Exploring Sleep Disturbance in Central Nervous System Disorders Workshop

Session 1: Sleep Disorders and Sleep Disruption in CNS Disorders

Sleep and Circadian Disturbances and Risk for Adverse Health Outcomes

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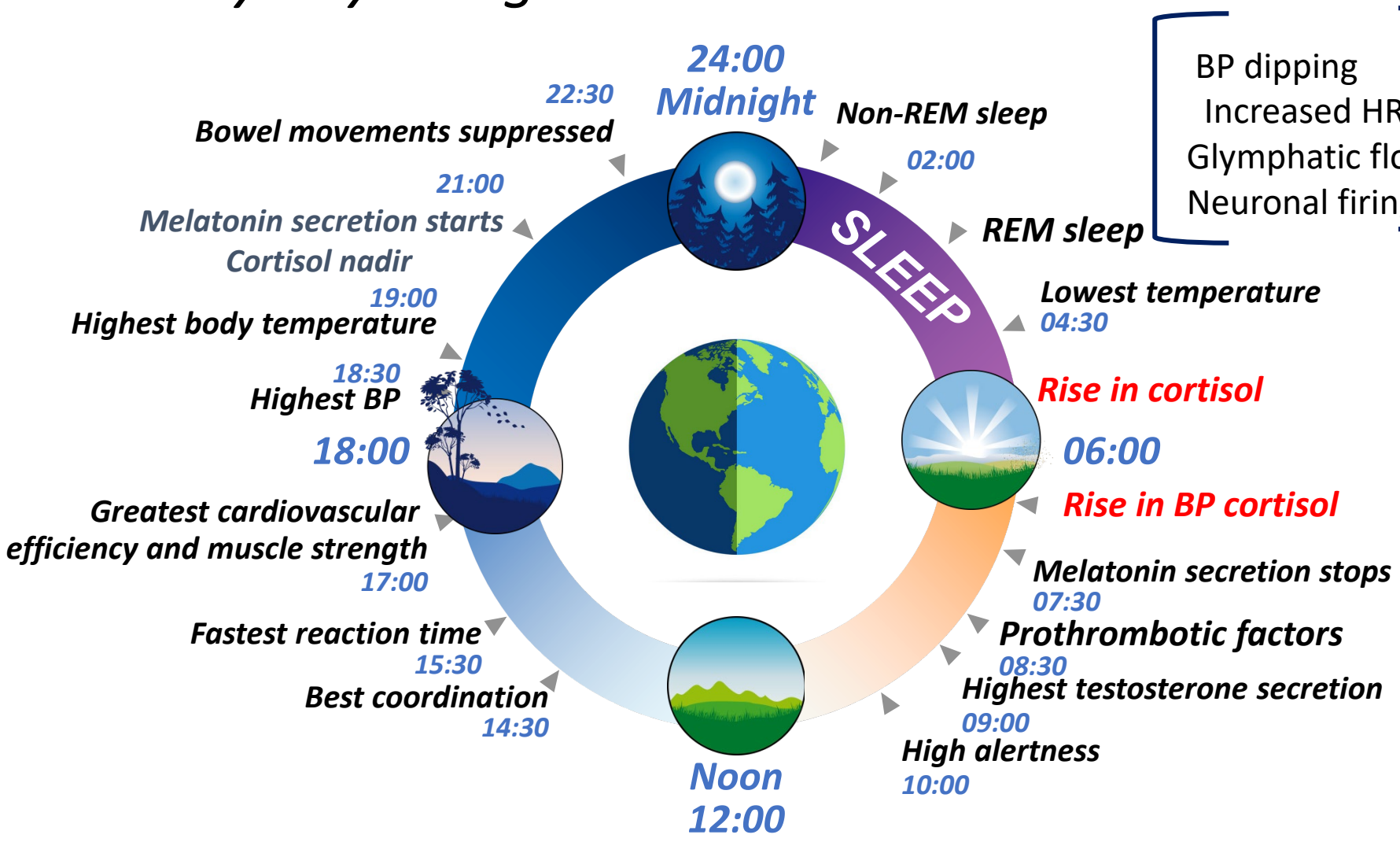
Conflict of Interest Disclosures

Type of Potential Conflict	Details of Potential Conflict
Grant/Research Support	Vanda
Consultant	Jazz, Eisai, CVS Caremark, Idorsia, Sleep Number
Speakers' Bureaus	NA
Financial support	
Other	Stock ownership: Teva

Circadian Rhythms and Sleep

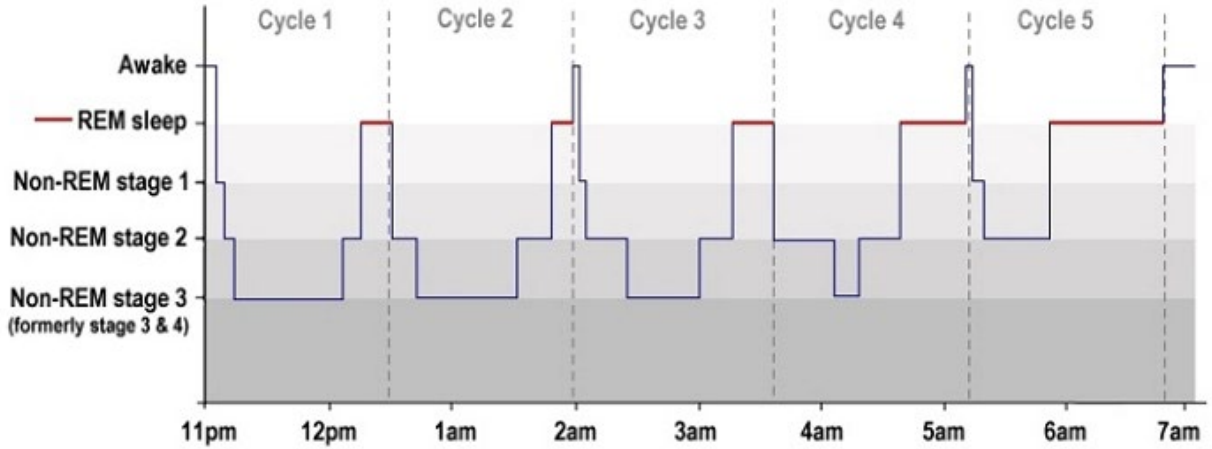
Daily Physiologic and Behavioral Patterns

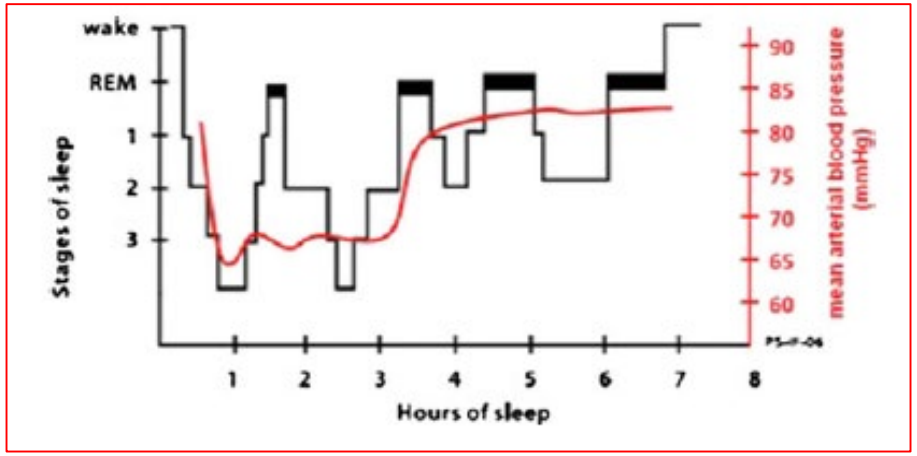


BP dipping
Increased HRV
Glymphatic flow
Neuronal firing

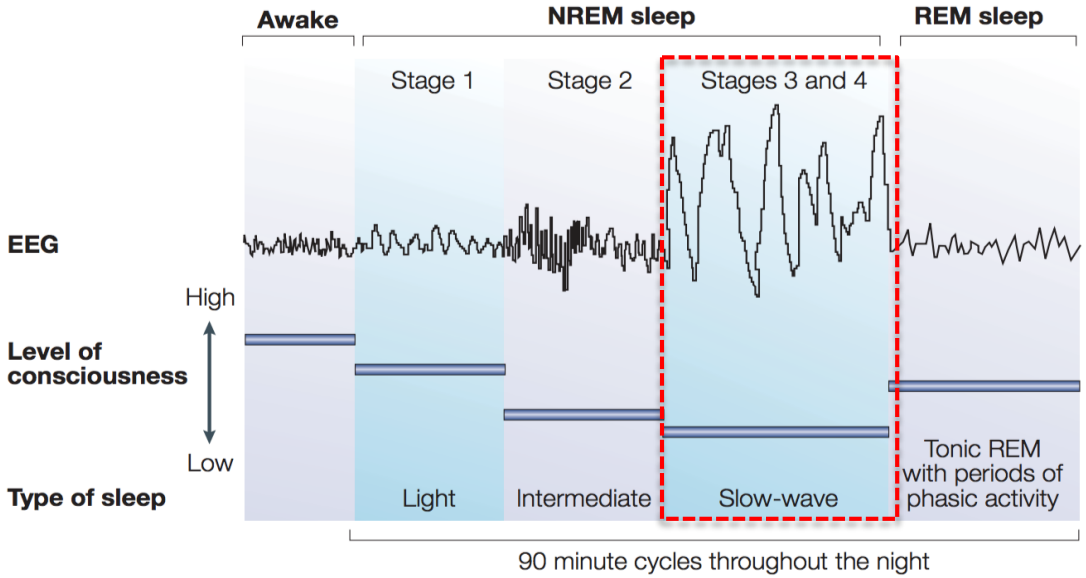
Modified from Smolensky M, Lamberg L. The Body Clock Guide to Better Health. New York, NY: Henry Holt and Company; 2001.

Sleep: Dynamic Brain Oscillations and Physiology

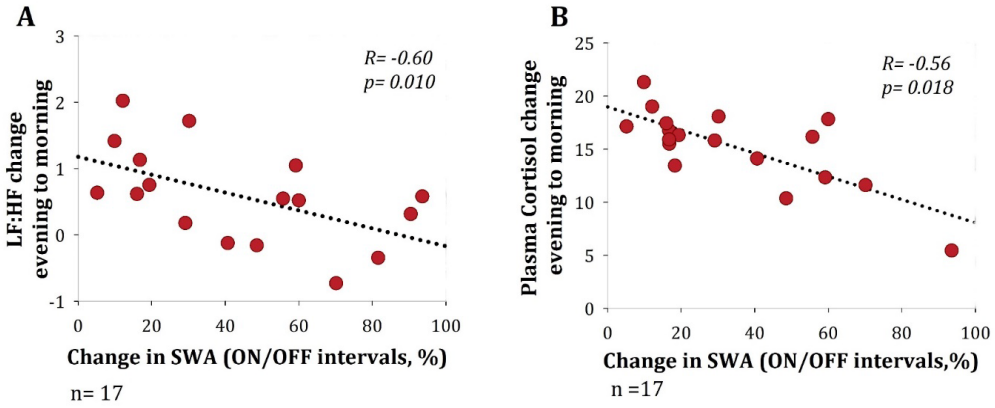




Javaheri S and Redline S. Current Hypertension Report 2012



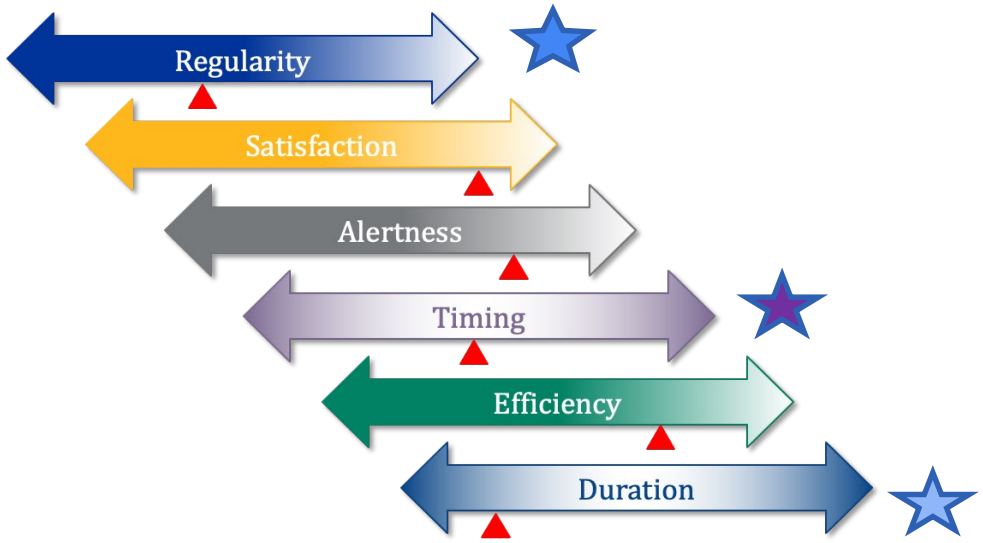
Ohayon MM, et al. Sleep 2004;27:1255-1273



Grimaldi D et al, Sleep 2019

SLEEP IS ESSENTIAL FOR HEALTH AND WELLNESS

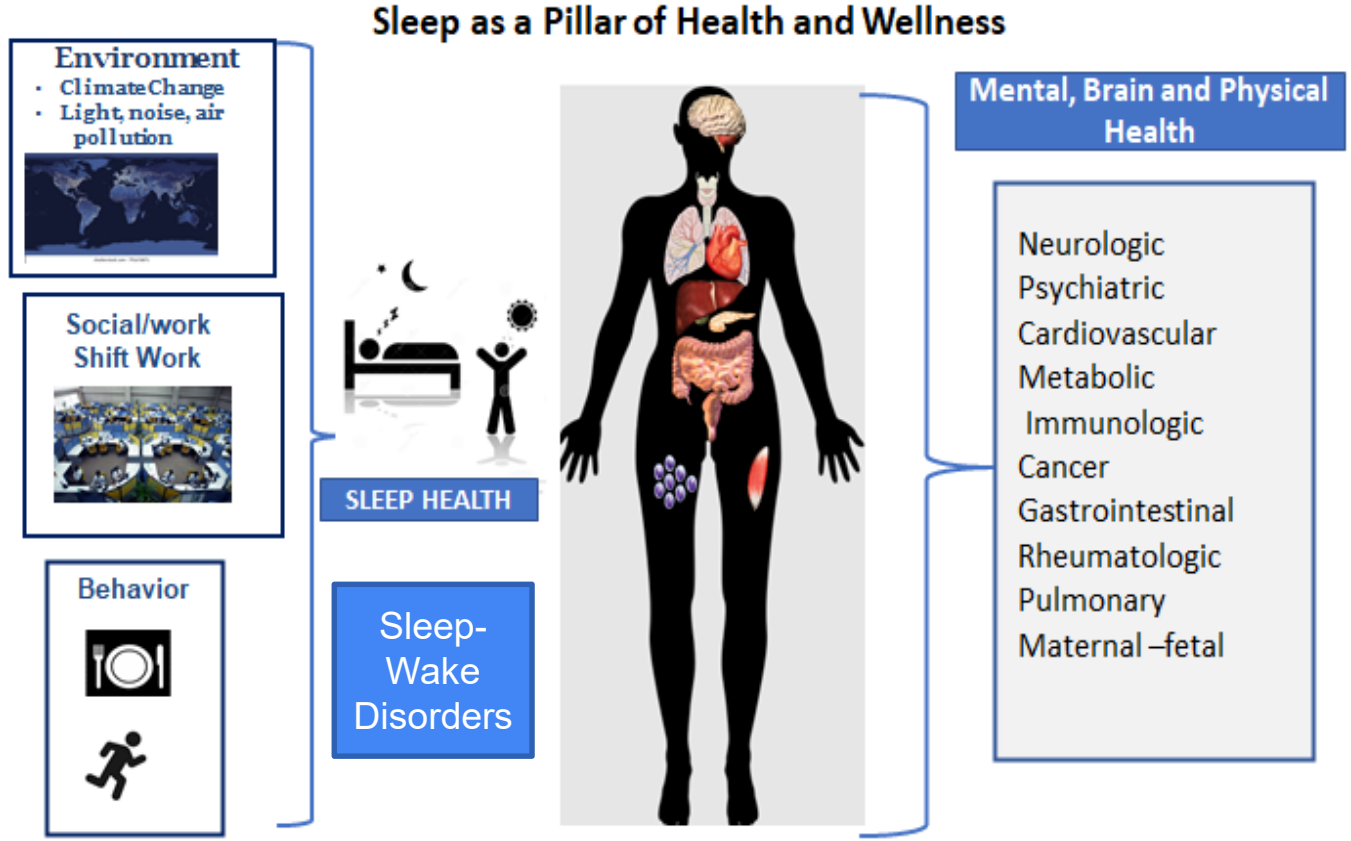
Sleep health is a multidimensional pattern of sleep-wakefulness that promotes physical and mental well-being.



Sleep Health=RU_SATED ↑ **Health**

Buysse, *SLEEP* 2014; 37(1):9-17

Modified slide: courtesy: Buysse



SHORT SLEEP and Cardio-Metabolic Health

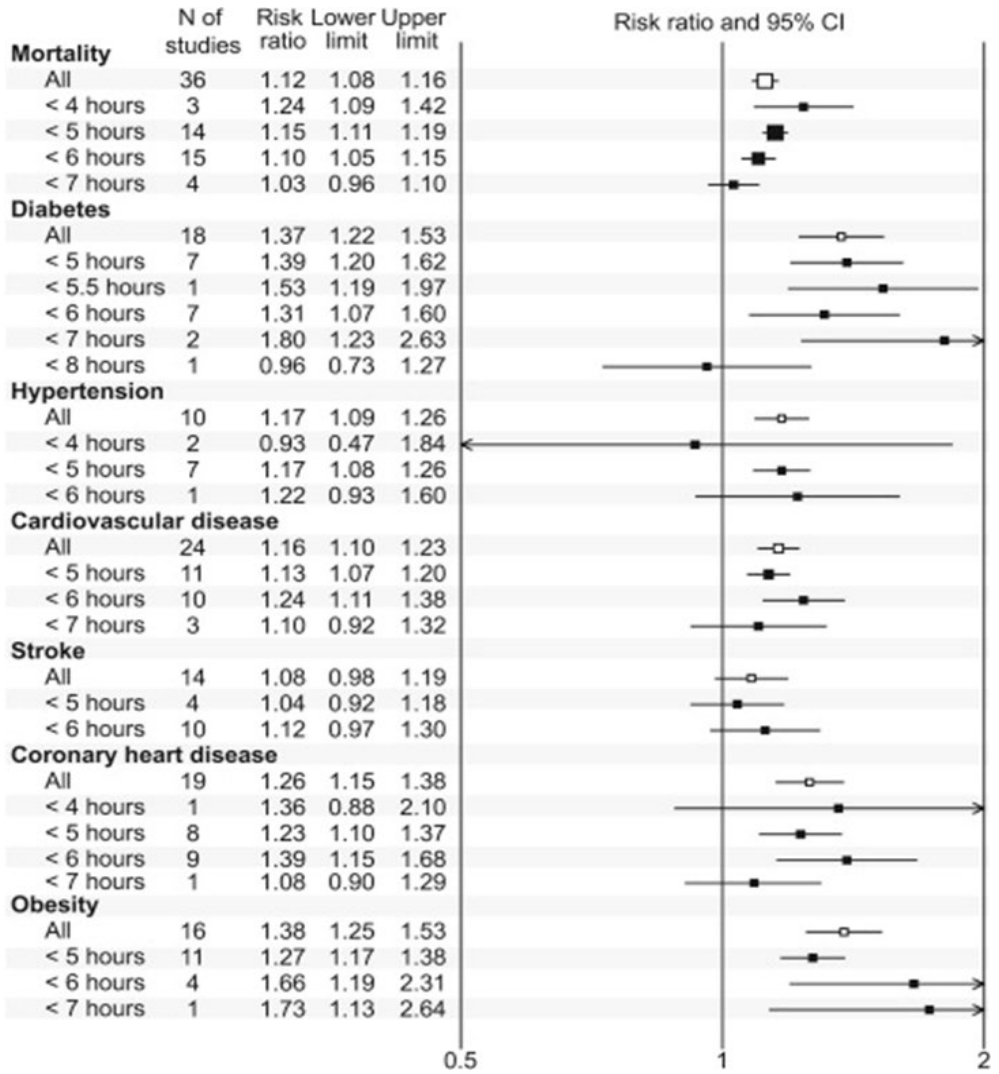
Mortality

Diabetes

Cardiovascular Disease

Coronary Heart Disease

Obesity



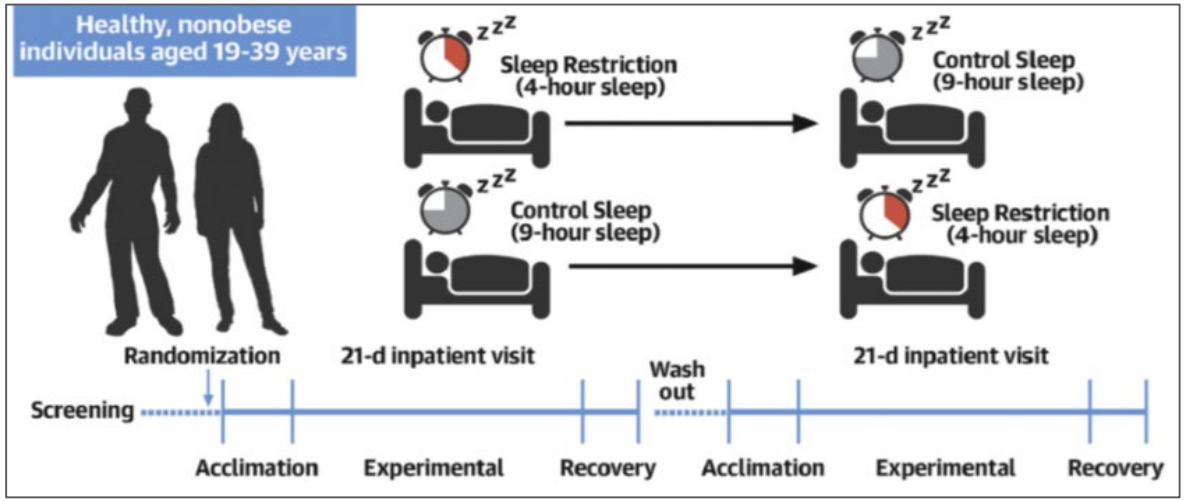
	N of studies	Risk ratio	Lower limit	Upper limit
Mortality				
All	36	1.12	1.08	1.16
< 4 hours	3	1.24	1.09	1.42
< 5 hours	14	1.15	1.11	1.19
< 6 hours	15	1.10	1.05	1.15
< 7 hours	4	1.03	0.96	1.10
Diabetes				
All	18	1.37	1.22	1.53
< 5 hours	7	1.39	1.20	1.62
< 5.5 hours	1	1.53	1.19	1.97
< 6 hours	7	1.31	1.07	1.60
< 7 hours	2	1.80	1.23	2.63
< 8 hours	1	0.96	0.73	1.27
Hypertension				
All	10	1.17	1.09	1.26
< 4 hours	2	0.93	0.47	1.84
< 5 hours	7	1.17	1.08	1.26
< 6 hours	1	1.22	0.93	1.60
Cardiovascular disease				
All	24	1.16	1.10	1.23
< 5 hours	11	1.13	1.07	1.20
< 6 hours	10	1.24	1.11	1.38
< 7 hours	3	1.10	0.92	1.32
Stroke				
All	14	1.08	0.98	1.19
< 5 hours	4	1.04	0.92	1.18
< 6 hours	10	1.12	0.97	1.30
Coronary heart disease				
All	19	1.26	1.15	1.38
< 4 hours	1	1.36	0.88	2.10
< 5 hours	8	1.23	1.10	1.37
< 6 hours	9	1.39	1.15	1.68
< 7 hours	1	1.08	0.90	1.29
Obesity				
All	16	1.38	1.25	1.53
< 5 hours	11	1.27	1.17	1.38
< 6 hours	4	1.66	1.19	2.31
< 7 hours	1	1.73	1.13	2.64

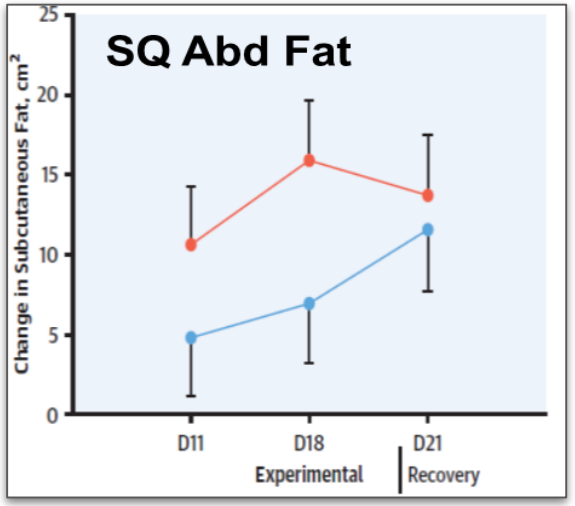
Itani O, Jike M, Watanabe N, Kaneita Y. Short sleep duration and health outcomes: a systematic review, meta-analysis, and meta-regression. Sleep Med. 2017 Apr;32:246-256. doi: 10.1016/j.sleep.2016.08.006. Epub 2016 Aug 26. PMID: 27743803.

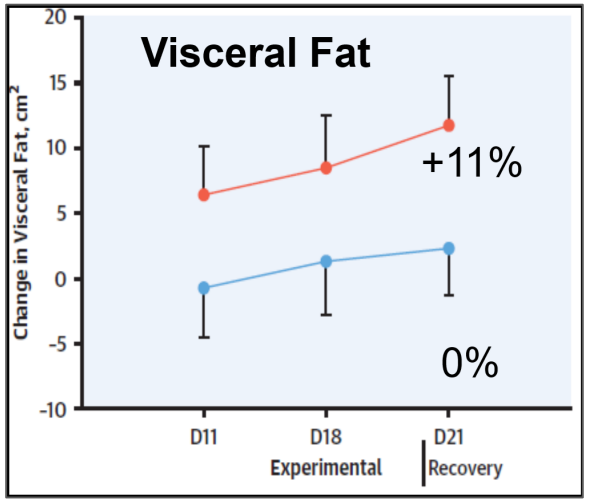
Short Sleep Increases Visceral Fat

- 14 nights of 4 h TIB vs 9 h TIB;
- Randomized crossover; N=12
- Caloric intake increased by 310 kCal/day;
- Serial assessment of body composition and fat
  distribution by dual-energy X-ray absorptiometry
  (DXA) and abdominal CT scan

Covassin et al, *JACC* 2022

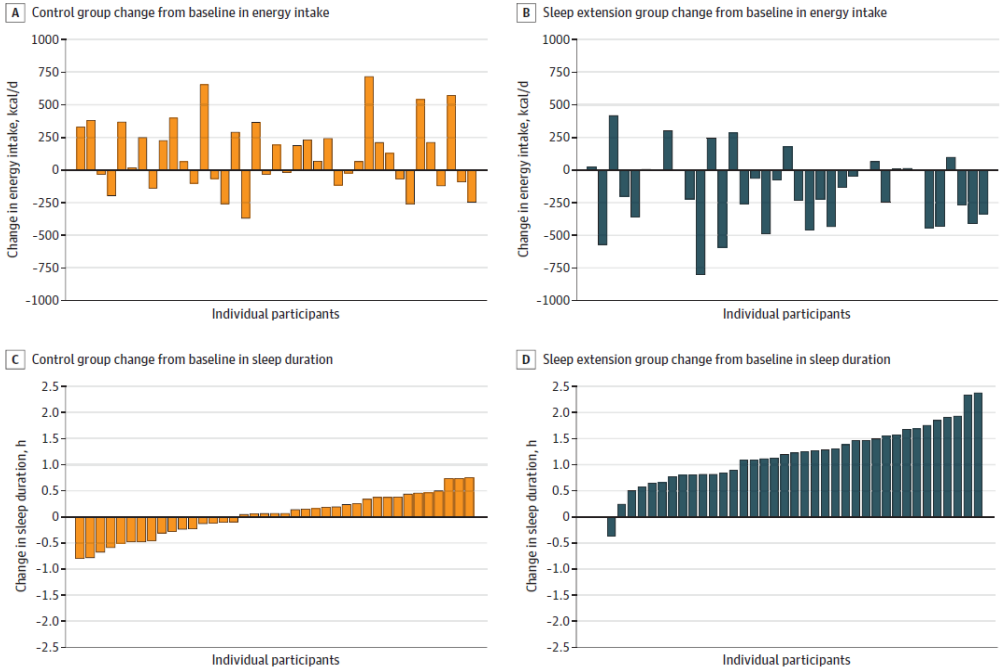




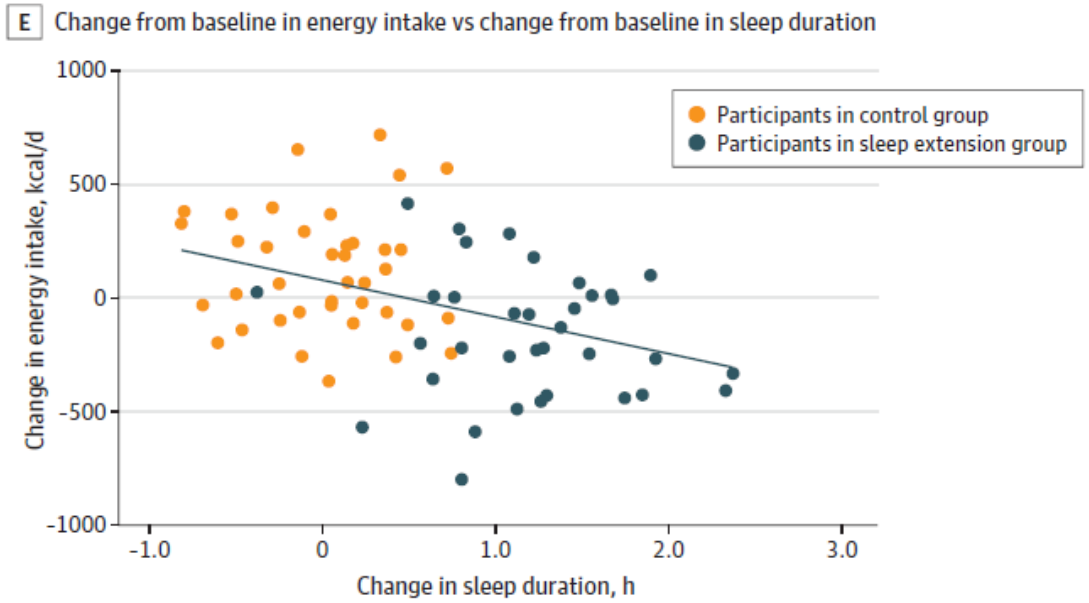


Effect of Sleep Extension on Energy Intake

- Real life – field intervention
- 80 (41 male) overweight (BMI 25-29.9); age 21-40
- Randomized 2 week of habitual (6.5 h or less) or 8.5 h time in bed.
- Sleep duration increased on average 1.2 hours



Average of - 270 Kcal



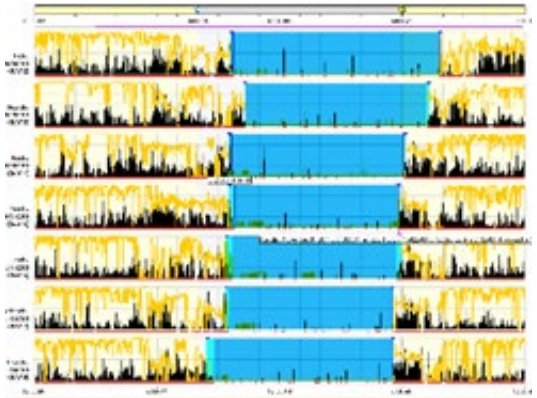
Tasali, E et al, JAMA Int. Med, 2022

Sleep Timing and Gestational Diabetes

OBSTETRICS

Objectively measured short sleep duration and later sleep midpoint in pregnancy are associated with a higher risk of gestational diabetes

Francesca L. Facco, MD, MSCI; William A. Grobman, MD, MBA; Kathryn J. Reid, PhD; Corette B. Parker, DrPH; Shannon M. Hunter, MS; Robert M. Silver, MD; Robert C. Basner, MD; George R. Saade, MD; Grace W. Pien, MD, MSCE; Shalini Manchanda, MD; Judette M. Louis, MD, MPH; Chia-Ling Nhan-Chang, MD; Judith H. Chung, MD, PhD; Deborah A. Wing, MD, MBA; Hyagriv N. Simhan, MD, MS; David M. Haas, MD, MS; Jay Iams, MD; Samuel Parry, MD; Phyllis C. Zee, MD, PhD



Total n=782

	Hypertensive disease of pregnancy		Gestational diabetes	
Sleep characteristic	N (%)	Crude OR (95% CI)	N (%)	Crude OR (95% CI)
Sleep duration				
<7 h	27/218 (12.4)	1.10 (0.68–1.78)	15/218 (6.9)	2.24 (1.11–4.53)
≥7 h	64/564 (11.3)	1.00	18/564 (3.2)	1.00
		P value = .6850		*P* value = .0246
Sleep midpoint				
>5 AM	17/148 (11.5)	0.98 (0.56–1.72)	12/148 (8.1)	2.58 (1.24–5.36)
≤5 AM	74/634 (11.7)	1.00	21/634 (3.3)	1.00
		P value = .9497		*P* value = .0114

K Knutson

Sleep and Timing: Risk for Obesity, Diabetes

(N=13,429/16,415)

	BMI (kg/m^2)	Log of Fasting Glucose	Log of HOMA - Insulin Resistance	2-hour glucose (mg/dl)	HbA1c
	Regression coefficient (SE)	Regression coefficient (SE)	Regression coefficient (SE)	Regression coefficient (SE)	Regression coefficient (SE)
Weekly Bedtime[a] (per clock hour)	-0.0895(0.046)	Diabetes[c]: 0.0266(0.009)** No diabetes: 0.0010(0.001)	0.0128(0.007)	-0.4410(0.218)*	Diabetes: 0.0691(0.0363) No diabetes: -0.0066(0.0036)
Weekly Wake time[a] (per clock hour)	-0.0008(0.046)	0.0026(0.001)*	0.0133(0.007)	-0.1250(0.212)	0.0032(0.005)
Weekly mid sleep point[b] (per clock hour)	-0.0664(0.041)	Diabetes[c]: 0.0232(0.009)* No diabetes: 0.0012(0.001)	0.0145(0.006)*	-0.3283(0.235)	0.0008(0.005)
Chronotype[b] (per clock hour)	-0.0120(0.035)	0.0017(0.001)	0.0118(0.005)*	-0.1740(0.186)	0.0008(0.004)

[a] Adjusted for age, gender, ethnic subgroup, study site, income, education, household size, years in US (<10 vs ≥10 y), marital status, sleep duration, AHI category (<15 vs ≥15), diabetes, employment/shift work status.

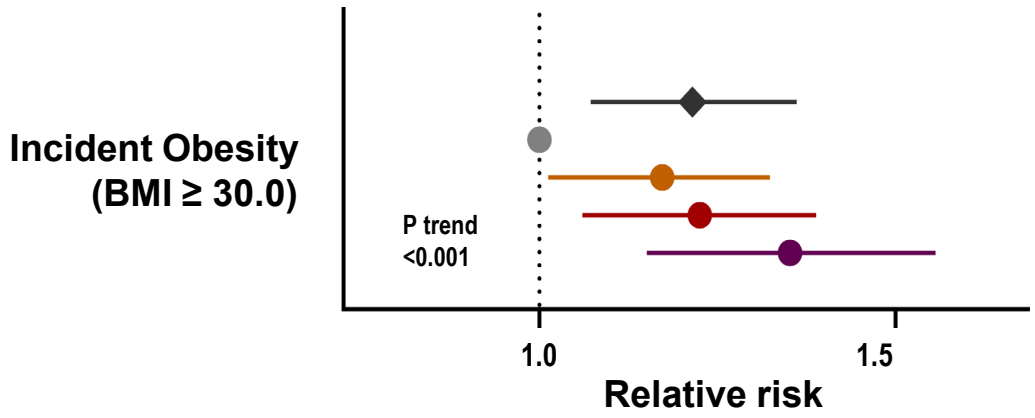
[b] Adjusted for age, gender, ethnic subgroup, study site, income, education, household size, years in US (<10 vs ≥10 y), marital status, AHI category (<15 vs ≥15), diabetes, employment/shift work status.

[c] The effect by diabetes status based on the model with interaction term.

***:P<0.001,**:P<0.01, *:P<0.05

Knutson K et al, SLEEP, 2017

Artificial Light at Night while Sleeping and Obesity Risk, N=43,722



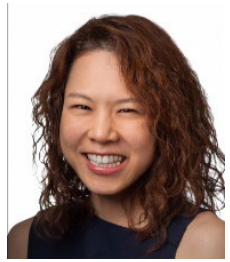
Adjustments:
Age at enrollment, race/ethnicity, residential area, educational attainment, household income, household composition, marital status, smoking status, alcohol consumption, caffeine consumption, menopausal status at baseline, depression, and perceived stress.

Prevalence of sleeping with light/TV:

Race/Ethnicity	With light/TV on in room
Non-Hispanic Black	36%
Hispanic/Latino	18%
Non-Hispanic White	9%

Park M, White A, Jackson CL, Weinberg C, Sandler DP. JAMA Internal Medicine. 2019

Courtesy: CL Jackson



M. Kim

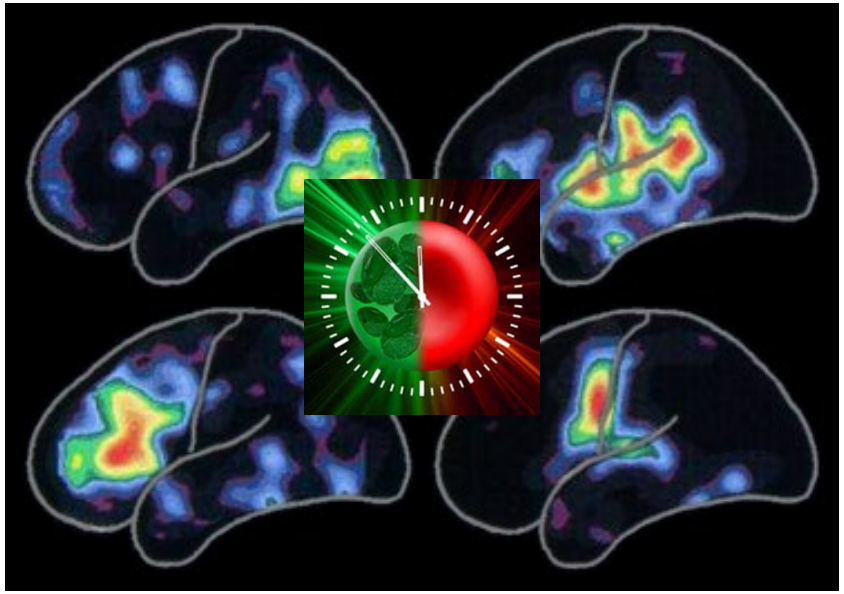
Kim M et al, SLEEP, 2022

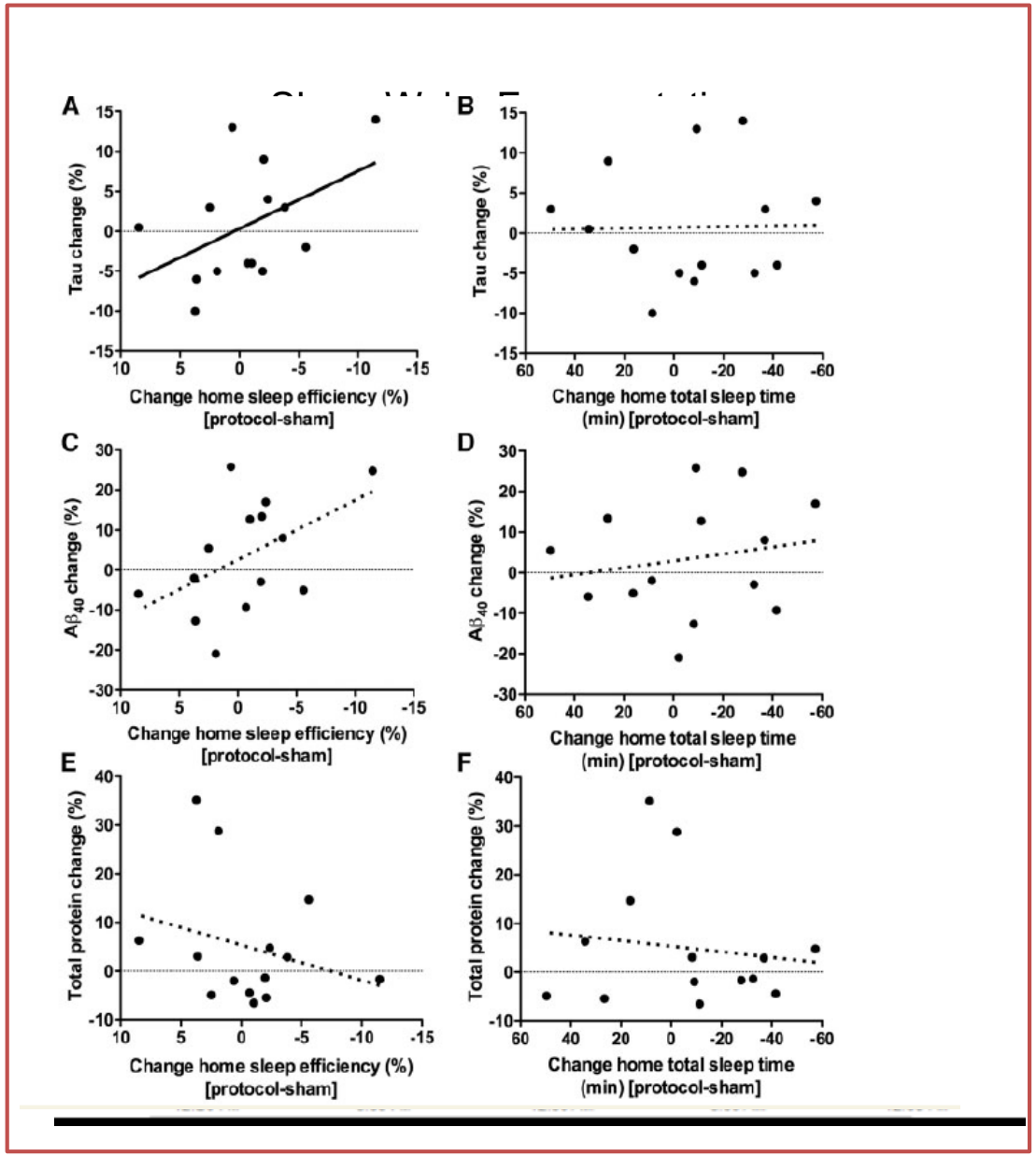
Light at night (LAN) in older age is associated with obesity, diabetes, and hypertension

CVD Risk Factor	No-LAN, N = 255	LAN, N = 297	p-value
Obesity			
Prevalence (%)	26.7	40.7	
Unadjusted OR (95% CI)	1 [Reference]	1.89 (1.32-2.72)	0.001
Multivariable-adjusted OR (95% CI)[1]	1 [Reference]	1.82 (1.26-2.65)	0.002
BMI change >= 10%			
Prevalence (%)	45.1	61.6	
Unadjusted OR (95% CI)	1 [Reference]	1.95 (1.39-2.75)	<0.001
Multivariable-adjusted OR (95% CI)[1]	1 [Reference]	1.87 (1.31-2.69)	0.001
Diabetes			
Prevalence (%)	9.8	17.8	
Unadjusted OR (95% CI)	1 [Reference]	2 (1.21-3.37)	0.008
Multivariable-adjusted OR (95% CI)[1]	1 [Reference]	2 (1.19-3.43)	0.010
Hypertension			
Prevalence (%)	59.2	73	
Unadjusted OR (95% CI)	1 [Reference]	1.86 (1.3-2.67)	0.001
Multivariable-adjusted OR (95% CI)[1]	1 [Reference]	1.74 (1.21-2.52)	0.003

[1]Adjusted for age at follow-up, sex, race, and season of actigraphy recording.

Sleep, Clocks and Brain Health

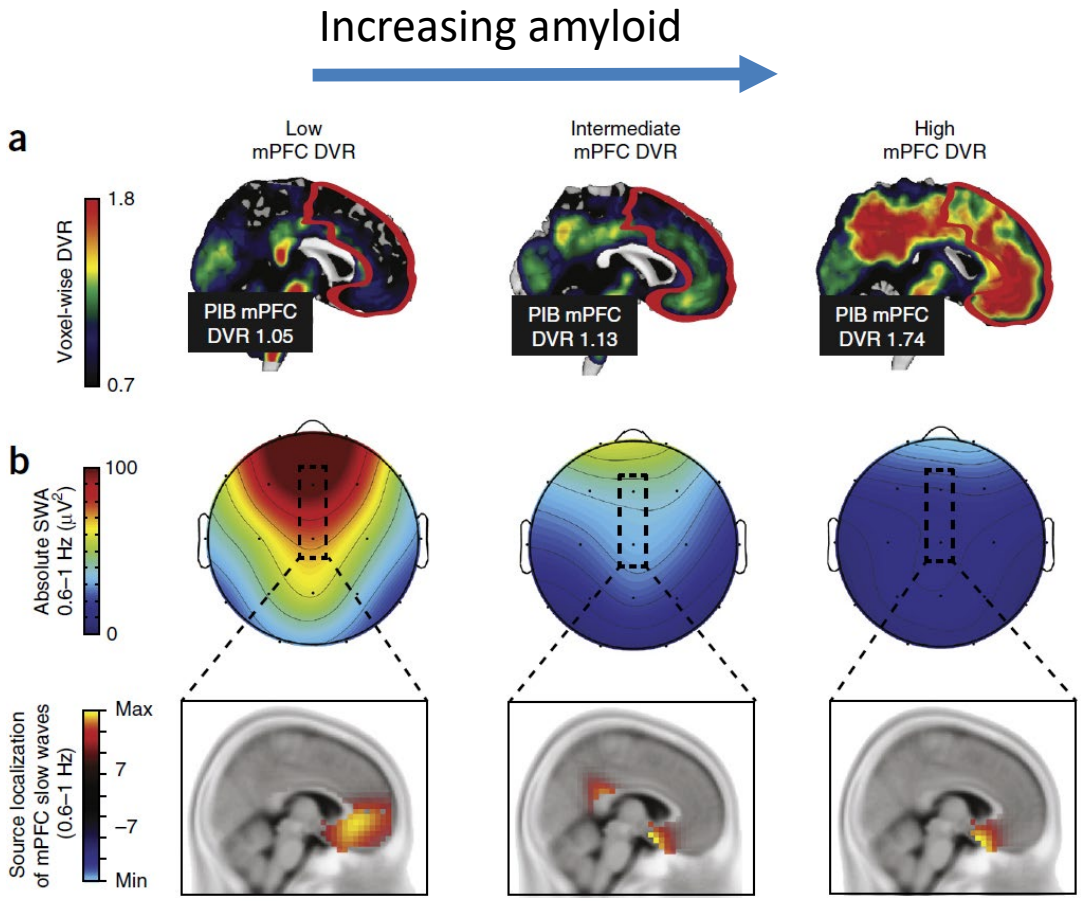




Ju J et al, Brain, 2017

Sleep architecture and Amyloid Deposition

- Meta-analysis of 3557 healthy persons aged 5-102 years
- Most age-related sleep changes occur in early and mid-years of human life span
- In healthy older adults:
  - Sleep efficiency decreases
  - Wake after sleep onset increases
  - Slow wave sleep decreases



Mander et al, *Nat Neurosci* 2015

Ohayon MM, et al. Sleep 2004;27:1255-1273;Van den Berg JF et al, Sleep 2009; Dijk DJ, Neurobiology Aging, 1989; Cappuccio FP et al, Hypertension, 2007; Carrier J et al. Front Neuroendocrinology, 2017; Grander M et al, JCSM 2018; Rosinvil T et al, Sleep 2021

Sleep fragmentation is associated with a higher risk of incident Alzheimer's disease and cognitive decline

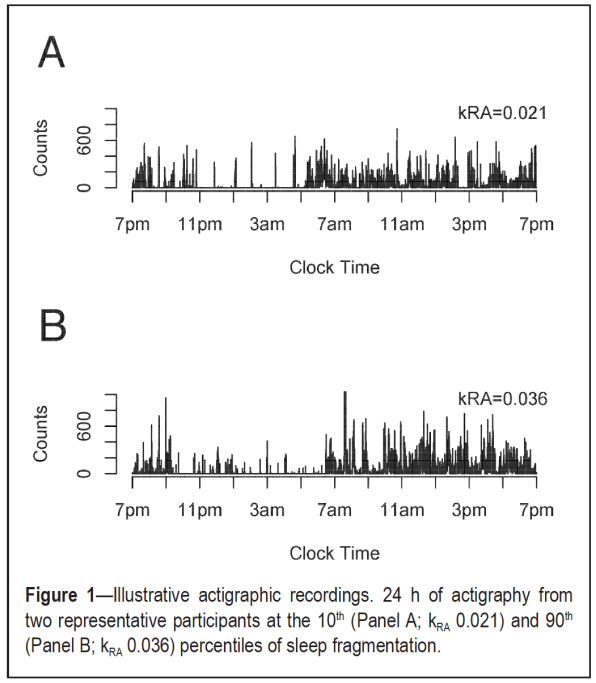


Figure 1—Illustrative actigraphic recordings. 24 h of actigraphy from two representative participants at the 10th (Panel A; k_{RA} 0.021) and 90th (Panel B; k_{RA} 0.036) percentiles of sleep fragmentation.

Incident Alzheimer's Disease

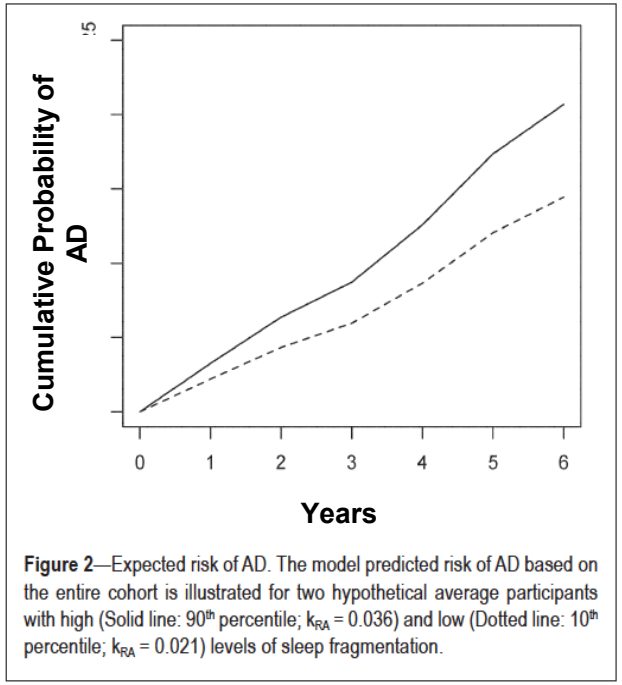


Figure 2—Expected risk of AD. The model predicted risk of AD based on the entire cohort is illustrated for two hypothetical average participants with high (Solid line: 90th percentile; k_{RA} = 0.036) and low (Dotted line: 10th percentile; k_{RA} = 0.021) levels of sleep fragmentation.

Cognitive Decline

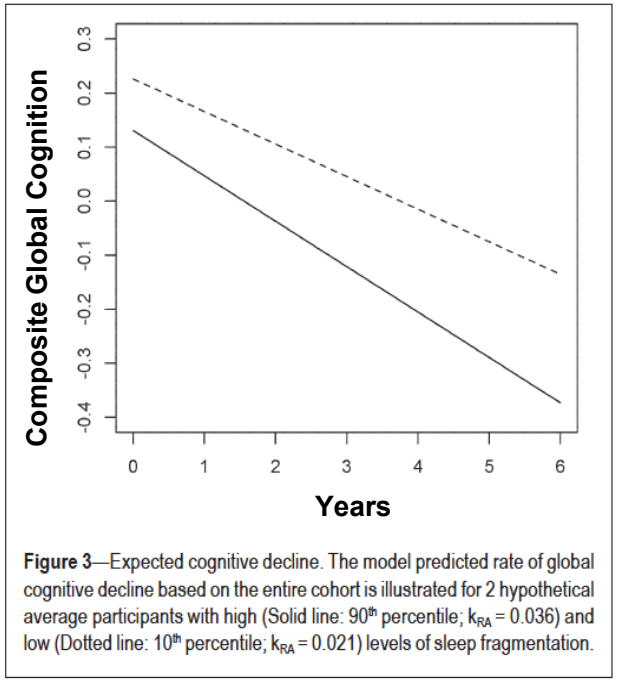


Figure 3—Expected cognitive decline. The model predicted rate of global cognitive decline based on the entire cohort is illustrated for 2 hypothetical average participants with high (Solid line: 90th percentile; k_{RA} = 0.036) and low (Dotted line: 10th percentile; k_{RA} = 0.021) levels of sleep fragmentation.

Lim et al, Sleep, 2013 (n=737; Rush Memory and Aging Project)

Circadian, Sleep/Wake Disruption and Health

Insomnia
Prevalence (10-25%) ♀ > ♂

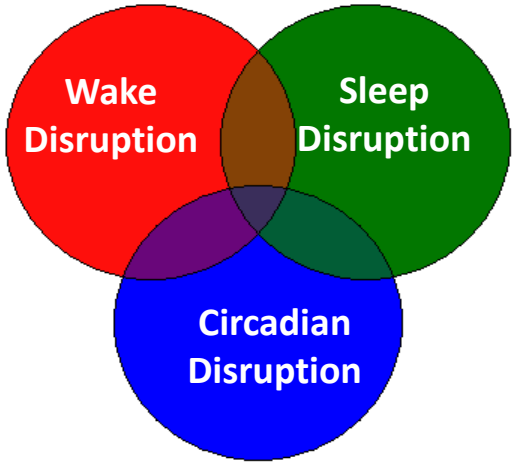
Sleep Apnea ((6%-20%)

Before menopause ♂ > ♀
After menopause ♂ = ♀

PLMS/Restless Legs
Prevalence (10%) ♀ > ♂

Hypersomnias
Narcolepsy (10%)

Circadian Rhythm Disorder
Prevalence?



Metabolism
Inflammation
Oxidative stress
Autonomic function

Cardio-metabolic
Neuropsychiatric

Age **Sex** **Race**

Behavioral lifestyle
Psychological well-being
Socio-economic status
Work schedules
Physical activity level
Light exposure

Health
Metabolic
Cardiovascular
Neurologic / Mental

Zee and Turek, Arch Int Med, 2006; Young T, et al. *Am J Respir Crit Care* 2002; Hornyak M, et al. *J Clin Psychiatry* 2005;Ohayon MM, Roth T. *J Psychosom Res* 2002;53:547-554. Dean DA et al, Sleep 2015

SLEEPING WELL & STAYING IN RHYTHM

Clocks

Sleep/Wake

Neural, Cardio-Metabolic Function

Cardio-Metabolic
Neurologic
Psychiatric
Health

Circadian and sleep function essential for cell function, neural connectivity and plasticity

Women (menopause) are a population at risk for circadian and sleep disruption which can contribute to cardio-metabolic disorders, neurological and psychiatric disorders

Improving sleep and circadian rhythm as targets for prevention and disease modification across the lifespan