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Stage-Specific Hypoxic Burden Better Tracks REM Sleep Loss Than AHI

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INTRODUCTION

Obstructive sleep apnea (OSA) is traditionally quantified using the apnea-hypopnea index (AHI), a frequency-based metric representing the number of respiratory events per hour of sleep. However, AHI does not account for the physiological severity of individual respiratory events, particularly the magnitude and duration of oxygen desaturation (Malhotra et al., 2021).

Hypoxic burden (HB) has emerged as a physiologically informed metric that quantifies the cumulative area-under-the-curve desaturation associated with respiratory events and has shown stronger associations with cardiovascular and mortality outcomes than AHI alone (Azarbarzin et al., 2019; de Chazal et al., 2022). Recent evidence suggests HB may better capture the biological impact of sleep-disordered breathing across diverse clinical phenotypes.

Despite growing interest in HB, limited work has examined whether stage-specific HB metrics differentially relate to sleep architecture disruption. REM sleep and slow wave sleep (N3) are particularly important due to their roles in emotional regulation, cognition, memory consolidation, metabolic regulation, and cardiovascular health (Mokhlesi & Varga, 2022; Xie et al., 2013).

The present study evaluated whether:

- REM-specific HB more strongly predicts REM sleep loss than REM-specific AHI
- NREM-specific HB more strongly predicts NREM sleep loss (particularly N3) than NREM-specific AHI

METHODS

Dataset

- Sleep Heart Health Study (SHHS) (Punjabi, 2008)
- ~5,500 adults with full-night polysomnography
- XML sleep staging and respiratory event annotations
- 1 Hz SpO2 recording analyzed across the full night

Hypoxic Burden Calculation

HB was calculated using an event-synchronized desaturation ensemble averaging approach based on previously published methods (Azarbarzin et al., 2019; de Chazal et al., 2022). Respiratory events were aligned at event termination, ensemble averaged, low-pass filtered, and integrated to estimate cumulative desaturation area normalized to sleep duration.

Stage-specific HB metrics were computed separately for:

- REM sleep
- NREM sleep

Stage-specific AHI metrics were similarly computed:

- REM-AHI
- NREM-AHI

Sleep Architecture Outcomes

Primary outcomes:

- REM sleep duration (REM_min)
- N3 sleep duration (N3_min)

Statistical Analysis

Analyses included:

- Pearson correlations
- Quintile analyses
- One-way ANOVA across quintiles
- Bonferroni correction for multiple comparisons

Participants were stratified into quintiles separately for each metric.

RESULTS

REM Sleep

REM-specific HB demonstrated substantially stronger associations with REM sleep duration than REM-AHI.

REM Sleep Findings

METRIC	REM-HB	REM-AHI
Pearson r	-0.185	-0.059
Q1 -> Q5 REM reduction	13.4 min	4.3 min
Percent RM reduction	17.3%	5.8%
ANOVA	F(4,5614)=46.31	F(4,5620)=8.17
ANOVA p-value	2.43×10^{-38}	1.46×10^{-6}

REM-specific HB explained approximately 8.5× more variance in REM duration than REM-AHI and demonstrated over 3× greater REM sleep reduction across quintiles.

These findings suggest that cumulative desaturation severity during REM sleep may better capture REM-related sleep disruption than respiratory event frequency alone.

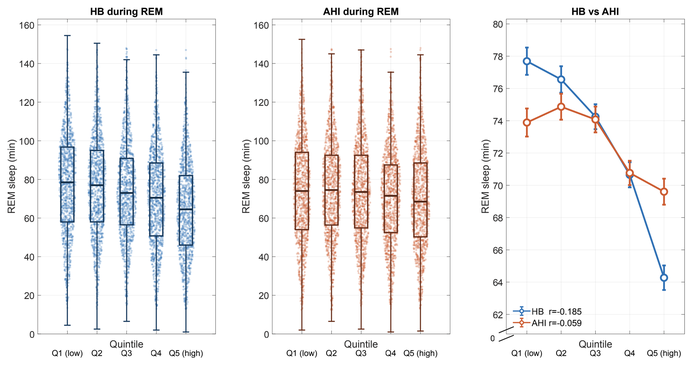

Figure 1

NREM (N3) SLEEP

Both NREM-HB and NREM-AHI demonstrated strong associations with N3 sleep duration.

N3 Sleep Findings

METRIC	NREM-HB	NREM-AHI
Pearson r	-0.169	-0.201
Q1 -> Q5 N3 reduction	21.2 min	22.2 min
Percent N3 reduction	29.2%	30.3%
ANOVA	F(4,5487)=55.96	F(4,5492)=62.35
ANOVA p-value	2.48×10^{-46}	1.31×10^{-51}

Unlike REM sleep, NREM-AHI slightly outperformed NREM-HB for predicting N3 reduction.

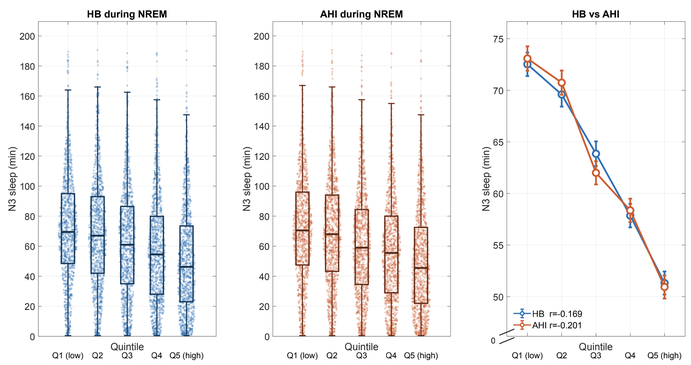

Figure 2

DISCUSSION

These findings suggest that REM and N3 sleep may be disrupted through partially different physiological mechanisms in OSA. The strongest finding was that REM-specific HB substantially outperformed REM-AHI for predicting REM sleep loss, suggesting that REM architecture may be more sensitive to the cumulative severity of oxygen desaturation than to respiratory event frequency alone.

This distinction is important because REM sleep has a unique respiratory physiology. During REM, reduced upper-airway muscle tone, diminished ventilatory responsiveness, and greater autonomic instability can contribute to longer respiratory events and deeper desaturations. Prior work has emphasized that REM-related OSA may carry distinct cardiovascular, metabolic, and neurocognitive relevance, and that AHI may incompletely capture this risk profile (Mokhlesi & Varga, 2022; Bonsignore et al., 2024). Our findings extend this concept by suggesting that REM sleep architecture itself may be disproportionately sensitive to cumulative desaturation burden rather than simple event count.

In practical terms, REM-HB may identify a form of REM-disruptive sleep-disordered breathing that is under-characterized by AHI alone. This aligns with the broader argument that OSA severity metrics should move beyond purely frequency-based measures toward physiologically weighted measures of burden (Azarbarzin et al., 2019; Malhotra et al., 2021; de Chazal et al., 2022).

N3 sleep showed a different pattern. Both NREM-HB and NREM-AHI strongly tracked N3 reduction, with AHI slightly stronger overall. This suggests that slow wave sleep disruption may reflect a broader burden of respiratory instability and fragmentation rather than primarily hypoxic severity. This also makes physiologic sense because N3 is a high-stability sleep state that may be progressively eroded by repeated respiratory interruptions and arousals, even when individual desaturations are not especially severe.

Together, these findings indicate that:

- REM sleep disruption may be more tightly coupled to desaturation severity
- N3 disruption may be more closely linked to respiratory event frequency and fragmentation
- Different sleep stages may exhibit distinct physiological vulnerability profiles in OSA

CONCLUSION

- These findings suggest that the physiological impact of OSA on sleep architecture cannot be fully understood using respiratory event frequency alone
- REM sleep loss appeared far more tightly linked to cumulative desaturation severity than to event count, whereas N3 disruption appeared influenced by both respiratory fragmentation and hypoxic burden
- Patients with similar AHI values may experience substantially different physiological disruption depending on the depth and duration of associated desaturation, particularly during REM sleep
- Stage-specific HB metrics may therefore capture clinically meaningful aspects of sleep-disordered breathing that are incompletely characterized by conventional AHI-based approaches
- Overall, these results support a more physiology-driven framework for evaluating OSA, in which different sleep stages exhibit distinct vulnerability profiles to respiratory instability and hypoxic stress

LIMITATIONS

- Cross-sectional analysis
- SHHS population demographics may limit generalizability
- Associations remain modest in absolute variance explained
- Sleep staging based on historical SHHS scoring conventions

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