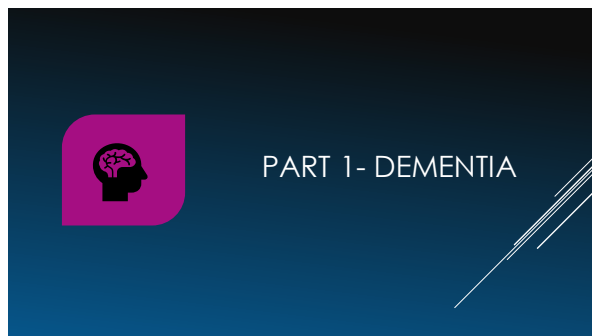




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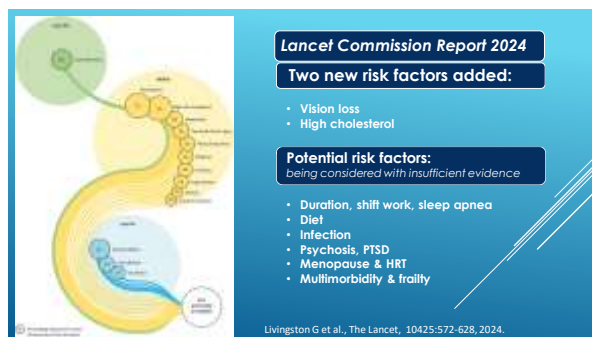
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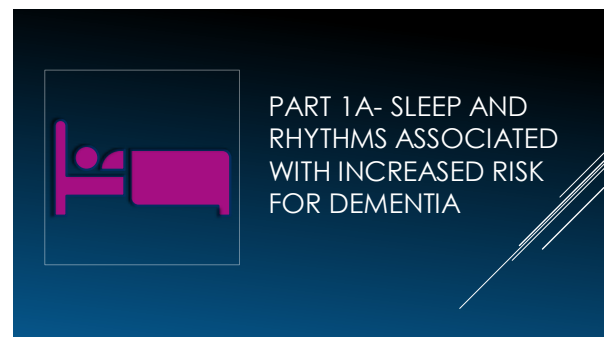
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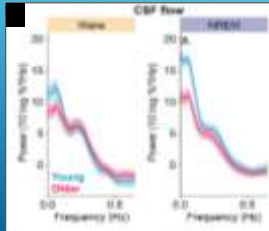


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6

CSF FLOW REDUCED IN AGING IN COGNITIVELY NORMAL SUBJECTS



CSF flow measured with simultaneous EEG-fMRI: CSF data in young (18-39 y/o, n=25) and older (60-84 y/o, n=39) adults

CSF flow in sleep reduced in older adults and linked to both decreased frontal delta EEG and gray matter atrophy

Bailes SM et al., bioRxiv [Preprint]. 2025 Feb 24:2025.02.22.639649.

7

META-ANALYSIS OF SLEEP DISORDERS AND DEMENTIA, AD, AND COGNITIVE DECLINE



Meta-analysis of 39 cohort studies that reported risk estimates for dementia, AD, or cognitive decline associated with obstructive sleep apnea, insomnia, or other sleep disorders



Other sleep disorders included restless leg syndrome, circadian rhythm sleep disorders, excessive daytime sleepiness, and other non-specific sleep disturbances



Results demonstrate associations between a range of sleep disorders and an elevated risk of dementia

Ungvari Z & Fekete M et al., GeroScience doi: 10.1007/s11357-025-01637-2, 2025.

8

HAZARD RATIOS FOR ALL-CAUSE DEMENTIA RISK

- Pooled HRs:
- 1.33 (95% CI 1.09-1.61) for apnea
- 1.36 (95% CI 1.19-1.55) for insomnia
- 1.33 (95% CI 1.24-1.43) for other sleep disorders

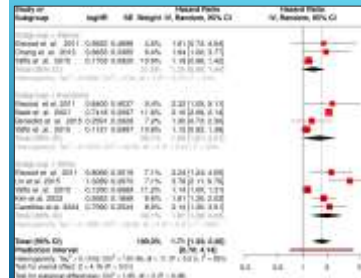


Ungvari Z & Fekete M et al., GeroScience doi: 10.1007/s11357-025-01637-2, 2025.

9

HAZARD RATIOS FOR VASCULAR DEMENTIA

- Pooled HRs:
- 1.35 (95% CI 0.99-1.84) for apnea (NS)
- 1.59 (95% CI 1.01-2.51) for insomnia
- 1.97 (95% CI 1.28-3.02) for other sleep disorders

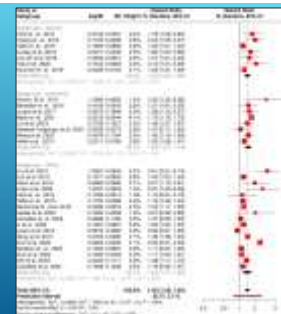


Ungvari Z & Fekete M et al., GeroScience doi: 10.1007/s11357-025-01637-2, 2025.

10

HAZARD RATIOS FOR AD

- Pooled HRs:
- 1.45 (95% CI 1.24-1.69) for apnea
- 1.49 (95% CI 1.27-1.74) for insomnia
- 1.42 (95% CI 1.11-1.83) for other sleep disorders

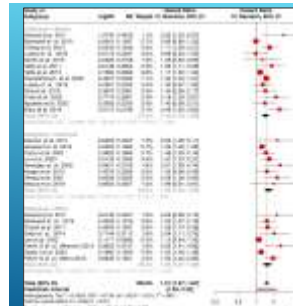


Ungvari Z & Fekete M et al., GeroScience doi: 10.1007/s11357-025-01637-2, 2025.

11

HAZARD RATIOS FOR COGNITIVE DECLINE

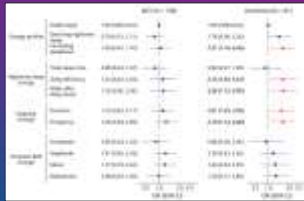
- Pooled HRs:
- 1.44 (95% CI 1.24-1.68) for apnea
- 1.63 (95% CI 1.36-1.95) for insomnia
- 1.55 (95% CI 1.27-1.90) for other sleep disorders



Ungvari Z & Fekete M et al., GeroScience doi: 10.1007/s11357-025-01637-2, 2025.

12

INCREASING SLEEPINESS IN OLDEST OLD WOMEN ASSOCIATED WITH DEMENTIA RISK



733 women (82.5±2.9 y/o)

Changes in actigraphic sleep assessed after 5 yrs (3.5-6.3 yrs)

Women with increasing sleepiness had double the risk of dementia (OR 2.21, 95% CI 1.14-4.26) compared to those with stable sleep.

Milton S et al., *Neurology* 104(8):e213403, 2025.

13

SLEEP DISTURBANCE ASSOCIATION WITH INCIDENT DEMENTIA STRONGER WITH LONG LAG TIMES

Data from Longitudinal Aging Study Amsterdam that assessed association of sleep disturbance with incident dementia with lag times of 2.2-23.8 yrs (n=2,218; 55-85 y/o at entry; 11% developed dementia)

Self-reported sleeping ≤ 6 h, interrupted sleep, and early awakening associated with incident dementia

Associations stronger with lag times ≥ 15 yrs

Sleeping ≥ 9 h associated with increased incident dementia with lag time of 3 yrs but not when lag time > 5.5 yrs.

Alders P et al., *J Prev Alzheimer Dis* 12(2):100024, 2025.

14

OSAS AND RISK OF DEMENTIA

Data from 2.3 million adults in UK Clinical Practice Datalink

193,600 subjects with OSAS matched to 536,701 individuals without OSAS; median follow-up of 4 yrs

Presence of OSAS associated with higher risk of all-cause dementia (aHR 1.12, 95% CI 1.07-1.17) and vascular dementia (aHR 1.29, 95% CI 1.19-1.41) but unchanged risk for Alzheimer's disease

Those treated with CPAP had similar risk of all-cause dementia as matched counterparts

Wang J et al., *Thorax* 80:167-174, 2025.

15

INCREASED DEMENTIA RISK WITH EARLIER OSA ONSET

UK Biobank study including 445,023 participants without dementia or sleep disorders other than OSA at baseline

12.6 year median follow-up

Subjects with OSA had higher risks for dementia than matched subjects without OSA with hazard ratios as follows:

- All-cause dementia 4.243 (95% CI: 3.678-4.897)
- AD 5.668 (95% CI: 4.380-7.336)
- Vascular dementia 6.064 (95% CI: 4.008-9.175)

OSA present at age < 52 associated with higher risks for all 3 types of dementia

Gang C & Chen C, *J Psychiatr Res* 184:170-175, 2025.

16

SLEEP DISTURBANCE AS A RISK FACTOR FOR NEURODEGENERATION

Data from 3 biobanks

- Secure anonymized Information Linkage (SAIL)
- UK Biobank
- FinnGen datasets

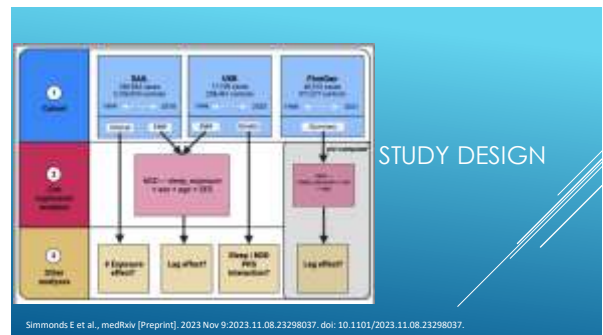
Used first reported date of an ICD10 sleep code but excluded codes occurring after neurodegenerative disorder diagnosis

- F51 – Nightmares, generalized insomnia
- G47 – Narcolepsy, apnea, hypersomnia, parasomnia, sleep movement disorders

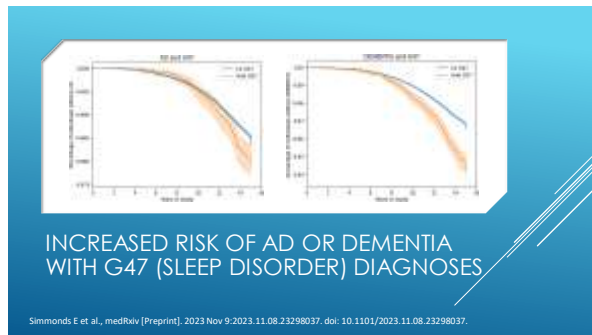
Associations seen across multiple biobanks

Simmonds E et al., *medRxiv* [Preprint]. 2023 Nov 9:2023.11.08.23298037. doi: 10.1101/2023.11.08.23298037.

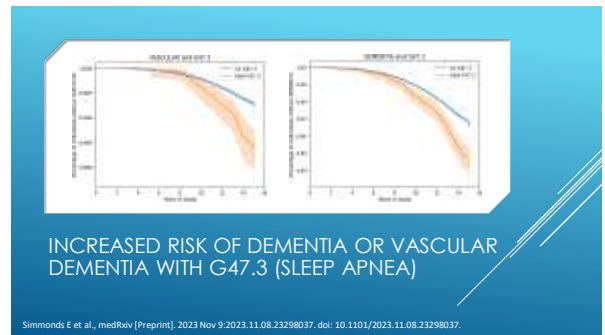
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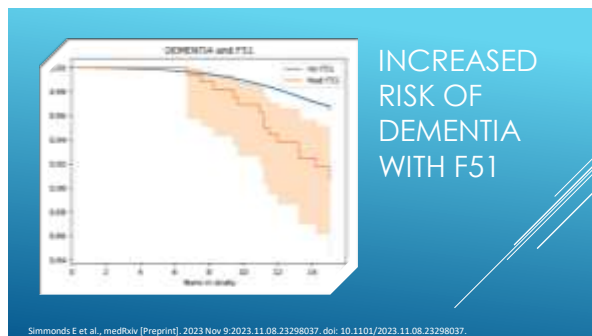
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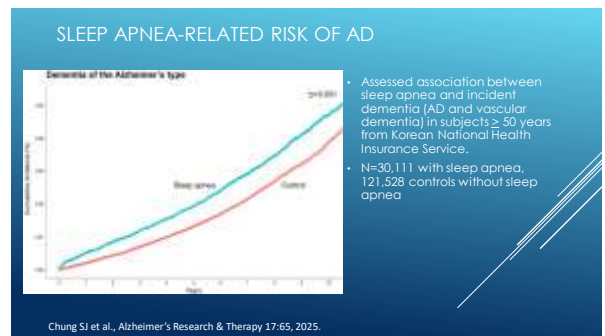
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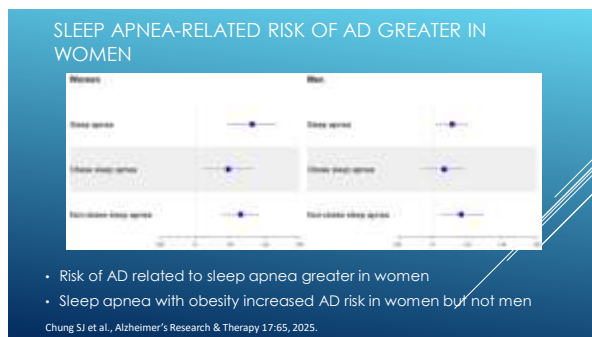
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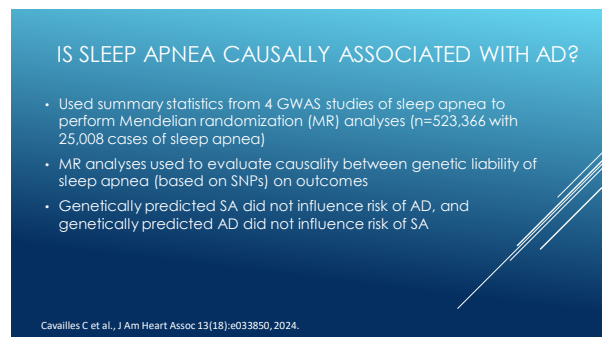
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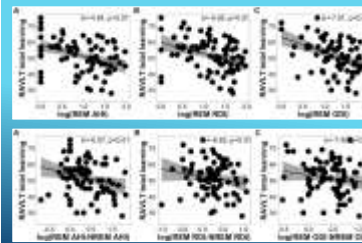
EFFECTS OF OSA ON VERBAL MEMORY IN SUBJECTS AT RISK FOR AD

- N=81 adults underwent clinical polysomnography including assessment of OSA
 - Mean age: 61.6 ± 6.0 y/o, 62% women
 - 31.7% apolipoprotein E $\epsilon 4$ allele (APOE4) carriers, 69.5% with parental history of AD
- Verbal memory learning and recall tested (Rey Auditory Verbal Learning Test; RAVLT)
- Relationships between OSA and RAVLT scores assessed, adjusting for sex, age, time between assessments, education years, and APOE4 status or parental history of AD
- Significant main effects of OSA features on RAVLT and moderating effects of AD risk factors (i.e., sex, age, APOE4 status, and parental history of AD) examined in these models

Liu K, Mander B, Benca R et al. *Alzheimers Res Ther* 16(1):102, 2024.

25

OSA SEVERITY BY SLEEP STAGE AND LEARNING



Greater AHI, RDI, & ODI were significantly associated with impaired learning ability

REM ODI FDR significant

Relationships more specific to REM sleep (all NREM $p > 0.40$)

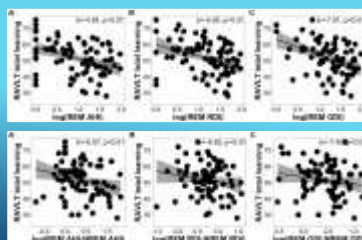
The degree of REM dominant AHI, RDI, and ODI predicted impaired learning ability

Relationships driven by events, but not REM duration per se

Liu K, Mander B, Benca R et al. *Alzheimers Res Ther* 16(1):102, 2024.

26

OSA SEVERITY BY SLEEP STAGE AND DELAYED RECALL



Greater AHI, RDI, and ODI were significantly associated with impaired memory retention (FDR)

Relationships more specific to REM sleep (all NREM $p = 0.93$)

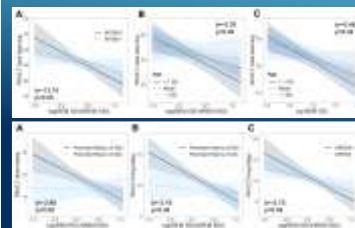
Steiger's Z revealed correlations differed by sleep stage for AHI ($p = 0.004$) and ODI ($p = 0.03$)

The degree of REM dominant AHI, RDI, and ODI predicted impaired memory retention

Liu K, Mander B, Benca R et al. *Alzheimers Res Ther* 16(1):102, 2024.

27

AGE, APOE4 STATUS, AND PARENTAL HISTORY MODERATE MEMORY ASSOCIATIONS



- AD risk factors moderate associations between REM-related OSA severity and learning & memory

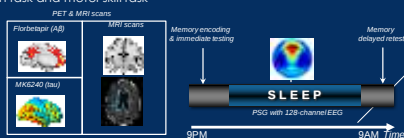
Note: These moderation effects occur in a largely AB- cohort that is at risk for AD.

Liu K, Mander B, Benca R et al. *Alzheimers Res Ther* 16(1):102, 2024.

28

Sleep Apnea, Local Sleep & Alzheimer's (SALSA) study

- 40 clinically intact older adults (72.3 ± 5.8 y/o, 26 women) recruited from the UCI BEACoN Cohort (PI Yassa) completed to date; enriched for OSA with STOP-BANG questionnaire screening (PSG AHI: 14.0 ± 17.6 , range 0.5-79.8)
- MRI data used to assess white matter hyperintensities (WMH), MTL structure
- In-lab clinical PSG with hdEEG (128 channels); focus on hypoxemia severity (minimum O_2 saturation)
- Sleep-dependent memory assessed before and after sleep with emotional pattern separation task and motor skill task



Berisha D et al. *Neurology* 104 (11), 2025.

29

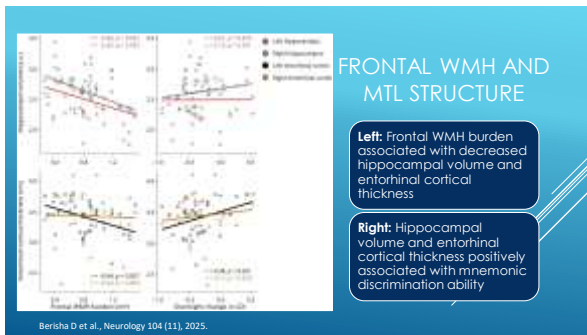
REGIONAL WMH VOLUME AND HYPOXEMIA SEVERITY IN REM SLEEP



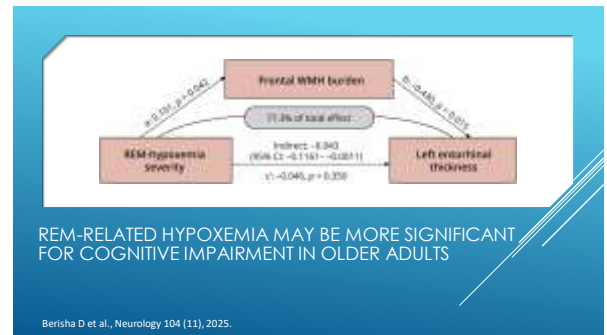
- Associations between REM sleep SpO_2 nadir and WMH volume strongest in frontoparietal cortex
- Could cerebrovascular pathology be a candidate mechanism?

Berisha D et al. *Neurology* 104 (11), 2025.

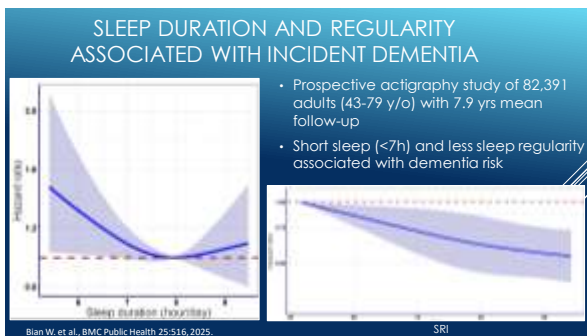
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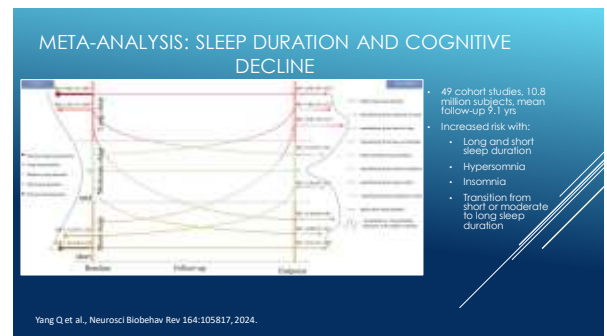
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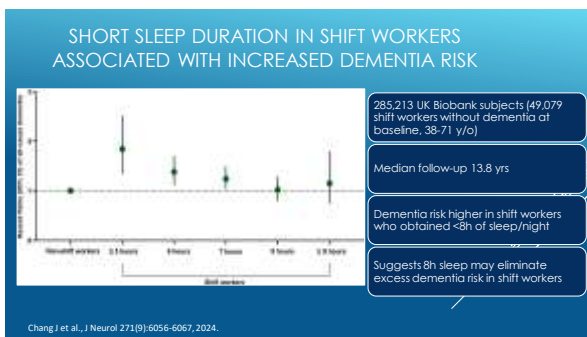
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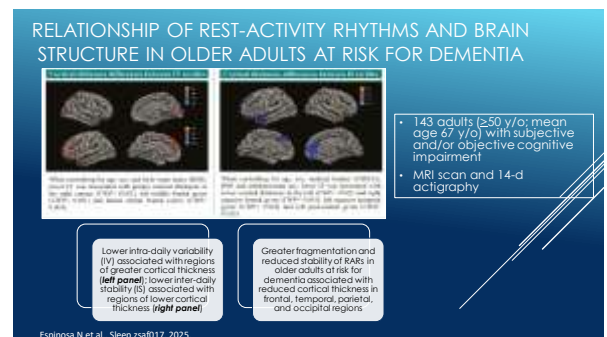
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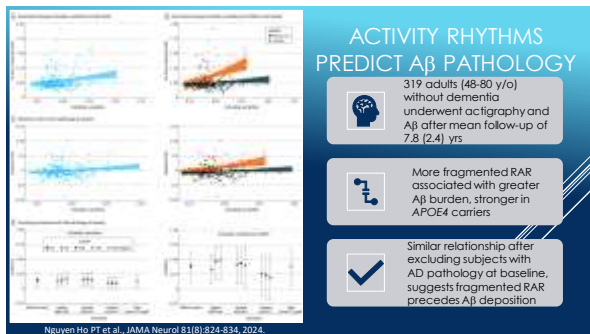
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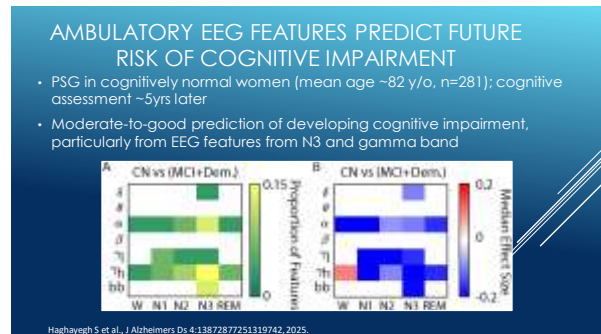
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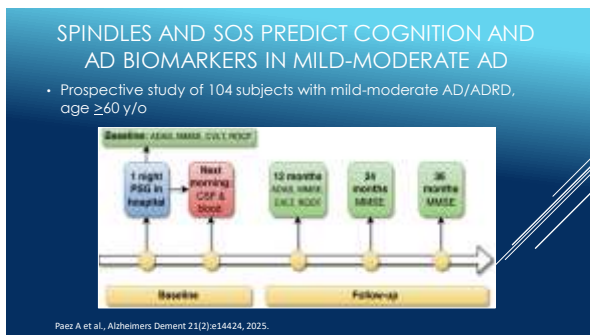
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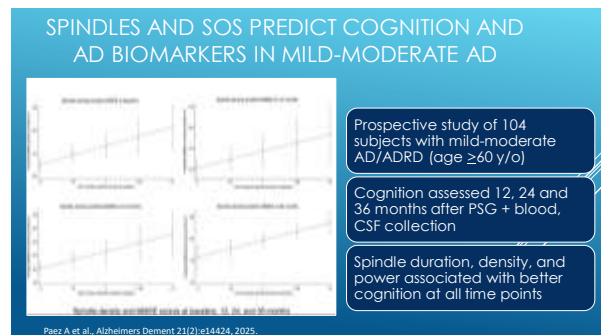
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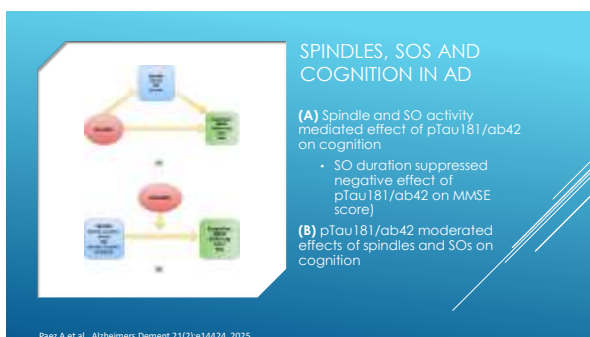
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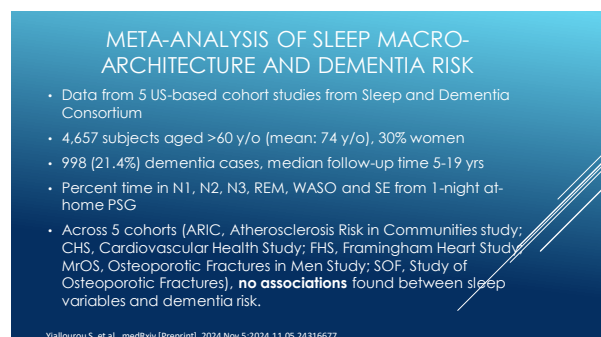
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PART 2- AUTISM

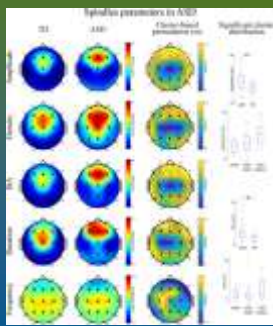
43

SLEEP EEG OSCILLATION ABNORMALITIES IN AUTISM

- Sleep spindles implicated in learning and abnormalities in spindle development in childhood reported in autism spectrum disorder (ASD)
- Sleep recorded during afternoon naps in typically developing (TD) and ASD children ages 2-6
- 50 children studied, including TD children (n=18) and those with ASD (n=32)
- ASD children included
 - ASD diagnosis only (ASDo) (n=6)
 - Co-occurring General Developmental Delay (ASD-GDD) (n=19)
 - Both GDD and EEG epileptic abnormalities (ASD-GDD-E, without clinical history of epilepsy and free from EEG seizures) (n=7)

D'Ambrosio S et al., Autism Research 0:1-11, 2025.

44



SLEEP EEG OSCILLATION ABNORMALITIES IN AUTISM

- Significant increases in sleep spindle (sigma) seen in frontal regions
- Increases in adjacent alpha and beta power also seen
- No differences in delta, theta or gamma power
- Naps sufficient to detect abnormalities in sleep oscillations in children

D'Ambrosio S et al., Autism Research 0:1-11, 2025.

45



PART 3- CLIMATE CHANGE

46

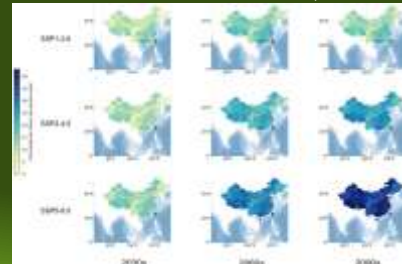
EFFECTS OF CLIMATE WARMING ON SLEEP DURATION AND QUALITY

Parameters	Estimate (95%CI)	
Percentage change (%)		
Sleep insufficiency	20.1 (19.9, 20.3)	• Sleep monitoring data from 214,445 subjects across mainland China for 23 million days
Absolute change (min)		• Effect of daily average temperature on sleep analyzed
Total sleep duration	-9.67 (-9.74, -9.60)	• Table: %age change in odds of various sleep parameters associated with each 10 °C temp. increase
Light sleep duration	-4.04 (-4.09, -4.00)	
Deep sleep duration	-3.58 (-3.62, -3.55)	
Dream sleep duration	-2.01 (-2.04, -1.99)	
Absolute change (%)		
Light sleep proportion	-2.02 (-2.05, -2.00)	
Deep sleep proportion	-2.82 (-2.85, -2.80)	
Dream sleep proportion	-2.20 (-2.22, -2.17)	

Li A et al, Nat Commun 16:2609, 2025

47

PROJECTED PERCENTAGE INCREASES IN SLEEP LOSS UNDER DIFFERENT CLIMATE SCENARIOS IN 2030S, 2060S AND 2090S



Li A et al, Nat Commun 16:2609, 2025

48



49

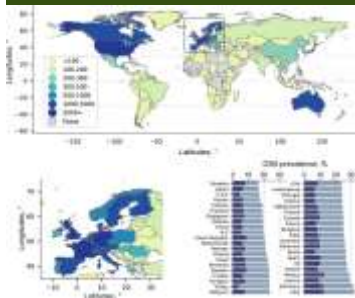
RELATIONSHIP BETWEEN HIGHER AMBIENT TEMPERATURES AND OSA

- Data from 116,620 adult subjects who used under-mattress sleep sensor (Withings Sleep Analyzer) ≥ 28 nights with ≥ 4 nights data/week between Jan 2020 and Sept 2023
- Weather information time-matched for each day of data for each user based on their closest location, collected from the Copernicus Climate Change Service
- Subjects were 77.3% male, mean age 49

Lechat B et al., Nat Commun 16:5100, 2025.

50

MODERATE AND SEVERE OSA BY COUNTRY

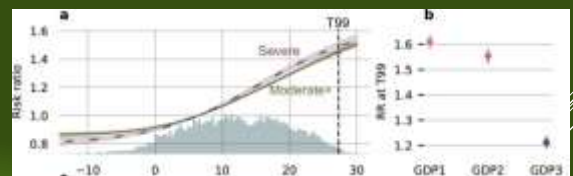


- Geographical location of under-mattress regular users on maps
- OSA prevalence by country:
- Lt blue – AHI 15-30
- Dk blue – AHI ≥ 30

Lechat B et al., Nat Commun 16:5100, 2025.

51

EXPOSURE-RESPONSE BETWEEN DAILY AMBIENT TEMP AND NIGHTLY OSA STATUS BY LOCATION

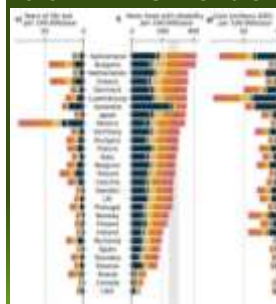


- Probability of having OSA **45% higher** (risk ratio (RR) [95%CI]: 1.45 [1.44, 1.47]) on nights following days with high temperatures (27.3°C) vs. following days with lower temperatures (25.6°C). Probability of having severe OSA was 49% [1.46, 1.52] higher in high vs. low temperature days.
- Probability of nightly OSA higher at T99 in countries with lower gross domestic product (GDP) per capita

Lechat B et al., Nat Commun 16:5100, 2025.

52

FUTURE IMPLICATIONS OF GLOBAL WARMING ON OSA



Lechat B et al., Nat Commun 16:5100, 2025.

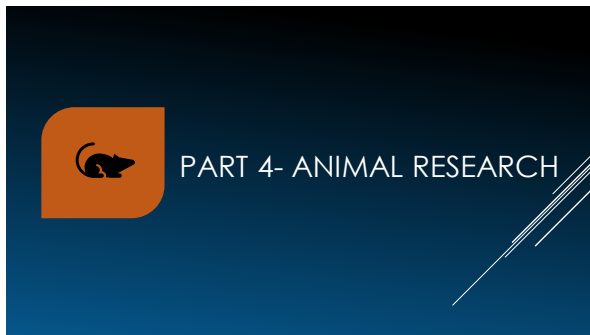
53

IMPLICATIONS

- Increased OSA prevalence in 2023 due to global warming associated with loss of 788,198 healthy life years, and productivity loss of ~105 million days in the 29 studied countries.
- In 2023, estimated economic cost associated the increased OSA prevalence was ~98 billion USD.
- Global warming modelled to increase by 2.1 to 3.4 °C by 2100. The increase in OSA prevalence due to rising temperatures may double the overall OSA burden.

Lechat B et al., Nat Commun 16:5100, 2025.

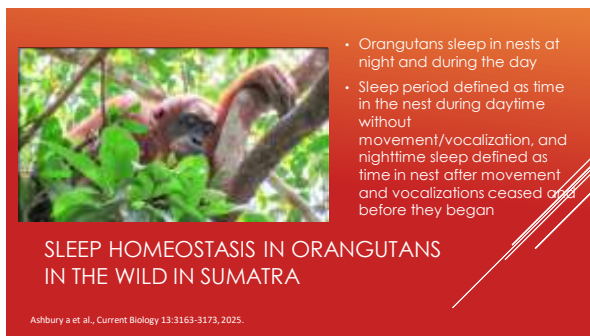
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• Orangutans sleep in nests at night and during the day

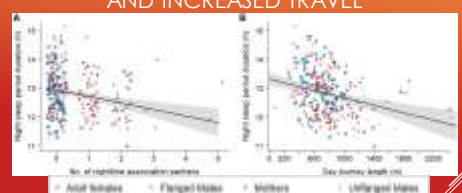
• Sleep period defined as time in the nest during daytime without movement/vocalization, and nighttime sleep defined as time in nest after movement and vocalizations ceased and before they began

SLEEP HOMEOSTASIS IN ORANGUTANS IN THE WILD IN SUMATRA

Ashbury a et al., Current Biology 13:3163-3173, 2025.

57

SHORTER NIGHTTIME SLEEP WITH MORE PARTNERS AND INCREASED TRAVEL

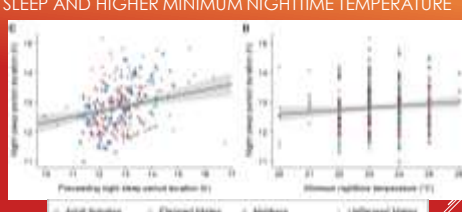


Orangutans had shorter nighttime sleep periods (A) they had more nighttime association partners and (B) they traveled farther on the preceding day.

Ashbury a et al., Current Biology 13:3163-3173, 2025.

58

LONGER NIGHTTIME SLEEP AFTER A LONG PRIOR NIGHT OF SLEEP AND HIGHER MINIMUM NIGHTTIME TEMPERATURE

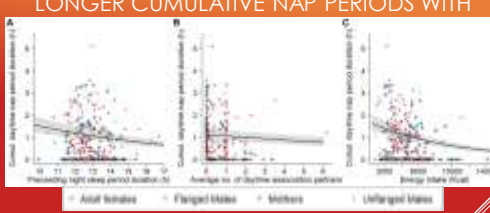


Orangutans had longer nighttime sleep periods when (C) the duration of their nighttime sleep period during the preceding night was longer and (D) the minimum nighttime temperature was higher.

Ashbury a et al., Current Biology 13:3163-3173, 2025.

59

LONGER CUMULATIVE NAP PERIODS WITH

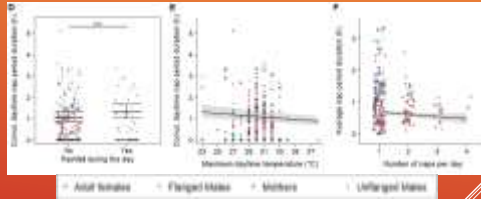


(A) a shorter nighttime sleep period the preceding night, (B) association with fewer association partners over the course of the day, (C) lower total energy intake

Ashbury a et al., Current Biology 13:3163-3173, 2025.

60

LONGER CUMULATIVE NAP PERIODS WHEN



(D) there was rain during the day, (E) the maximum daytime temperature was lower, (F) their nap periods were, on average, shorter.

Orangutans use daytime naps to compensate for lost sleep at night

Ashbury et al., Current Biology 13:3163-3173, 2025.

61

SLEEP HOMEOSTASIS IN ORANGUTANS: CONCLUSIONS



- Orangutans use daytime naps to compensate for lost sleep at night
- Social and ecological factors lead to variations in nighttime sleep and daytime naps
- "The costs and benefits of sleep are traded off with those of other critical activities, such as travel and sociality."

Ashbury et al., Current Biology 13:3163-3173, 2025.

62

FIRST NIGHT EFFECT IN HORSES



- Horses often transported to new locations for sporting events
- Horses from professional sports horse barn who were frequently transported (n=5) compared to horses from a breeding barn who were not (n=6)
- EEG recorded to detect First Night Effect, comparing sleep in the home box to a guest box (1 night each)

Bergeler J et al., Sci Rep 15(1):30075, 2025.

63

SLEEP PATTERNS

- No significant differences in feeding, lying down or drowsiness between home and guest boxes for either group of horses
- Sport horses tended to spend more time lying down, significant only for home box



Bergeler J et al., Sci Rep 15(1):30075, 2025.

64

First night effect in horses:
Results and conclusions

- No clear First Night Effects based on behavioral data
- EEG recordings showed evidence of First Night Effect in both groups of horses
- Interhemispheric correlations between electrode pairs greater in the guest boxes for both groups
- Occipital delta band intrahemispheric coherence increased in the 1-10 Hz delta range and up to 3 Hz in the guest box compared to home box in both groups
- Findings interpreted as showing a higher degree of arousal during sleep
- Even sport horses show evidence of sleep disturbance in novel settings

Bergeler J et al., Sci Rep 15(1):30075, 2025.

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PART 5- WAKING UP

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HOW THE BRAIN AWAKENS AFTER SLEEP



20 normal subjects (38.3±7.4y)

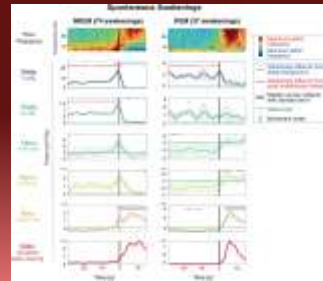
Sleep recorded with hdEEG (256 electrodes)

1,073 awakenings and arousals recorded

Stephan AM et al., Current Biology 35(16):3812-3824.e3, 2025.

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GLOBAL CHANGES IN POWER DURING AWAKENINGS

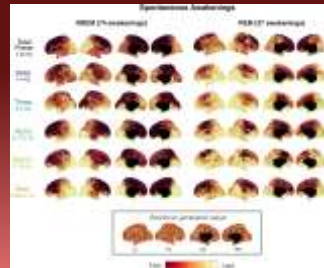


- In awakenings and arousals from NREM sleep, transient increases in low-frequency EEG power precede increases in high-frequency power
- In awakenings from REM sleep, only increases in high-frequency power observed

Stephan AM et al., Current Biology 35(16):3812-3824.e3, 2025.

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SPATIO-TEMPORAL PATTERN OF EEG CHANGES IN AWAKENING

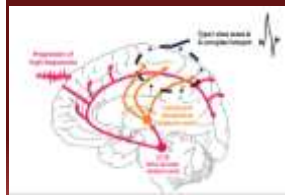


- Low-frequency changes in NREM awakening start in centro-parietal areas, then proceed frontally and reach occipital and inferior temporal regions last
- High frequency changes in both NREM and REM awakenings start frontally and are seen last in occipital and inferior temporal regions

Stephan AM et al., Current Biology 35(16):3812-3824.e3, 2025.

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SPATIO-TEMPORAL PATTERN OF EEG CHANGES IN AWAKENING



- Full awakenings usually preceded by a type I K-complex
- Frequency gradient:
 - Intralaminar thalamic nucleus (subcortical activation) drives K-complex (short)
 - Locus coeruleus drives high-frequency activity (sustained activation)
- Understanding how the brain awakens may be relevant for clinical conditions such as parasomnias and insomnia

Stephan AM et al., Current Biology 35(16):3812-3824.e3, 2025.

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DOSE AND TIMING EFFECTS OF CAFFEINE ON SUBSEQUENT SLEEP



Gardiner CL et al., SLEEP 48(4):zsa0230, 2025.

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QUESTIONS?

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