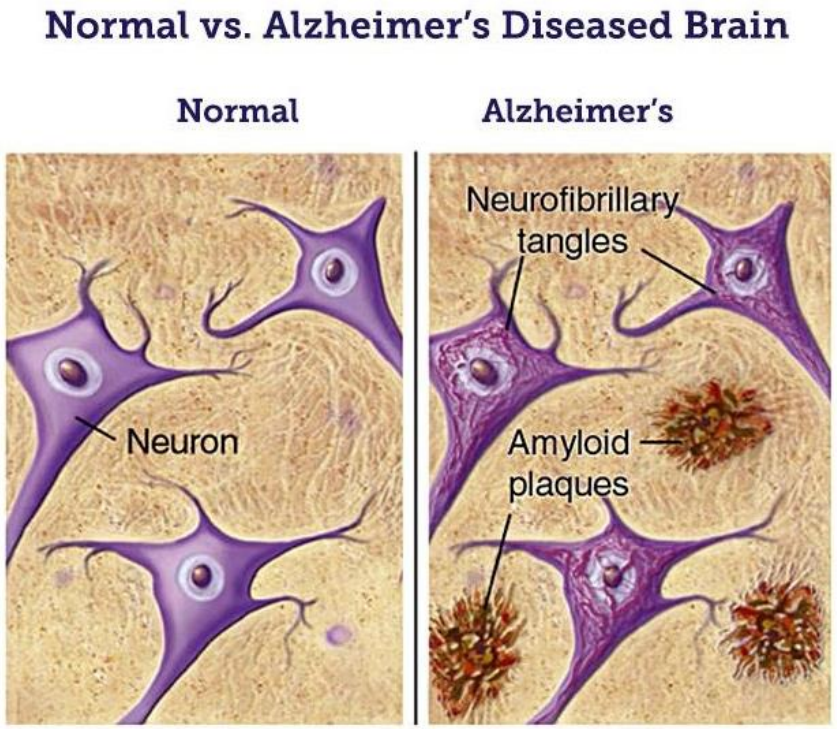
	MMSE<26	Trails B >278s	P-value
SE<70%	1.61 (95% CI 1.20–2.16)	1.96 (95% CI 1.43–2.67)	<0.05
Higher sleep latency (30m)	1.23 (95% CI 1.13–1.33)	1.13 (95% CI 1.04–1.24)	<0.05
Higher WASO (30m)	1.15 (95% CI 1.06–1.23)	1.24 (95% CI 1.15–1.34)	<0.05

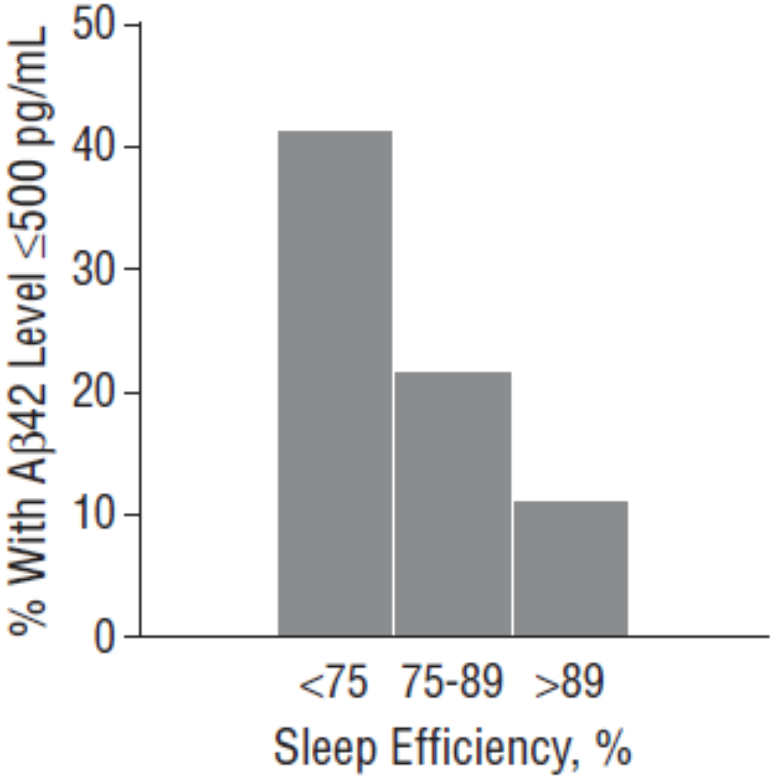
All analyses adjusted for age, race, depression, education, body mass index, health status, history of stroke, history of hypertension, functional status, smoking, alcohol use, caffeine, antidepressant use, and physical activity.

Blackwell, Yaffe, Ancoli-Israel et al, J Gerontol: MED SCI, 2006, 61A(4):405–410

Sleep and Aβ/Tau deposition

- In cognitively normal adults (mean 65.6 y/o) followed for 3 years, worse SE and more frequent napping (>3x/week) was associated with Aβ deposition





Ju et al., *JAMA Neurology*. 2013;70(5):587-593;

Sleep and Aβ/Tau deposition

- Baltimore Longitudinal Study of Aging Neuroimaging Substudy (mean 60 y/o), those with
  - [1]EDS had >3 times the odds of being Aβ+ on follow-up PET scans 16 years later [odds ratio [OR] = 3.37, 95% CI: 1.44, 7.90, p = 0.005]
  - [2]reported shorter TST (6-7 hrs) and lower sleep quality were associated with greater Aβ burden
- [3]In cognitively normal elderly, reduced and fragmented SWS is associated with increases in CSF Aβ, suggesting that disturbed sleep might drive an increase in soluble brain Aβ levels prior to amyloid deposition.

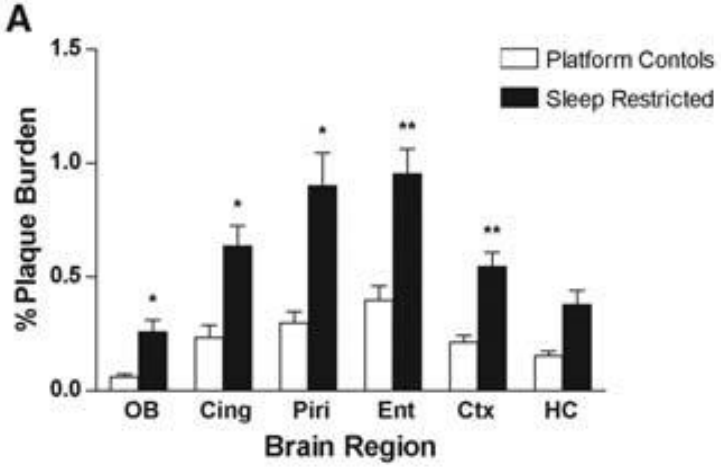
- [4]One night of sleep deprivation, relative to baseline, resulted in a significant increase in Aβ burden in the brain regions that have been implicated in Alzheimer's disease.

1. Spira et al. Sleep, 2018, 1–7; 2. Spira A et al. JAMA Neurol 2013, 70(12):1537-43; 3. Varga AW et al. Sleep. (2016); 4. Shokri-Kojori E et al Proc Natl Acad Sci U S A. 2018, 24;115(17):4483-4488, Ooms et al., *JAMA Neurol*, 2014 Lucey et al., *Ann Neurol*, 2018 Holth et al., *Science*, 2019

Sleep and β-amyloid (Aβ)

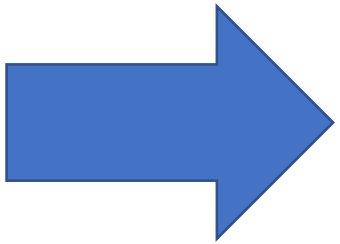
- Extracellular levels of Aβ and tau fluctuate during the normal sleep-wake cycle
- Disturbed sleep and increased wakefulness acutely lead to increased Aβ production and decreased Aβ clearance; Aβ aggregation and deposition is enhanced by chronic increased wakefulness in animal models.
- Once Aβ accumulates, there is evidence in both mice and humans that this results in disturbed sleep.
- Acute sleep deprivation increases levels of tau in mouse brain interstitial fluid (ISF) and human cerebrospinal fluid (CSF)

- Chronic sleep deprivation accelerates the spread of tau protein aggregates in neural networks.
- Accumulation of tau aggregates in the brain correlates with decreased nonrapid eye movement (NREM) sleep slow wave activity.



Kang et al., *Science* 2009;326:1005-7; Tabuchi et al., *Current Biology* 2015;25:702-712; Winer et al. 2020. *Current Biology,;* Wang and Holtzman,. Neuropsychopharm, 2020, 45(1):104-120

Neurodegenerative disease



Sleep/ wake disturbance

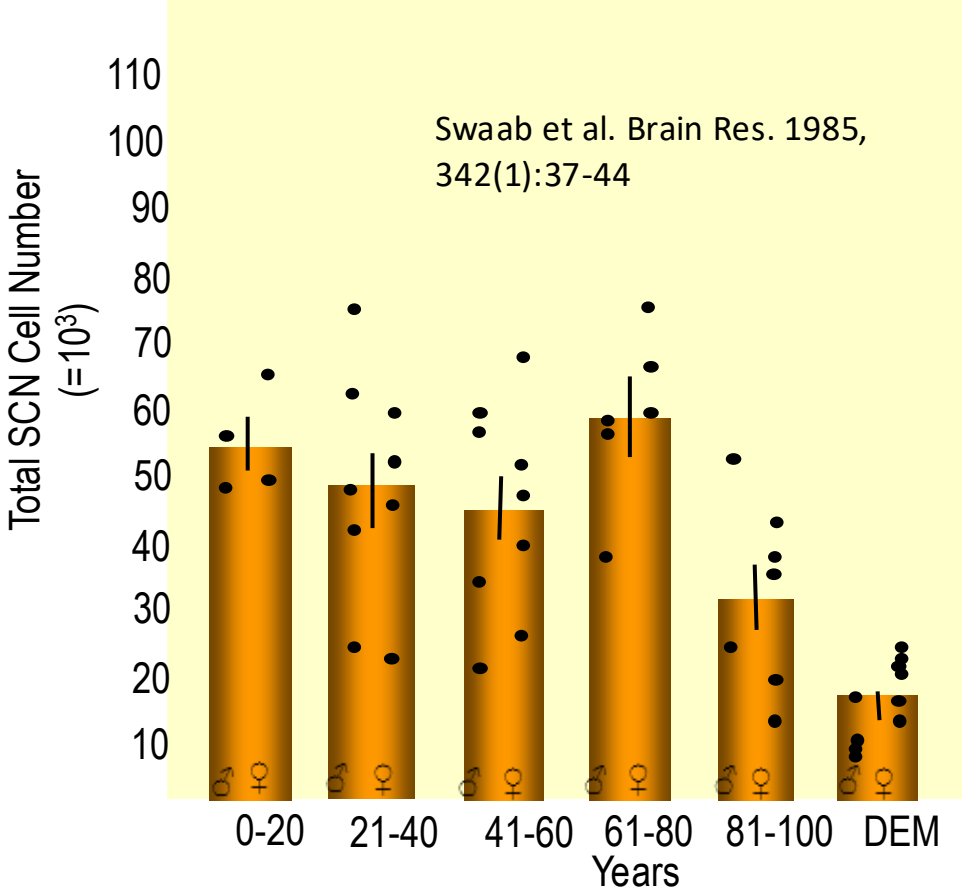
Sleep in Alzheimer's Disease/Dementia

- In AD one sees:
  - Exaggeration of normal age-related changes
    - Shorter, more fragmented sleep
    - Lower sleep efficiency
    - Reduced slow-wave sleep and REM
  - Greater dementia severity linked to greater sleep fragmentation

Ancoli-Israel, et al., Sleep, 1997; Feinberg et al., *J Psychiatr Res,* 1967; Moe et al., *J Sleep Res,* 1995; Prinz et al., *J Am Geriatr Soc,* 1982; Prinz et al., *Neurobiol Aging,* 1982; Vitiello et al., *J Gerontol.,* 1990; Mortimer et al., *Neurology,* 1992

?Mechanisms

- **Loss of brain volume**
  - **Suprachiasmatic nucleus**
- Reduced exposure to bright light
- Reduced daytime activity + more napping
- Alterations in cholinergic system
- >60% loss of wake-promoting neurons in AD compared to controls



Swaab et al., *Brain Research,* 1985; Lim et al., *Brain,* 2014; Campbell et al., *Physiology & Beh,* 1988; Montplaisir et al., *SLEEP,* 1995; Platt & Riedel, *Beh Brain Res,* 2011; Oh et al., *Alzheimer's & Dementia*

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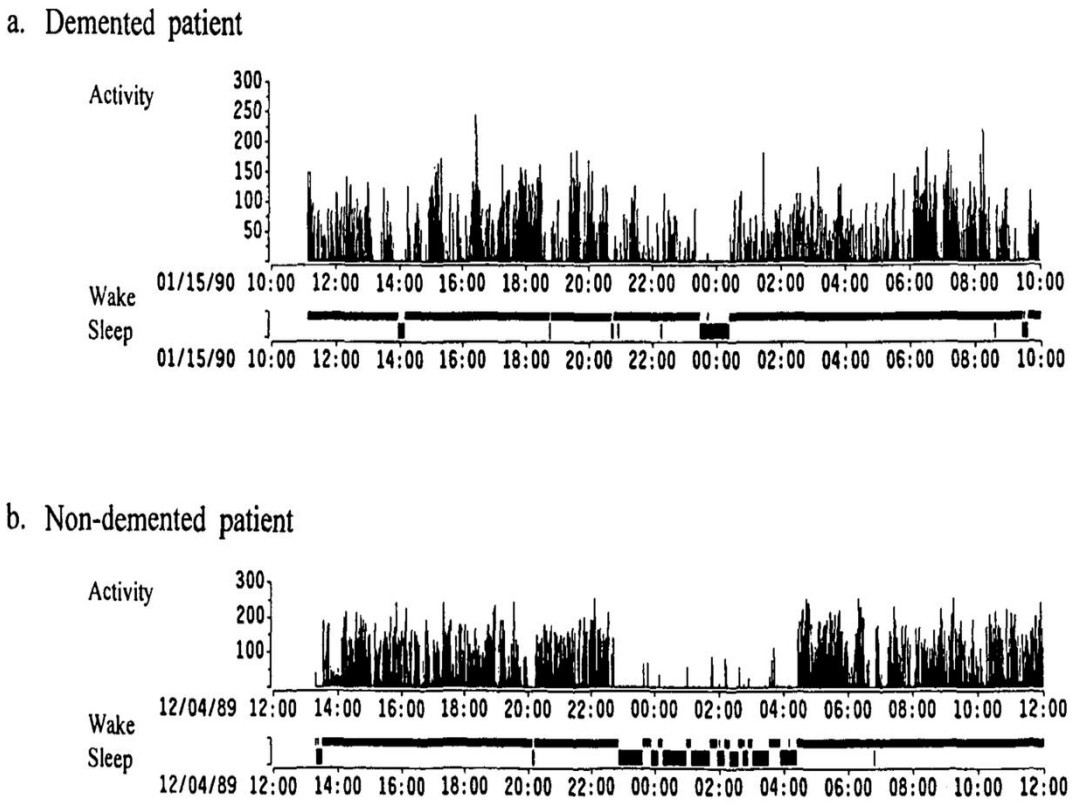
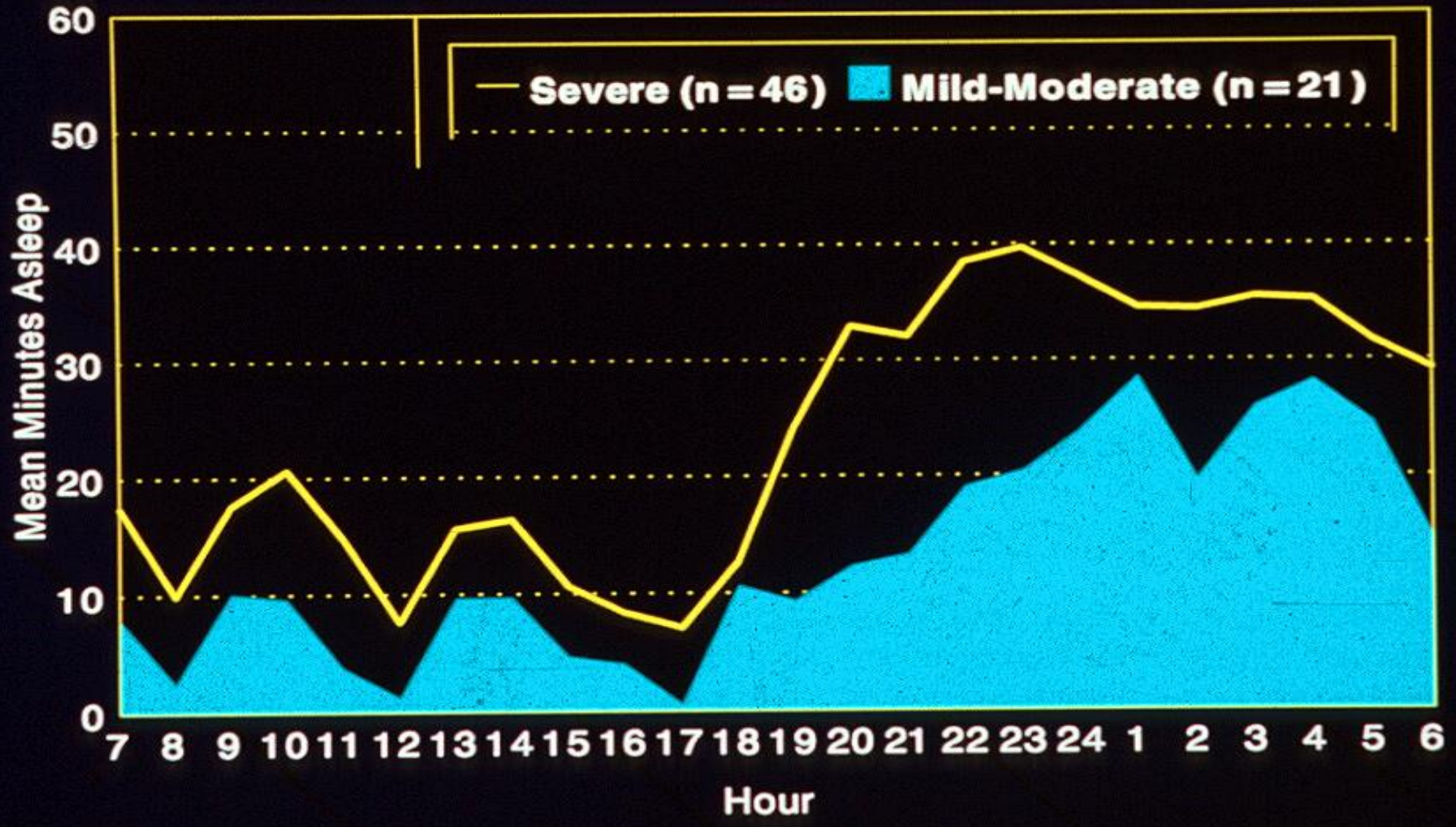


FIG. 1. Activity plot of a nursing-home patient with severe sleep fragmentation. There were no long intervals of consolidated wake or sleep.

Ancoli-Israel et al., Sleep 1997;20:18-23. (p. 20)

Mean Minutes Awake and Asleep Per Hour
Nursing Home Study

Pat- Horenczyk, Ancoli-Israel, et al, Aging Clin Exp Res, 1989, 10:308-15



?Mechanisms

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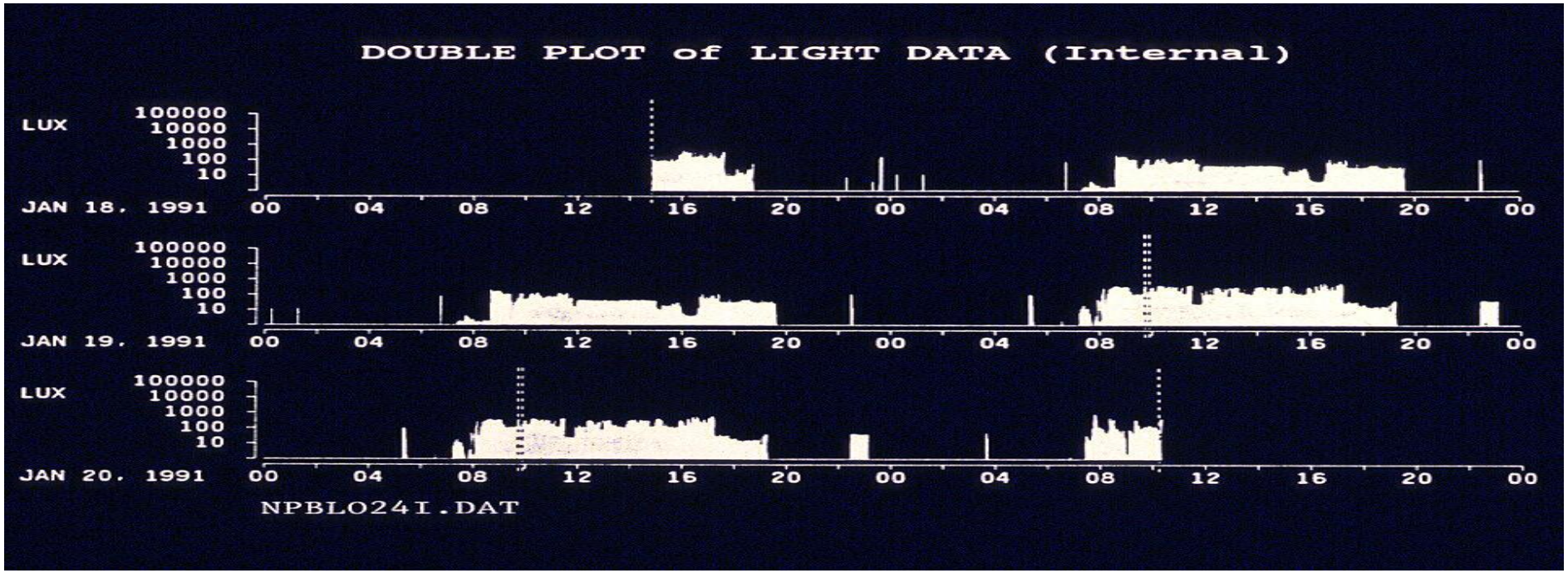
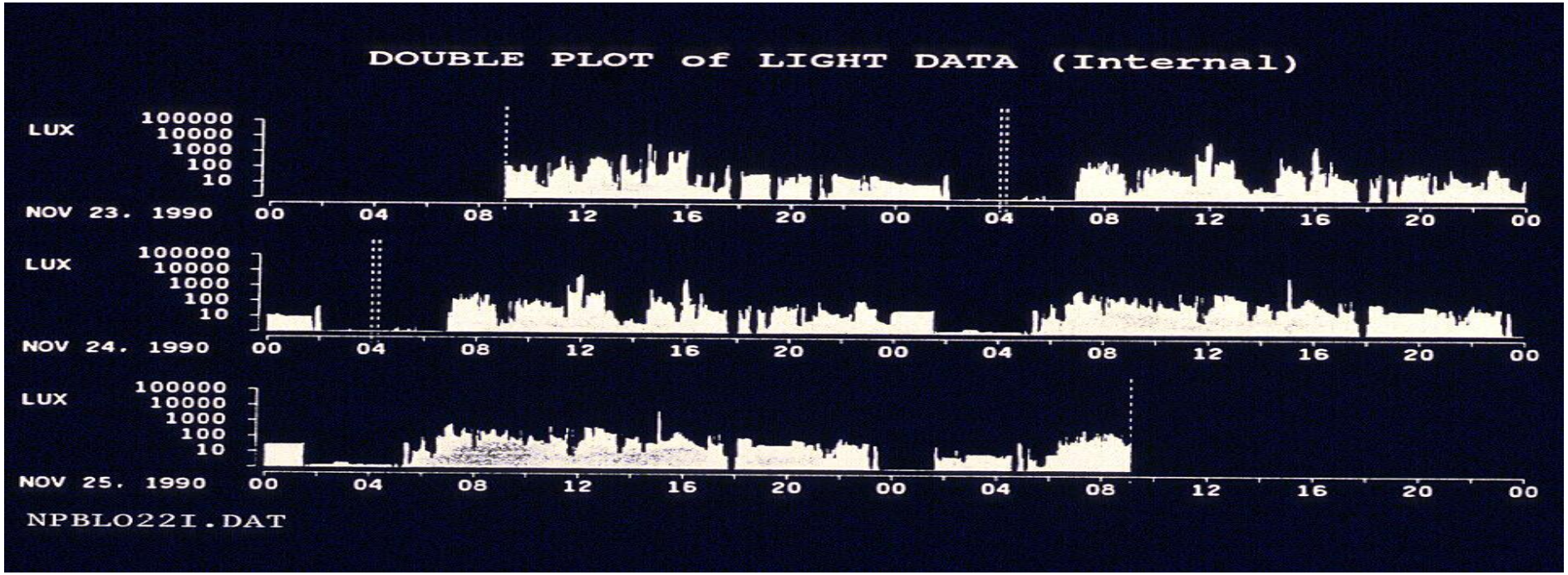
- **Reduced exposure to bright light**
- Alterations in cholinergic system
- >60% loss of wake-promoting neurons in AD compared to controls

Ancoli-Israel et al., Sleep 1997;20:18-23. (p. 20); Ancoli-Israel, et al. In Sleep and Respiration in Aging Adults (Eds. Kuna et al) 1991, p.77-84





Ancoli-Israel, et al. In Sleep and Respiration in Aging Adults (Eds. Kuna et al) 1991, p.77-84

Light and Sleep in Dementia

- Median daily bright light exposure in demented NH residents was only 10m
- 47% of demented residents were <u>never</u> exposed to light > 1000 lux

- Higher illumination during the day, independent of level of dementia

→

- Fewer nighttime awakenings **($F_{2,63}$=3.36, p=.041)**

Patients exposed to higher average illumination levels during the day had more consolidated sleep at night, even when level of dementia was included in the model.

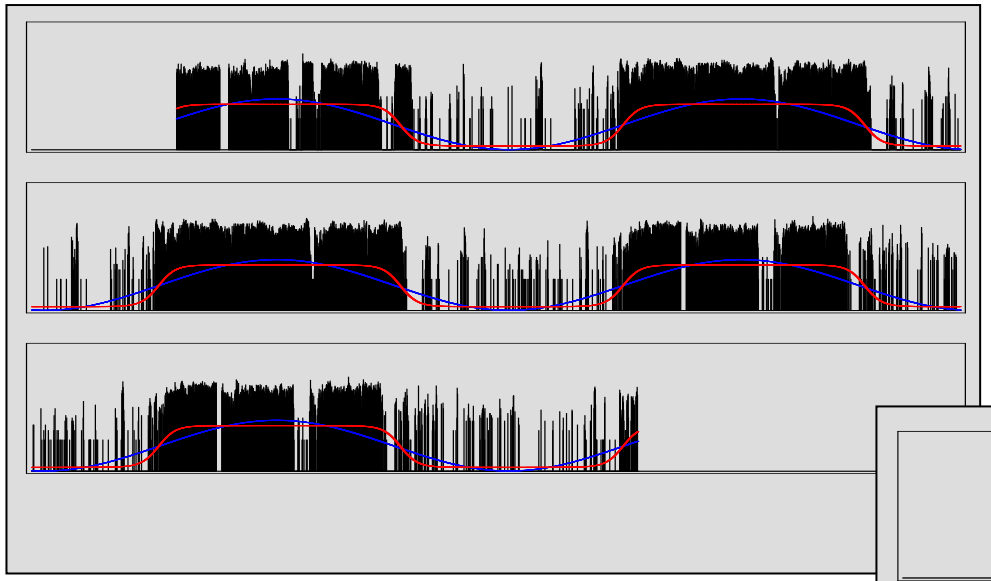
Ancoli-Israel et al. Sleep 20:18-23, 1997 ; Shochat et al, J of Sleep Res, 2000, 9:373-9.

Effect of Bright Light on Sleep

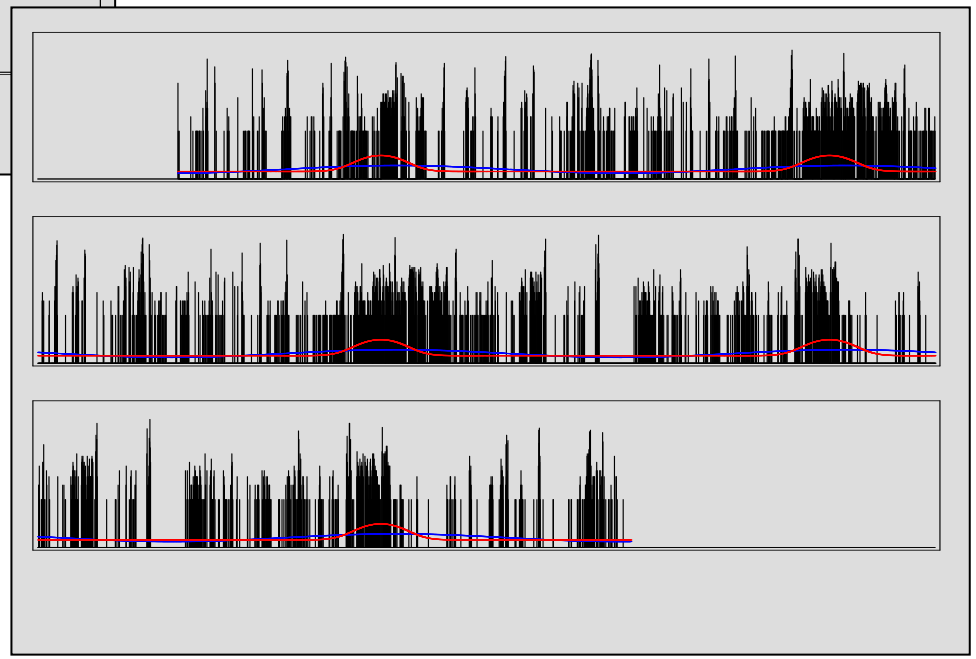
- Increased light exposure has been shown to:
  - Have beneficial effect on sleep and on circadian rhythms in patients with dementia
  - Results in less cognitive decline (MMSE), functional limitations, nighttime restlessness, nighttime agitation and fewer depressive symptoms

Ancoli-Israel, et al., Behavioral Sleep Med, 2003, 1(1):22-36; Riemersma-van der Lek et al. (2008) JAMA 299:2642-2655.

Circadian Rhythms in Dementia



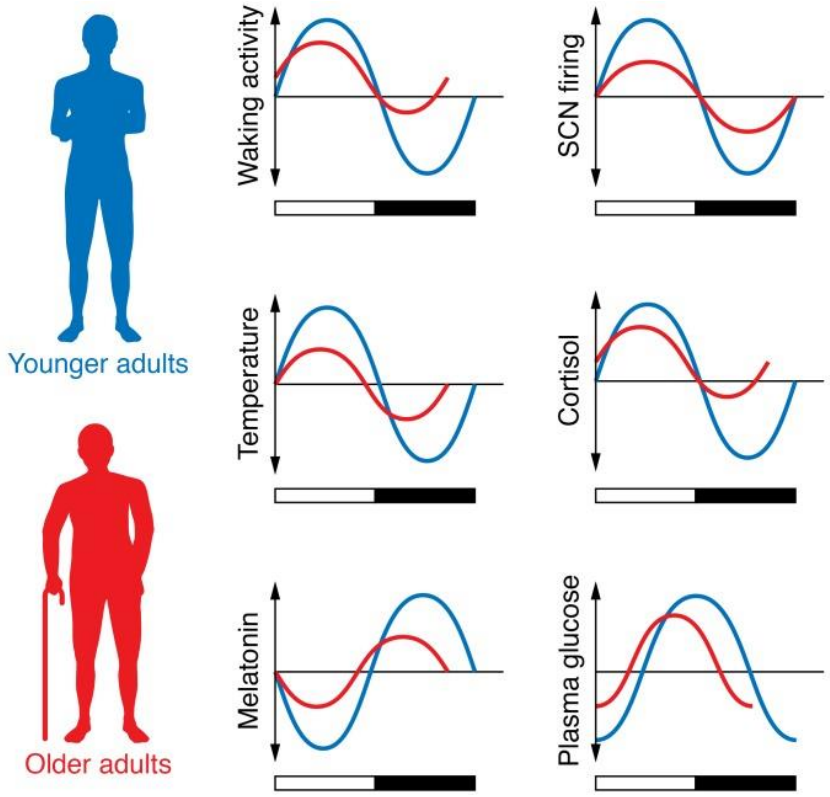
Activity Plot - Subject #12
(Note the Strong Circadian Rhythmicity)



Activity Plot - Subject #07
(Note the Lack of Circadian Rhythmicity)

Circadian Rhythm Disruption in Dementia Patients

- Disrupted sleep wake cycle
- Waking up often at night
- Wandering and agitation at night
- Increased daytime sleepiness and napping
- Changes to the suprachiasmatic nucleus



Saeed and Abott, Current Neurology and Neuroscience Reports, 2017; Hood and Amir, *J Clin Invest*, 201.

Circadian disturbances in Alzheimer's disease progression

- Prospective observational cohort study of 1401 healthy community-based older adults (aged >59 years)
- Circadian activity rhythms recorded with actigraphy:
  - Acrophase, amplitude, interdaily stability (quantified the day-to-day robustness of the rhythm) and intradaily variability (intradaily variability that quantified the fragmentation of the rhythm)
- Results:
  - Risk of developing Alzheimer's dementia was increased with lower amplitude, increased intradaily variability and decreased interdaily stability
  - Circadian amplitude, acrophase, and interdaily stability progressively decreased over time, and intradaily variability progressively increased over time
  - The longitudinal change of global cognition positively correlated with the longitudinal changes in amplitude and interdaily stability and negatively correlated with the longitudinal change in intradaily variability
- Conclusion: There is a link between circadian dysregulation and Alzheimer's progression, implying either a bidirectional relation or shared common underlying pathophysiological mechanisms

Li, Peng et al. The Lancet Healthy Longevity, Volume 1, Issue 3, e96 - e105

Circadian Rhythms and Cognition

- Nursing home patients (n=77) with severe AD have more disrupted rhythms than mild, moderate or no AD[1]
- Weaker circadian activity rhythms are associated with poorer executive function over 5 years (n=1287;SOF)[2]
- Older, healthy women (n=1282; SOF) with decreased circadian activity rhythm amplitude and robustness, and delayed rhythms have increased odds over 5 years of developing dementia and MCI [3]
- Men (n=2754, MrOs) with lower amplitudes, mesors, and less robustness had significantly greater cognitive decline ($p<0.001$) at 4-yr follow-up[4]

[1] Ancoli-Israel et al Sleep, 1997;20(1):18-23; [2]Walsh et al. Sleep, 2014;37(12):2009-16; [3]Tranah et al. Ann Neurol. 2011;70(5):722-32; [4]Rogers-Soeder et al, JAGS 00:1–8, 2018

Summary of Key Points – The Bottom Line

- It is not aging per se that results in poor sleep but rather all the things that go along with aging.
- Although the need to sleep does not change, the ability to sleep does change with age.
- Poor sleep in the older adult is most often associated with medical and psychiatric illness, medication, circadian rhythm changes and primary sleep disorders.
- No matter the age of the patient, sleep disorders should be treated if they are interfering with quality of life or if there is a medical risk associated with it.

Summary of Key Points – The Bottom Line (con't)

- The relationships between sleep/circadian dysfunction and neurodegenerative processes are bidirectional
  - Sleep and circadian disruption increase the risk of MCI and AD
  - Sleep and circadian disruption are common in AD
  - Behavioral, physiological and molecular markers of circadian system function suggest progressive deterioration of sleep and circadian rhythmicity as the AD progresses
- OSA increases the risk of MCI and AD
  - OSA treatment studies suggest that cognition may improve, but more studies are needed
- Because late-life sleep disturbance can be treated, interventions to improve sleep or maintain healthy sleep among older adults may help prevent or slow AD to the extent that poor sleep promotes AD onset and progression.

Aging seems to be the only available way to live a long life

Daniel Francois Esprit Auber