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Obstructive sleep apnea subtyping based on apnea and hypopnea specific hypoxic burden is associated with brain aging and cardiometabolic syndrome

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ABSTRACT

Background: Conventional metrics such as the apnea-hypopnea index (AHI) may not fully capture the diverse clinical manifestations of obstructive sleep apnea (OSA). This study aims to establish a novel OSA subtype classification based on the patterns of apneic and hypopneic hypoxic burden (HB), a potential biomarker that more accurately reflects the severity and duration of respiratory events. We further examined the associations of these HB-based subtypes with cardiometabolic risk and brain health outcomes.
Methods: We retrospectively analyzed polysomnography data from 1000 participants including normal, mild, moderate, and severe OSA patients. We performed hierarchical clustering based on apneic and hypopneic HB to identify OSA subtypes. We then compared the prevalence of cardiometabolic syndrome (CMS) and brain health outcomes using the brain age index (BAI) among these subtypes.
Results: Five distinct subtypes were identified: 'good sleepers' (subtype 1), 'light hypopneic HB' (subtype 2), 'mild HB' (subtype 3), 'moderate HB' (subtype 4), and 'severe HB with marked apneic HB' (subtype 5). The prevalence of CMS (particularly hypertension) was significantly higher in subtypes 2–5 ($p < 0.001$) compared to subtype 1. BAI was higher in subtypes 4 (3.2 years, $p < 0.0001$) and 5 (11.1 years, $p < 0001$) compared to subtype 1. Greater daytime sleepiness was observed in HB-based subtypes 2 and 5 compared to subtype 1 ($p < 0.001$), whereas no significant differences were found among groups classified by OSA severity using AHI.
Conclusion: Our study demonstrates that the HB-based subtypes of OSA are significantly associated with various clinical features and outcomes. These insights could be utilized to improve risk stratification and guide the design of future OSA studies.

1. Introduction

Obstructive sleep apnea (OSA) is a common sleep disorder, affecting approximately 20–30 % of men and 10–15 % of women [1,2]. Characterized by recurrent airway obstruction during sleep, OSA leads to hypoxia, sleep fragmentation, and sympathetic activation [3,4]. When left untreated, it has been associated with neurocognitive deficits [5,6], metabolic complications [7], and cardiometabolic syndrome (CMS) [8–10].

Research examining the relationship between OSA, CMS, and cognitive function has produced inconsistent findings [11–13]. Currently, the primary metric used for diagnosing and assessing the severity of OSA is the apnea-hypopnea index (AHI), with an AHI ≥5 indicating an OSA diagnosis. OSA is commonly categorized based on AHI levels: mild (5–15), moderate (15–30), and severe (≥30) [14]. Many studies on OSA focus on moderate-to-severe cases as defined by the AHI [8–10]. However, the AHI only measures the frequency of respiratory events during sleep and does not provide data about the duration of hypoxia or the intensity of oxygen desaturation during these events [15]. As a result, it may lack the ability to predict OSA's impact on the cardiovascular system and the central nervous system (CNS). Additionally, the AHI does not adequately reflect the heterogeneity of

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OSA, overlooking the diverse clinical manifestations observed across patients [16,17]. Recently, researchers have begun classifying OSA patients into phenotypes to explore these variations in clinical presentation and prognosis [16–18]. Unfortunately, the AHI fails to capture these distinctive OSA clinical phenotypes in the aforementioned studies, highlighting its limitations.

The search for biomarkers that more accurately represent OSA's pathophysiological complexity is therefore crucial. Such biomarkers could refine patient subtyping and support more personalized management strategies. While some studies have explored quantitative polysomnography (PSG) metrics—such as event duration, arousal ratios, minimum oxygen saturation, positional and sleep state-dependent AHI, and sleep architecture patterns—to subtype OSA, their results have been inconsistent, particularly regarding cardiovascular outcomes [18–20]. Moreover, none of these PSG-based approaches have examined how OSA subtypes relate to brain health outcomes.

Hypoxia is one of the primary mechanisms through which OSA contributes to various adverse health outcomes, prompting numerous efforts to quantify hypoxia as an index [21,22]. Among these efforts, hypoxic burden (HB)—calculated as the "area under the curve" of oxygen desaturation during each apneic and hypopneic event—stands out due to its ability to capture not only the frequency of hypoxic events but also their duration and severity (depth) [23]. This characteristic gives HB a unique advantage over other OSA metrics, and it has become one of the most widely studied indices in recent OSA research. Prior studies have established associations between HB and multiple health risks, including cardiovascular mortality, heart failure, hypertension, major adverse cardiovascular events, and stroke [23–27].

Despite its potential, HB has not yet been explored as a biomarker for OSA subtyping. In this study, we propose a novel approach: decompose the conventional HB metric into apnea- and hypopnea-specific components, use these components to identify distinct OSA subtypes, and then assess whether these subtypes correlate with the prevalence of CMS, brain health outcomes, and responses to continuous positive airway pressure (CPAP) treatment. Through this HB-based approach, we aim to uncover pathophysiologically relevant OSA subtypes that may offer advantages over traditional AHI-based classifications.

2. Methods

2.1. Participants

We retrospectively studied participants older than 18 years who underwent PSG at the sleep clinic of the Samsung Medical Center from 2015 to 2017. Based on the traditional OSA categorization using AHI, we enrolled 250 participants each for normal (AHI <5), mild ($5 \leq$ AHI <15), moderate ($15 \leq$ AHI <30), and severe (AHI ≥ 30) OSA patients. We excluded patients with a history of OSA treatment (e.g., CPAP, mandibular advancement devices [MAD], or upper airway surgery). To avoid confounding by central sleep apnea, we also excluded patients with a central apnea index >5. Lastly, we excluded subjects with a history of neurological (neurodegenerative disease, brain tumor, epilepsy, or severe head trauma) and psychiatric diseases (psychosis or current depression).

To investigate whether HB-derived OSA subtypes could benefit from CPAP therapy or not, we also included 98 OSA patients who were treated with CPAP and underwent PSG assessments both at baseline and follow-up (without CPAP usage during the PSG). The interval between baseline and follow-up assessment was at least 12-month. These participants participated in the same sleep clinic from 2015 to 2019, throughout which they underwent CPAP treatment and continued their treatment, ensuring regular visits to the sleep clinic and maintaining a minimum average daily use of 4 h. We meticulously collected compliance data daily throughout the study's duration. The selected data aligned with the "CPAP-treated OSA patient group" in our previous study [28].

All participants underwent a detailed clinical interview and sleep-related questionnaire including Pittsburgh sleep quality index (PSQI), insomnia severity index (ISI), Epworth sleepiness scale (ESS), and Beck depression inventory (BDI). Information on the history or current presence of CMS such as hypertension, coronary artery disease, cerebrovascular disease, congestive heart failure, diabetes, and cardiac arrhythmia was collected at the time of conducting the PSG. SMC Institutional Review Board approved PSG data use for this retrospective analysis (IRB No.2023-07-007/2021-09-039). All participants provided written informed consent prior to their inclusion in the study.

2.2. Data collection

Oxygen saturation (SpO2) records and manually annotated respiratory events records were extracted from Embla® RemLogic™ (Natus Medical Inc., USA) to evaluate HB. Each PSG is scored by one of seven electroencephalogram (EEG) technicians according to the American Academy of Sleep Medicine (AASM) manual version 2.4 [29]. Apnea was defined as a reduction in airflow by 90 % and more lasting at least 10 s. Hypopnea was defined as a reduction in airflow by 30 % and more lasting at least 10 s with at least 3 % oxygen desaturation or arousal. In this study, patients with more than 20 % of recorded SpO2 below 60 % were excluded from HB calculation. SpO2 data below 60 % were replaced with the SpO2 value detected right before.

2.3. Observers: hypoxic burden calculation

We calculated the HB using the method proposed by Ali Azarbarzin, which focuses on the area under the oxygen desaturation curve for each respiratory event [23]. The rationale for using the area under the curve (AUC) is to capture not only the frequency but also the depth and duration of each respiratory event, aspects that are not reflected by traditional metrics like the AHI, oxygen desaturation index, or arousal index, which are frequency-based measures. This approach allows for distinguishing events with profound, prolonged desaturation (typically seen in apneas) from events with subtle saturation changes associated with slight flow limitations (often observed in hypopneas with low arousal threshold) [24]. While frequency-based indices may record both types of events similarly, HB's AUC-based calculation differentiates them by yielding distinct values according to the severity and duration of each event. Additionally, we expanded on this concept by separately analyzing HB specific to apnea and hypopnea events for more precise characterization of respiratory events for each individual. We defined the apneic HB as the HB calculated exclusively from apnea events and the hypopneic HB as that derived exclusively from hypopnea events. When calculating the apneic HB, we identified the peak points of the search window considering only apnea events, as indicated by the magenta triangles in Supplementary Fig. 1B. Conversely, for the hypopneic HB, we defined the peak points considering only hypopnea events, as shown by the yellow triangles in Supplementary Fig. 1B. Further details on the calculation of HB are provided in Supplementary Fig. 1.

2.4. Cardiometabolic syndrome and brain health outcome

2.4.1. Cardiometabolic syndrome

We included the following components of CMS in this study: hypertension, coronary artery disease (angina or myocardial infarction), cerebrovascular disease (stroke or transient ischemic attack), congestive heart failure, diabetes mellitus, and cardiac arrhythmia [30]. We then calculated the prevalence of the CMS as 1 if any components of CMS are present, otherwise 0.

2.4.2. Brain health outcome: brain age index

We analyzed sleep EEG data from eight channels, including frontal (F3, F4), central (C3, C4), occipital (O1, O2), and behind-the-ears channels (A1, A2), sampled at 200 Hz. Data during sleep latency was excluded. After filtering the data (0–50 Hz) and removing

electrocardiogram (ECG) and electrooculogram (EOG) artifacts using the Automatic artifact removal (AAR) plugin of EEGLAB, a MATLAB (Mathworks Inc., USA) toolbox for EEG data analysis, we corrected amplitude values exceeding 5 standard deviations using spline interpolation, affecting about 3.8 % of the data. We then standardized each EEG channel's amplitude using z-score normalization.

For BAI prediction, we employed a sleep EEG-based brain age prediction model with a proven low Mean Absolute Error (MAE) of 4.8 years [31]. This model combines sleep stage information and sleep EEG, resulting in input data with dimensions of 2000 (time points) by 16 (frequency bands) by 7 (EEG channels and sleep stage). The BAI, indicating relative brain health, was derived by subtracting chronological age from predicted brain age. However, due to potential biases in age prediction, we adjusted the BAI using methods from prior research to ensure accuracy [31]. Further details can be found in Supplementary Method 1.

To assess the health outcome changes after a long-term CPAP treatment, we computed ΔBAI as $BAI_{follow\text{-}up}$ minus $BAI_{baseline}$ where *baseline* and *follow-up* indicate baseline PSG before treatment and follow PSG after at least 1-year CPAP treatment. Given the variability of time intervals across individuals in the CPAP longitudinal study, we employed an annualized ΔBAI (ΔBAI per year). Similarly, we computed annualized ΔESS, ΔPSQI, ΔISI, and ΔBDI to investigate various CPAP outcomes.

2.5. Statistical analysis

2.5.1. Cluster analysis

Hierarchical cluster analysis was performed to categorize all the subjects into characteristic subtypes based on variables including apneic HB and hypopneic HB to explore OSA subtypes. We performed five-fold cross-validation to avoid possible bias.

The whole procedure is outlined below:

Initially, the observer values were transformed to a logarithmic scale to account for significant variability. These values were then standardized using z-score normalization to minimize the influence of varying dimensions on the clustering outcome. The optimal number of subtypes was determined using the Calinski-Harabasz (CH) index and Gap statistic. The CH index evaluates the clustering structure by calculating the ratio of between-cluster variance to within-cluster variance, defined as:

$$CH(k) = \frac{T_r(B_k)}{T_r(W_k)} \times \frac{N-k}{k-1} \quad (1)$$

Where $T_r(B_k)$ is the trace of the between-cluster dispersion matrix, $T_r(W_k)$ is the trace of the within-cluster dispersion matrix, N is the total number of observations, and k is the number of clusters. A higher CH index value indicates that the clusters are well-separated and compact, reflecting an optimal clustering solution.

The Gap statistic compares the within-cluster dispersion to that expected under a null reference distribution, helping to identify the number of clusters that maximize the difference between observed clustering and random chance. It is defined as:

$$Gap(k) = \frac{1}{B}\sum_{b=1}^{B} \log\left(W_k^{(b)}\right) - \log(W_k) \quad (2)$$

Where W_k is the within-cluster dispersion for the observed data with kkk clusters, $W_k^{(b)}$ is the within-cluster dispersion for the b-th reference dataset with k clusters, and B is the number of reference datasets.

Subsequently, subjects were grouped into consistent subtypes through the hierarchical clustering analysis algorithm. The subtypes were renumbered in ascending order based on the total HB levels. To enhance the reliability of the statistical analysis, subjects were resampled into subsets employing the bootstrap technique. Each of these subsets underwent clustering, and subjects were then predominantly grouped into the most frequently identified cluster.

The outcomes of this analysis were then visualized. The entire cluster analysis was executed using Matlab.

2.5.2. Comparison between subtypes

We sorted the subtypes by the level of total HB, with subtype 1 having the smallest total HB. To test whether the subtypes differed based on the patterns of apneic HB and hypopneic HB present with different demographic characteristics and observed PSG variables (AHI, ODI, Arousal Index, etc.), we performed analysis of covariance (ANCOVA) for continuous variables and chi-square tests for categorical variables. We adjusted for potential confounding factors such as age, sex, and BMI in the analysis of the prevalence of CMS (defined as "yes" or "no"), sleepiness (ESS, used as a continuous score), and brain health outcome variables (BAI as a continuous value). We then ran post-hoc tests to compare the demographic, observed PSG parameters, and outcome variables between each pair of the subtypes using an independent Student's t-test for continuous variables and a Chi-square test for discrete variables.

2.5.3. Comparison between HB-subtypes and the AHI-based OSA severity groups in terms of CMS, brain health outcome, and CPAP-treatment outcome

We utilized the 5 models trained via 5-fold cross-validation to classify 98 OSA patients who underwent CPAP treatment, employing a majority voting approach to determine their subtypes. We then analyzed how the OSA severity scoring criteria, based on AHI — namely, normal (AHI <5), mild ($5 \leq$ AHI <15), moderate ($15 \leq$ AHI <30), and severe (AHI ≥ 30) — are delineated within the clustering model driven by HB.

We examined differences in brain health outcome (BAI), the prevalence of CMS, and CPAP-treatment outcome (ΔBAI, ΔESS, ΔPSQI, ΔISI, and ΔBDI) across HB-driven subtypes within each of AHI-based OSA severity groups. We only included those subtypes where the OSA severity group constituted more than 5 % of the distribution for the comparison.

All findings were adjusted using the Bonferroni correction to account for multiple comparisons.

3. Results

3.1. Demographics and clinical characteristics

Out of the initial pool of 1000 subjects, we excluded 46 due to poor quality of SpO2 or EEG data, or because their total sleep time was less than 1 h. This resulted in a final cohort of 954 participants, including 218 classified as normal, 237 with mild OSA, 249 with moderate OSA, and 250 with severe OSA. The demographics and clinical details of these individuals are presented in Table 1.

The separate 98 OSA patients who underwent CPAP treatment consisted of 88 males and 10 females, with an average age of 53.3 ± 9.5 years. Their mean follow-up duration was 4.7 ± 2.5 years. They comprised 9 patients with mild OSA, 30 with moderate OSA, and 58 with severe OSA. More detailed demographics and clinical information are found in Supplementary Table 1 [28].

3.2. Determination of five subtypes

To identify the optimal number of clusters for characterizing OSA subtypes, we employed the CH and Gap criteria as well as considered the clinical relevance in terms of whether each subtype the relationship with outcome. Our analysis indicated that five clusters were the most suitable choice, supported by several key considerations.

Firstly, as depicted in Fig. 1A, the CH index reached its most pronounced value at two clusters (1454.5), closely followed by five clusters (1352.3), and then, with a marginal difference, by three clusters (1351.9). Similarly, Fig. 1B illustrates that the Gap statistic favored

Table 1
Demographic and clinical characteristics of participants. our study included a total of 954 participants, comprising 218 with normal sleep, 237 with mild OSA, 249 with moderate OSA, and 250 with severe OSA.

	Overall (n = 954)	Normal[a] (n = 218)	Mild[b] (n = 237)	Moderate[c] (n = 249)	Severe[d] (n = 250)	p-value[a]	post-hoc[b]
Age	48.3 (13.3)	41.4 (48.3)	48.3 (13.7)	50.4 (11.3)	51.1 (10.7)	**<0.001**	a<b,c,d
Male, %	74.0	48.2	72.9	80.7	90.8	**<0.001**	a<b < c < d
BMI	25.1 (3.6)	23.3 (3.4)	24.7 (3.1)	25.1 (3.0)	27.0 (3.7)	**<0.001**	a <b,c < d
PSQI	6.4 (2.7)	6.6 (3.0)	6.6 (2.9)	6.3 (2.5)	6.3 (2.6)	0.390	
ISI	8.1 (4.0)	8.3 (4.0)	8.0 (4.1)	7.8 (4.0)	8.2 (4.9)	0.648	
ESS	10.0 (4.8)	9.1 (4.8)	9.8 (5.0)	10.0 (4.6)	10.8 (4.6)	0.004	
BDI	11.2 (7.6)	11.8 (8.3)	11.2 (7.8)	10.9 (7.0)	11.0 (7.3)	0.567	
TST, hours	6.3 (1.0)	6.5 (1.0)	6.4 (0.9)	6.3 (0.9)	5.9 (1.0)	**<0.001**	a,b,c > d
AHI	21.8 (20.4)	2.1 (1.3)	9.7 (3.0)	21.6 (4.3)	50.4 (16.3)	**<0.001**	a<b < c < d
Apnea Index	7.9 (14.2)	0.2 (0.4)	1.2 (1.7)	5.1 (4.6)	23.8 (19.6)	**<0.001**	a,b < c < d
Hypopnea Index	13.8 (11.9)	1.9 (1.2)	8.5 (2.8)	16.5 (5.0)	26.6 (13.5)	**<0.001**	a<b < c < d
ODI	17.0 (19.0)	1.7 (2.1)	6.7 (3.9)	15.7 (6.2)	41.5 (20.2)	**<0.001**	a<b < c < d
Arousal Index	23.8 (14.3)	13.1 (6.4)	17.0 (6.8)	23.7 (7.3)	39.8 (15.6)	**<0.001**	a<b < c < d
HB_total[c]	3.2 (1.5)	1.2 (0.6)	2.7 (0.5)	3.8 (0.5)	4.9 (0.7)	**<0.001**	a<b < c < d
HB_apnea[c]	1.9 (1.8)	0.2 (0.4)	0.9 (0.8)	2.3 (1.2)	4.1 (1.3)	**<0.001**	a<b < c < d
HB_hypopnea[c]	2.7 (1.2)	1.1 (0.6)	2.5 (0.5)	3.3 (0.5)	3.8 (0.8)	**<0.001**	a<b < c < d

Data are presented as mean (standard deviation) or percentages.
BMI, body mass index; PSQI, Pittsburg sleep quality index; ISI, insomnia severity index; ESS, Epworth sleepiness scale; BDI, Beck depression inventory; TST, total sleep time; AHI, apnea-hypopnea index; ODI, oxygen desaturation index.
[a] Each p-value was computed by analysis of variance (ANOVA) for continuous variables and chi-square tests for categorical variables. Bold values indicate the statistical significance after Bonferroni correction for multiple comparisons.
[b] Post-hoc tests were performed using Bonferroni adjustment.
[c] Values are presented in logarithmic form.

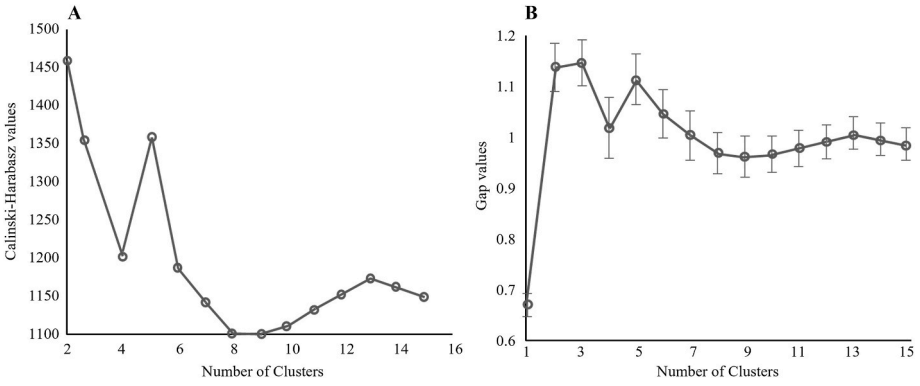

Fig. 1. Optimal cluster determination using Calinski-Harabasz (CH) and gap criteria. A. The CH values for different numbers of clusters, where higher values indicate better-defined clusters. The highest values were observed for two clusters, three and five clusters. B. The Gap values for varying cluster numbers. The highest Gap values were found for two, three and five clusters. We determined the ideal number of clusters among these candidates considering their clinical relevance and the relationship with clinical outcome.

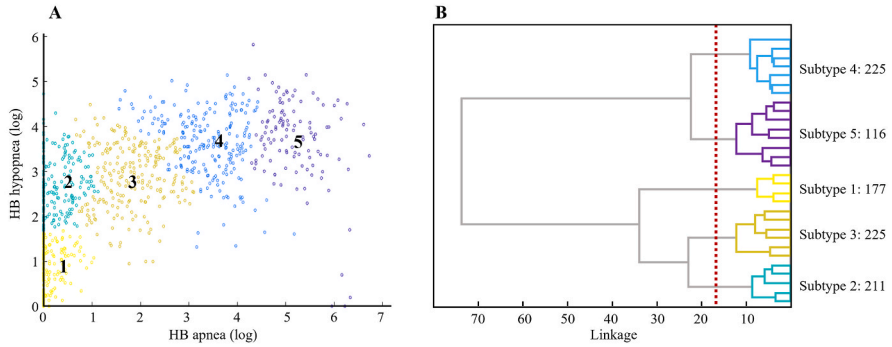

Fig. 2. Distribution of data based on hypoxic burden subtypes. A. Scatter plot depicting the segmentation of five distinct subtypes based on the log-transformed values of apneic HB and hypopneic HB. B. Dendrogram illustrating the hierarchical clustering of individuals into five subtypes: Subtype 1 (177 individuals), Subtype 2 (211 individuals), Subtype 3 (225 individuals), Subtype 4 (225 individuals), and Subtype 5 (116 individuals). The red dashed line marks the linkage cut-off used to define the subtypes. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

three clusters (1.15 ± 0.05) as the primary consideration, followed by two clusters (1.14 ± 0.05), and then five clusters (1.11 ± 0.06) with only minimal differences. The overlapping standard errors among these Gap values indicate that the differences between two, three, and five clusters are not statistically significant. Consequently, we considered two, three, and five clusters as potential candidates for our analysis.

Secondly, selecting two clusters would impose limitations on interpreting subtypes across the diverse severity levels and clinical outcome of OSA. Opting for three clusters, on the other hand, would result in subtypes 4 and 5 being grouped together, as shown in Fig. 2B. However, as shown in Fig. 3A and B, subtype 5 exhibits hypopneic HB levels similar to subtype 4, yet it presents significantly higher apneic HB along with a sharp increase in BAI. Plus, subtype 4 and 5 displayed a significant difference in BAI as a brain health outcome measure. Dividing the data into three clusters would obscure these critical distinctions, making it difficult to identify and interpret the nuanced differences between these subtypes.

Taking these considerations into account, and as shown in Fig. 2A, we identified five distinct subtypes based on the logarithmic scale of apneic and hypopneic HB. The distribution of subjects across these subtypes is illustrated by the dendrogram in Fig. 2B: subtype 1 included 177 individuals, subtype 2 included 211 individuals, subtype 3 included 225 individuals, subtype 4 also included 225 individuals, and subtype 5 included 116 individuals.

3.3. Identification of subtypes

The characteristics of each subtype are outlined below and presented in Table 2.

Subtype 1 (n = 177, namely 'good sleepers') exhibited the lowest values in total HB (1.9 ± 1.3), apneic HB (0.2 ± 0.4), and hypopneic HB (1.6 ± 1.2). Demographically, this subtype was the youngest, averaging 40.2 ± 14.9 years, with a slight female predominance (56.5 %). Furthermore, subtype 1 had the lowest arousal index, AHI, apnea index, and hypopnea index compared to the other subtypes. Notably, 79.4 % of the Normal group (AHI<5) were represented in this subtype.

Subtype 2 (n = 211, namely 'light hypopneic HB group') exhibited the second-lowest values of total HB (17.2 ± 13.3) and AHI (10.7 ± 6.5) following subtype 1. Its hypopneic HB (16.8 ± 13.3) was similar to that of subtype 3, but its apneic HB (0.4 ± 0.5) remained minimal and not significantly different from subtype 1. In terms of AHI classification, the majority (56.1 %) were categorized as mild OSA, with some also falling into the normal (15.1 %) and moderate OSA (16.9 %) categories. This subtype was older, averaging 47.2 ± 13.9 years, and had a male predominance (72.5 %).

Subtype 3 (n = 225, namely 'mild HB group') exhibited higher values for both apneic (6.2 ± 4.5) and hypopneic HB (21.2 ± 14.3) compared to subtype 1, but these values were lower than those of subtypes 4 and 5. The majority of this subtype were classified as either mild (40.5 %) or moderate OSA (41.8 %). Demographically, this subtype was similar to subtype 2.

Subtype 4 (n = 225, namely 'moderate HB group') exhibited higher

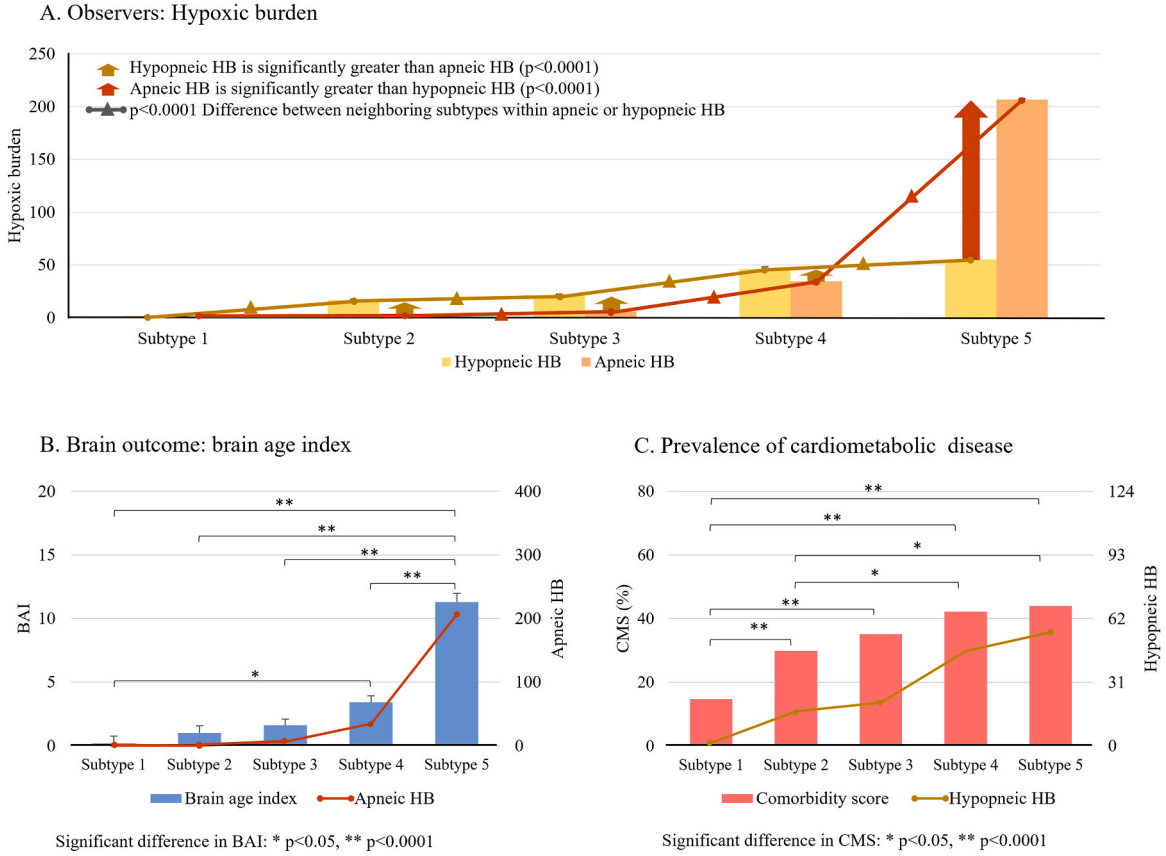

Fig. 3. Characteristics of apneic and hypopneic HB, BAI, and prevalence of CMS across the five subtypes. A. The clustering observers, hypopneic HB (yellow line) and apneic HB (orange line), showed a continuous increase across subtypes, except for apneic HB between subtype 1 and subtype 2. Additionally, in subtypes 2, 3, and 4, hypopneic HB (yellow bar) was greater (yellow arrow) than apneic HB (orange bar), whereas in subtype 5, apneic HB was greater (orange arrow). B. The pattern of increases in BAI (blue bar) from subtype 1 to 5 is similar with that of apneic HB (orange line), suggesting the close relationship between BAI and Apneic HB. C. The pattern of increases in the prevalence of CMS (coral bar) is similar with that of hypopneic HB (yellow line) across subtypes. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Table 2
Characteristics and distribution of the identified subtype.

	Subtype 1 (n = 177):'normal'	Subtype 2 (n = 211): 'light hypopneic HB'	Subtype 3 (n = 225): 'mild HB'	Subtype 4 (n = 225): 'moderate HB'	Subtype 5 (n = 116): 'severe HB with marked apneic HB'	p-value[a]	post-hoc[b]
HB_total	1.9 (1.3)	17.2 (13.3)	27.5 (14.7)	81.1 (34.6)	262 (136.8)	**<0.001**	#1<#2<#3<#4<#5
Input observers for clustering							
HB_apnea	0.2 (0.4)	0.4 (0.5)	6.2 (4.5)	34.5 (21.4)	206.8 (139.6)	**<0.001**	#1,#2<#3<#4<#5
HB_hypopnea	1.6 (1.2)	16.8 (13.3)	21.2 (14.3)	46.2 (30.1)	55.3 (45.2)	**<0.001**	#1<#2<#3<#4<#5
Demographic & clinical characteristics							
Age	40.2 (14.9)	47.2 (13.9)	49.9 (12.2)	51.9 (11.2)	50.1 (9.9)	**<0.001**	#1<#2<#4, #1<#3, #5
Male, %	43.5	72.5	77.8	84.0	96.6	**<0.001**	#1<#2,#3,#4<#5, #2<#4
BMI	23.0 (3.2)	25.3 (3.3)	24.6 (3.0)	25.7 (3.4)	27.5 (3.8)	**<0.001**	#1<#2,#3,#4<#5
PSQI	6.4 (2.9)	7.0 (2.8)	6.3 (2.7)	6.2 (2.6)	6.1 (2.4)	0.016	
ISI	8.0 (4.0)	8.5 (4.0)	7.6 (4.0)	8.1 (3.9)	8.0 (3.9)	0.299	
ESS	8.9 (4.8)	10.6 (4.8)	9.6 (4.7)	10.1 (4.6)	11.2 (4.6)	**<0.001**	#1,#3<#5, #1<#2
BDI	11.1 (7.8)	11.9 (8.1)	11.4 (7.8)	10.8 (6.8)	10.2 (7.2)	0.367	
TST, hours	6.5 (1.0)	6.2 (1.1)	6.4 (0.8)	6.1 (1.0)	5.8 (0.9)	**<0.001**	#1>#2,#4>#5, #3>#5
AHI	1.9 (1.4)	10.7 (6.5)	16.1 (7.8)	34.3 (13.1)	59.2 (17.4)	**<0.001**	#1<#2<#3<#4<#5
Apnea Index	0.2 (0.3)	0.3 (0.3)	2.8 (2.3)	10.7 (7.6)	38.4 (18.3)	**<0.001**	#1,#2<#3<#4<#5
Hypopnea Index	1.7 (1.3)	10.4 (6.5)	13.2 (7.5)	23.6 (12.6)	20.8 (13.6)	**<0.001**	#1<#2<#3<#4<#5
ODI	1.2 (1.9)	7.5 (6.0)	11.1 (6.9)	26.5 (13.3)	51.5 (21.6)	**<0.001**	#1<#2<#3<#4<#5
Arousal Index	13.3 (6.6)	18.5 (8.3)	20.1 (8.1)	28.7 (10.7)	47.5 (16.7)	**<0.001**	#1<#2<#3<#4<#5

Data are presented as mean (standard deviation) or percentages.
BMI, body mass index; PSQI, Pittsburg sleep quality index; ISI, insomnia severity index; ESS, Epworth sleepiness scale; BDI, Beck depression inventory; TST, total sleep time; AHI, apnea-hypopnea index; ODI, oxygen desaturation index.
[a] Each p-value was computed by ANOVA for continuous variables and chi-square tests for categorical variables. Bold values indicate the statistical significance after Bonferroni correction for multiple comparisons.
[b] Post-hoc tests were performed using Bonferroni adjustment.

values for apneic (34.5 ± 21.4) and hypopneic HB (46.2 ± 30.1) compared to subtype 3, but these values were lower than those of subtype 5. In terms of AHI classification, this group consisted of a mix of moderate (39.4 %) and severe (49.2 %) OSA patients. Like subtypes 2 and 3, the hypopneic HB was larger than the apneic HB. This subtype was older (51.9 ± 11.2 years) than subtypes 1 and 2 and had a higher male proportion than subtypes 1–3.

Subtype 5 (n = 116, namely 'severe HB with marked apneic HB group') exhibited the highest total HB at 262 ± 136.8. The apneic HB, at 206.8 ± 139.6, was predominant in this group. The hypopneic HB, at 55.3 ± 45.2, was slightly higher than that of subtype 4, but the apneic HB was considerably greater than in other subtypes. Demographically, the age (50.1 ± 9.9 years) was similar to subtypes 2–4, but there was a more pronounced male predominance (96.6 %), and this subtype had the highest BMI (27.5 ± 3.8).

3.4. Subtypes comparison with clinical features, CMS, and brain health outcome

As described in section 3.3, the apneic HB and hypopneic HB exhibited a significant increase across all subtypes, except for the apneic HB between subtype 1 and 2. The trend in changes among subtypes showed that while the hypopneic HB was predominant in subtypes of 2, 3, and 4, apneic HB was predominant only in subtype 5 (Fig. 3A).

As depicted in Fig. 3B, the BAI did not show any significant increase from subtype 1 to 3, while a dramatic mean increase of 7.9 years was observed at subtype 5 compared to subtype 4 (blue bars). This pattern aligned with the pattern observed in the apneic HB, which showed a relatively gradual increase from subtype 1 to 4, followed by a sudden increase at subtype 5 (orange line).

Conversely, according to Fig. 3C, the prevalence of CMS showed the greatest increase of 0.15 between subtypes 1 and 2, with no significant change observed between subtypes 2 and 3, and then a gradual increase thereafter (red bars). This trend is similar to the pattern of the hypopneic HB (yellow line) and total HB, which was predominant in subtype 2 with an increase from subtype 1, a relatively small increase between subtypes 2 and 3, and then a consistent increase starting from subtype 3 onwards. The similar pattern of increase is also observed in terms of the prevalence of hypertension across subtypes (Supplementary Fig. 2).

We observed a significantly higher ESS in subtype 2 compared to subtype 1. Furthermore, subtype 5 displayed a higher ESS than subtype 1 and 3 (Table 2). No differences in ISI, PSQI, and BDI were found among HB-subtypes.

3.5. Subtype comparison within the AHI-based OSA severity groups

We examined the distribution and proportion of HB-subtypes across different AHI-based OSA severity groups and analyzed how outcomes differed according to these HB-subtypes within each severity group, as illustrated in Fig. 4. Taking into account cases exceeding 5 %, we observed the widespread distributions of OSA severity groups across different HB-subtypes (Fig. 4A): the "normal" group, which was distributed across HB-subtypes 1 (79.4 %), 2 (15.1 %), and 3 (5.5 %). The "mild" group, with a 96.6 % presence in subtypes 2 (56.1 %) and 3 (40.5 %). The "moderate" group, with a 98 % presence in subtypes 2 (16.9 %), 3 (41.8 %), and 4 (39.4 %). The "severe" group, occupying 98.8 % of subtype 3 (5.2 %), 4 (49.2 %), and 5 (44.2 %).

Notably, no significant differences were observed in the brain health outcome variable, BAI, across HB-subtypes 1, 2, and 3 within the normal group. However, CMS variables, such as the prevalence of CMS and hypertension, were higher in subtype 3 than subtype 2 within the normal group (Fig. 4B-①). BAI was higher in subtype 3 than subtype 2 within the moderate group (Fig. 4B-②). BAI was higher in subtype 5 than subtype 4 within the severe group (Fig. 4B-③). Different from the significant differences in ESS among HB-subtypes, no differences were found among OSA-severity groups.

3.6. CPAP treatment outcomes in subgroups

We compared annual ΔBAI, ΔESS, ΔISI, ΔPSQI, and ΔBDI across

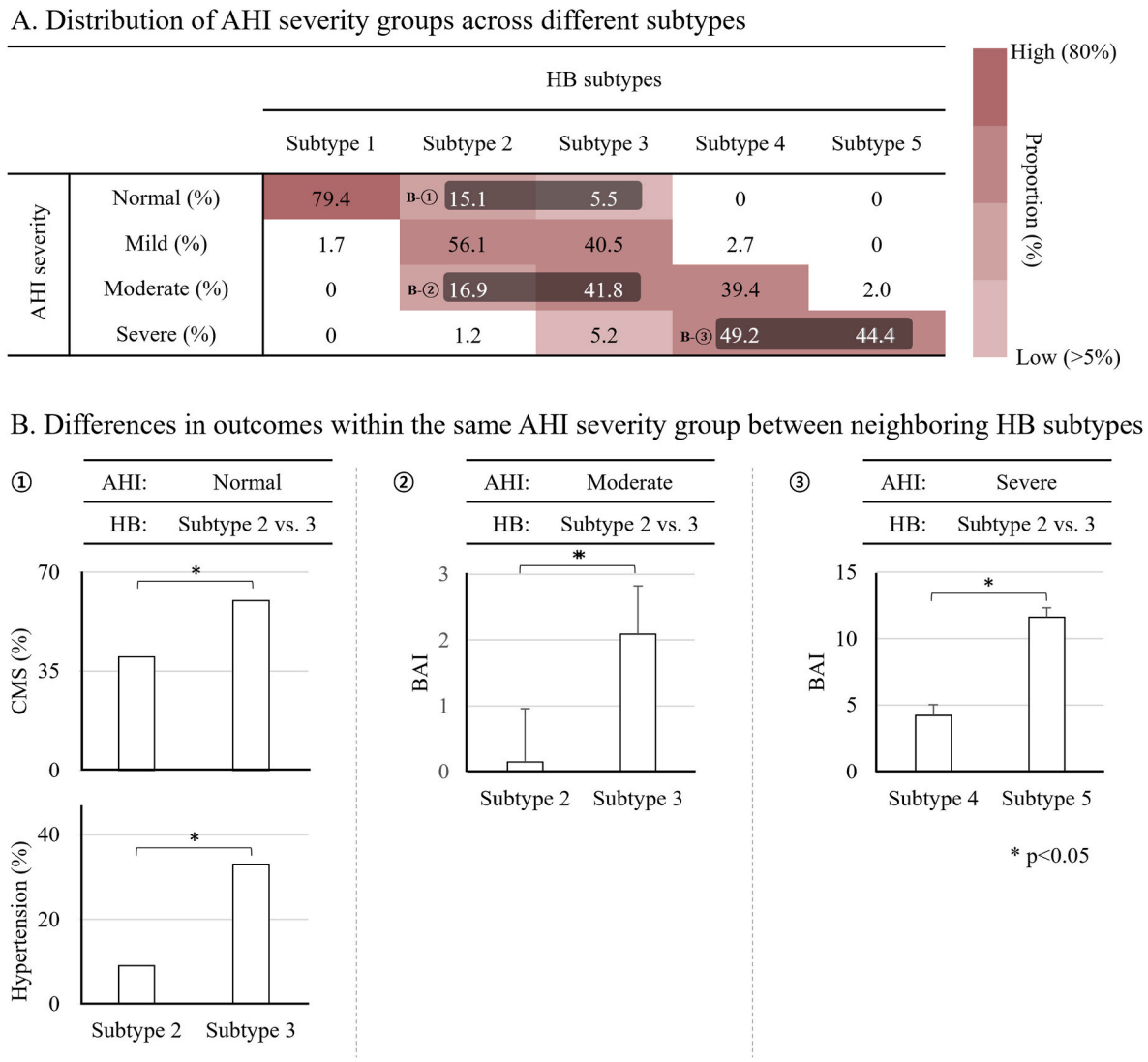

Fig. 4. Comparative analysis of AHI severity group distribution across HB subtypes and significant differences in outcomes among adjacent HB subtypes within the same AHI severity groups. **A.** Distribution of AHI-based OSA severity groups across different HB subtypes, with proportions exceeding 5 % color-scaled in red. B-①, B-②, and B-③ indicate instances where significant differences in outcome variables are observed between adjacent HB subtypes within the same AHI severity group, as detailed in panel B. **B.** Detailed comparisons of outcome variables between adjacent HB subtypes within the same AHI severity group: ① Within the normal AHI severity group, the prevalence of cardiometabolic syndrome (CMS) and hypertension was higher in subtype 3 compared to subtype 2. ② Within the moderate AHI severity group, the brain age index (BAI) was higher in subtype 3 than in subtype 2. ③ Within the severe AHI severity group, the BAI was higher in subtype 5 compared to subtype 4. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

different AHI-based OSA severity groups and subtypes, as well as different subtypes within specific AHI-based OSA severity groups to pinpoint CPAP treatment benefit subgroups.

The severe OSA group exhibited a trend of decrease in BAI, with an annual ΔBAI of −0.69, lower than that of the moderate group (Fig. 5A, $p = 0.13$, $T = 1.5$). When examining subtypes, subtype 5 had an annual ΔBAI of −0.84, significantly lower than that of subtype 4 (Fig. 5B, $p = 0.01$, $T = 2.6$). There were no differences in ΔESS, ΔISI, ΔPSQI, and ΔBDI among HB-subtypes ($p > 0.1$).

4. Discussion

This study presents a new method of subtyping OSA by incorporating a novel measure of HB. We refined the HB metric by separating it into apnea- and hypopnea-specific components, enabling a more comprehensive assessment of the characteristics and severity of hypoxic events in OSA. Using these decomposed metrics, we identified five distinct OSA subtypes, moving beyond traditional severity classifications based solely on the AHI. Furthermore, we discovered associations between these subtypes and a broad spectrum of OSA-related health issues, including CMS and accelerated brain aging. Notably, we observed significant increases in CMS and hypertension prevalence beginning in the 'light hypopneic HB group' (subtype 2) and continuing through the more severe HB subtypes. Meanwhile, increases in the BAI were observed in the 'moderate HB group' (subtype 4) and the 'severe HB with marked apneic HB group' (subtype 5), underscoring a strong relationship between elevated apneic HB and brain aging.

4.1. OSA subtype based on HB

Our study identified five distinct OSA subtypes based on the apneic and hypopneic HB; 1) 'good sleepers' with minimal HB, 2) 'light hypopneic HB group' with mildly increased hypopneic HB, 3) 'mild HB group' with mildly increased hypopneic and apneic HB, 4) 'moderate HB group' with moderately increased hypopneic and apneic HB, 5) 'severe HB with marked apneic HB group'. There are two major differences

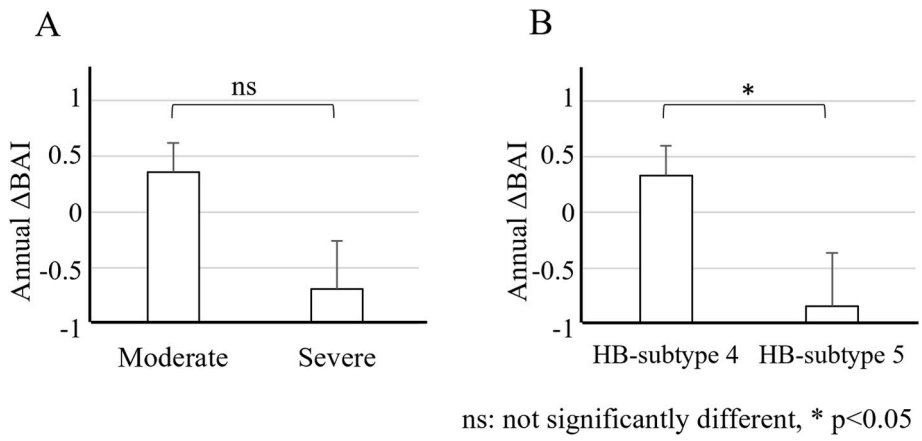

Fig. 5. Annual ΔBAI comparison as an indicator of the benefit of CPAP treatment on brain health. **A**. Among different AHI severity groups, the severe group exhibited a trend of lower annual ΔBAI compared to the moderate group. **B**. When categorized by HB-subtypes, subtype 5 had a significantly lower annual ΔBAI than subtype 4. (ns: not significantly different, *: $p < 0.05$).

between this classification and traditional categorization based on AHI. First, a proportion of patients with classical normal and mild OSA were classified into HB-subtype 2 - 'light hypopneic HB group'. Second, within classical severe OSA, there was a group of hyper-severe patients with severe HB with apnea predominance, which displayed the worst prevalence of CMS and brain health outcome. We also observed that varying severities (based on AHI) coexist within each subtype (especially for subtypes 2, 3, and 4), and patients with the same categories of AHI are widely distributed in five subtypes (Fig. 4). Consequently, this novel classification exhibited a distribution markedly distinct from the classic AHI-based categorization. This might stem from the fact that, while AHI only reflects the frequency of respiratory events, HB reflects both duration and depth of respiratory events. Notably, even among individuals within the same AHI-defined OSA severity category, distinct HB-based subtypes displayed different health outcomes. This finding underscores the potential utility of HB-based subtyping for more personalized OSA diagnosis and treatment.

Furthermore, we observed that there were no significant differences in daytime sleepiness, as measured by ESS, among different OSA severity groups classified using AHI. In contrast, HB-based subtyping revealed differences among various subtypes. In particular, we observed a higher ESS in subtype 2 - light hypopneic HB group compared to subtype 1 - good sleepers, indicating a more sensitive discrimination for the daytime sleepiness. This suggests that our novel HB-based subtyping, which incorporates both the duration and depth of nocturnal hypoxemia, provides a more nuanced assessment of OSA severity. It acknowledges the complex dimensions of sleep-disordered breathing that the AHI alone overlooks, aligning with existing research linking hypoxemia to daytime sleepiness [32,33].

Additionally, our clustering approach aligns with broader research that employs advanced computational methods to assess pathophysiology and its impact on health outcomes across various clinical domains. Prior studies have demonstrated that structural and biomechanical analysis techniques can elucidate complex interactions and support clinical stratification [34–44]. In optimizing our data processing methods, we aimed to follow best practices as outlined in prior research on data processing optimization [45].

4.2. Association between new OSA subtype based on HB and clinical outcomes

In this study, the novel classification of OSA based on decomposed HB revealed significant differences in clinical outcomes among the subtypes. One of the most crucial findings is that subtype 2, the 'light hypopneic HB group', exhibited significant increases in the prevalence of CMS and hypertension. This suggests that even mild degrees of desaturation events caused by hypopnea can have an impact on cardiovascular disorders such as hypertension. It is noteworthy that the majority of individuals in HB-subtype 2 fell into the category of mild OSA ($5 \leq AHI < 15$). Nevertheless, this group displayed significantly high prevalence of CMS compared to subtype 1. In contrast, most OSA studies investigating cardiovascular comorbidities and treatment effects have mainly focused on moderate to severe OSA cases ($AHI \geq 15$) [9,10,46–48]. As a result, in many countries including South Korea, CPAP treatment has been still reserved for patients with $AH \geq 15$, potentially overlooking the positive effects in mild OSA cases but with relatively high HB. Indeed, there has been a report that CPAP can benefit individuals with mild OSA who still demonstrate subjective sleepiness [49]. Our findings further suggest a need for caution regarding the risk of cardiovascular disease in individuals with mild OSA and even those categorized as 'borderline OSA' (AHI <15 with increased HB). This study highlights the importance of HB as a valuable tool for risk stratification.

Hypopneic HB consistently and linearly increased from subtype 1 to 5 while apneic HB was only seen notably high in subtype 4 and 5. We observed consistent and linear increases in the prevalence of CMS and hypertension across all HB subtypes (subtypes 2–5) and significant high BAIs were observed in subtype 4 and 5. The brain health outcome metric, BAI, showed significant increases from subtypes 4 to 5, where a great increase of apneic HB is observed. Linear regression analysis also demonstrated a stronger correlation of BAI with apneic HB than with hypopneic HB (See Supplementary Table 2). The significant differences in BAI between subtypes 4 (moderate HB) and 5 (severe HB) can be attributed to the distinct pathophysiological impacts of apneic versus hypopneic HB. Apneic HB, characterized by complete airway obstructions, results in more profound and prolonged episodes of hypoxia compared to hypopneic HB, which involves partial obstructions. These severe hypoxic events trigger a cascade of detrimental biological processes that contribute to accelerated brain aging. Specifically, severe apneic events lead to intermittent hypoxia, which significantly increases the production of reactive oxygen species (ROS). Elevated ROS levels induce oxidative stress, damaging neuronal cells and disrupting cellular homeostasis. This oxidative damage is a well-established contributor to neurodegenerative processes and cognitive decline [50].

Moreover, prolonged hypoxia resulting from apneic HB activates microglia, the brain's resident immune cells. Chronic activation of microglia leads to sustained neuroinflammation, which has been implicated in the pathogenesis of various neurodegenerative diseases, including Alzheimer's disease and vascular dementia [51]. This persistent inflammatory response exacerbates neuronal damage and

accelerates brain aging, as reflected by the increased BAI observed in subtype 5. Additionally, severe hypoxic episodes affect cerebral vasculature by promoting endothelial dysfunction and altering cerebral blood flow dynamics. These vascular changes result in reduced cerebral perfusion and increased blood-brain barrier permeability, further contributing to neuronal injury and accelerated brain aging [52]. Impaired cerebral blood flow compromises the brain's ability to maintain metabolic homeostasis, leading to accelerated neuronal aging and increased BA [53].

While hypopneic HB contributes to intermittent hypoxia, the cumulative effect of frequent and severe apneic events imposes a greater burden on brain health. This is evidenced by the higher BAI in subtype 5, where apneic HB predominates. The enhanced severity of hypoxia in apneic events likely underlies the more pronounced brain aging observed, distinguishing subtype 5 from subtype 4 despite similar levels of hypopneic HB. The depth and duration of hypoxia during apneic events surpass those of hypopneic events, leading to more extensive and irreversible neuronal damage [54].

Understanding the differential impact of apneic and hypopneic HB on brain aging underscores the importance of targeted interventions. Specifically, therapies that effectively reduce apneic events may offer greater neuroprotective benefits and mitigate the risk of accelerated brain aging in OSA patients. This highlights the potential for HB-based subtyping to inform personalized treatment strategies, ensuring that patients with severe apneic HB receive more aggressive and tailored therapeutic interventions to preserve brain health [55].

Furthermore, our separate analysis, which involved longitudinal PSG during CPAP treatment, demonstrated that CPAP treatment could reverse the pathologic brain aging process associated with severe apneic events (Fig. 5). This underscores the importance of CPAP therapy, especially for patients with severe HB (i.e., subtype 5). These observations are also congruent with our prior study on the impact of CPAP on BAI, where we investigated longitudinal changes in BAI decrease for CPAP-treated and untreated male OSA patients (AHI$\geq$15). A higher apneic HB is correlated with an increased BAI over time in untreated patients and a decreased BAI after CPAP treatment, while hypopneic HB did not reveal a significant association [28].

4.3. Clinical implications

Our novel classification of OSA based on HB can not only enhance our understanding of OSA pathophysiology but also provide several new perspectives for clinical practice and future research. First, we observed that even among individuals commonly categorized as "normal" (AHI $<$5)—who are generally not considered candidates for OSA treatment—some exhibited a mild increase in HB, which was associated with different CMS outcomes. This finding suggests that evaluating HB in patients with AHI $<$5 who exhibit symptoms of OSA could help identify those who may benefit from treatment, even if they do not meet the traditional diagnostic criteria. Such subjects could also be targeted in studies evaluating the therapeutic effect of OSA treatment on health outcomes.

Second, the significant increase in BAI observed in subtypes 4 and especially subtype 5 implies that patients with high apneic HB may require closer evaluation for cognitive symptoms. This could involve more detailed clinical interviews and neuropsychological testing. Additionally, because CPAP therapy may particularly benefit patients with severe apneic HB in terms of cognitive improvement, highlighting these potential benefits might enhance treatment adherence in this subgroup.

4.4. Limitations and future directions

Several limitations of this study should be noted. First, the cross-sectional design limits our ability to infer causality between HB-based subtypes and clinical outcomes. Long-term prospective cohort studies are needed to establish these causal relationships between subtypes and various components of CMS. Additionally, applying this HB-based subtyping to previously studied OSA cohort data in western countries [23,25,27] would be useful in validating its reproducibility and investigating its association with long-term outcomes, including mortality. Second, our sampling approach, simply recruiting 250 participants across each OSA severity based on AHI, has led to selection bias particularly leaning towards middle aged males. This might not reflect the heterogeneity of OSA as affected by age and sex. Future subtyping studies encompassing women and younger populations will be helpful for more tailored approaches to management of OSA. Third, we were unable to calculate a central apneic HB because hypopneas were not classified as obstructive or central in our PSG data set. Central sleep apnea or Cheyne-Stokes respiration also were known to predict cardiovascular disorders, particularly heart failure [11], could potentially influence our findings. Although we attempted to minimize the impact of central sleep apnea by excluding subjects with a central apnea index $>$5, the residual effects of central sleep apnea/Cheyne-Stokes respiration on HB cannot be entirely ruled out. Lastly, although we performed additional subgroup analyses on patients who underwent longitudinal PSG during CPAP treatment, their numbers were limited and biased towards subtypes with moderate to severe HB (subtype 4–5). Some subtype studies revealed varying benefits from CPAP across different subtypes, emphasizing the importance of personalized approach for OSA patients. In our subtype classification, it is essential in future studies to explore whether traditional OSA treatments like CPAP could potentially reduce risk of CMS such as hypertension in each subtype, especially subtype 2.

5. Conclusion

In conclusion, our study introduced a new subtype classification for OSA using HB decomposed into those occurring in apneic and hypopneic events. Although this innovative classification solely relied on simple metrics, it revealed the limitations of traditional categorization of OSA based on AHI. Notably, this subtyping demonstrated significant associations with clinical outcomes, providing a new perspective of subtype classification and understanding the complexity of OSA. These insights could be utilized in future risk stratification and treatment outcome studies for OSA.

CRediT authorship contribution statement

Soonhyun Yook: Writing – original draft, Visualization, Validation, Software, Methodology, Formal analysis. **Hea Ree Park:** Writing – original draft, Validation, Formal analysis, Data curation. **Dongjin Seo:** Formal analysis. **Eun Yeon Joo:** Writing – review & editing, Supervision, Resources, Project administration, Funding acquisition. **Hosung Kim:** Writing – review & editing, Validation, Supervision, Funding acquisition, Conceptualization.

Ethics statements

SMC Institutional Review Board approved PSG data use for this retrospective analysis (IRB No.2023-07-007/2021-09-039). All participants provided written informed consent prior to their inclusion in the study.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.compbiomed.2024.109604.

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