Hypoxic burden of sleep apnea: measurement and associations with outcomes

Ali Azarbarzin, PhD

[1]Division of Sleep and Circadian Disorders, Brigham and Women's Hospital and Harvard Medical School, Boston, MA

Corresponding Author

Ali Azarbarzin, Sleep Apnea Health Outcomes Research Group, 221 Longwood Avenue, Boston, MA 02115, Tel: 617 732 5619, Fax: 617 732 7337, Email: aazarbarzin@bwh.harvard.edu

TABLE OF CONTENTS

ABSTRACT

Obstructive sleep apnea (OSA) is characterized by frequent partial ("hypopnea") or complete ("apnea") obstructions of the upper airway, leading to drops in oxygen saturation and/or arousal from sleep. OSA is most often quantified by the apnea-hypopnea index (AHI) which is the total number of apneas/hypopneas per hour of sleep. It is well recognized that the AHI has several limitations, and it is unable to accurately quantify the true magnitude of nightly exposure to OSA. The sleep apnea-specific hypoxic burden has been recently proposed as an alternative measure of OSA severity that better captures the total burden of OSA during sleep because it integrates the key disease characterizing features, including the frequency, depth, and duration of respiratory events. In this paper, the limitations of current OSA metrics and measurement of hypoxic burden and its association with health outcomes will be discussed.

INTRODUCTION

Obstructive sleep apnea (OSA) is a common breathing disorder associated with adverse cardiovascular outcomes and neurocognitive impairment[1, 2]. OSA is characterized by recurrent partial ("hypopnea") or complete ("apnea") pauses in breathing during sleep and its severity is most often quantified using the apnea-hypopnea index (AHI), which is defined as the number of apneas plus hypopneas per hour of sleep. By definition, AHI is a simple frequency metric that has important limitations and is unable to adequately capture the substantial heterogeneity observed in OSA populations even after controlling for factors such as age, sex, race/ethnicity, and obesity[3, 4]. For example, the associations of OSA, defined by AHI, with its primary daytime sequalae (excessive daytime sleepiness), cardiovascular (CV) outcomes, and quality of life are modest and inconsistent[5, 6]. Additionally, randomized controlled trials of CPAP efficacy have not generally been able to detect a long-term cardiovascular benefit of CPAP[7-9], potentially due to imprecise selection of individuals who will profit most from CPAP using the AHI. One important limitation of the AHI is its assumption that all respiratory events are equal. Thus, the AHI is unable to quantify the severity of respiratory events (i.e. duration and depth) and their ensuing oxygen desaturation. However, there is in reality a wide spectrum of respiratory events in terms of their duration and depth[10, 11]. Hypoxic burden of sleep apnea[12, 13], which is defined as the total area under the event-related desaturation curve per hour of sleep, is a novel metric that has shown promise in risk stratification of individuals with OSA. In this paper, measurement of hypoxic burden and its associations with health outcomes will be discussed.

The American Academy of Sleep Medicine (AASM) recommends the AHI as the standard metric for OSA diagnosis and management[14, 15]. An AHI ≥ 5 events/hour is used as a diagnostic criterion while mild, moderate, or severe OSA is defined if AHI is 5-15, 15-30, or ≥30 events/hour, respectively[14, 15]. In addition to being a simple frequency counter, AHI suffers from ever-changing definitions of an hypopnea[14, 15]. Currently, there are two commonly used criteria for AHI calculation. Based on AASM criteria, a hypopnea is included if it was associated with an arousal or ≥3% desaturation, while, according to the Centers for Medicare and Medicaid Services, CPAP is only covered when hypopneas are associated with ≥4% desaturation regardless of the presence or absence of arousals. Both the prevalence of OSA and the

magnitude of its associations with daytime sequalae and adverse health outcomes depend on which AHI definition is used.

For any given AHI, there is a wide range in the severity of hypoxemia, measured by conventional and novel metrics. A small portion of this variation is explained by the differences in anthropometric/demographic variables; however, a much larger portion of variation is explained by the severity of individual respiratory events (i.e. duration and depth). These characteristics of respiratory events are potential key contributors to the development of adverse health outcomes, daytime symptoms, and impaired quality of life[16]. For example, longer and deeper respiratory events elicited a larger acute cardiovascular response (i.e. surges in heart rate and blood pressure upon event termination) than shorter and milder events[10, 11]. Longer and deeper respiratory events also lead to longer and deeper oxygen desaturations. In a recent study of 805 individuals with mild OSA, more severe desaturation at baseline (i.e. longer/deeper desaturations) significantly predicted worsening of OSA (mild to moderate or mild to severe) at a ~5-year follow-up visit[10].

In summary, the depth and duration of OSA-related desaturation are key characterizing features of respiratory events that could be used for risk stratification of individuals with OSA. In addition, over the past several years, the use of pulse oximetry for OSA diagnosis and management has grown substantially (home sleep apnea testing and wearable devices) as the oxygen saturation signal is readily available from in-lab and in-home sleep studies. Therefore, an OSA-specific metric that quantify the frequency, depth, and duration of desaturation is of interest. The hypoxic burden is a candidate metric that was designed to capture these three important dimensions of OSA severity[12, 13].

DEFINITION OF HYPOXIC BURDEN

Hypoxic burden (HB) is the area under the oxygen desaturation curve from a pre-event baseline saturation. HB is described as total desaturation area (%minute) per hour of sleep. Using AHI instead of a quantitative metric such as HB assumes that all individuals have an identical desaturation depth and duration per event. This is, however, not the case as there is substantial variability in the duration and depth of the respiratory events and their ensuing

desaturations for any given AHI (**Figure 1**). To reliably estimate HB from overnight in-home and in-lab studies that may be prone to noise and artifact, an automated algorithm was developed. The inputs to this algorithm were scored respiratory events and the raw pulse oximetry (SpO_2) signal. To calculate HB:

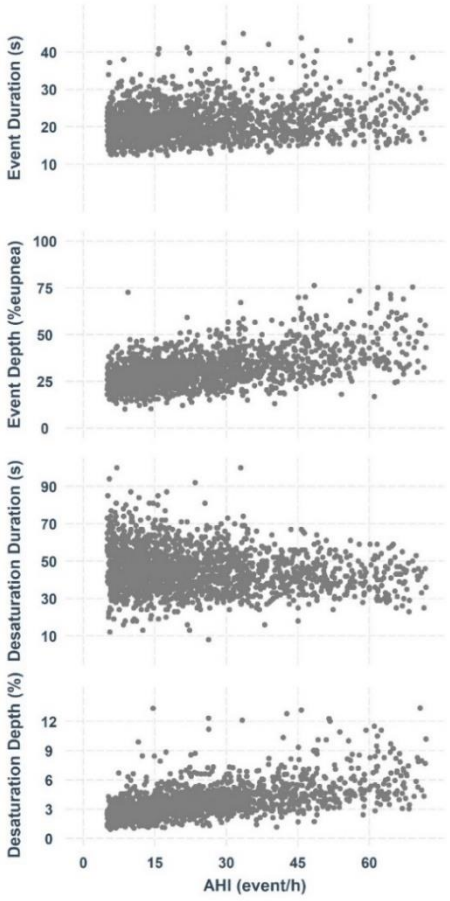

Figure 1: Quantifying sleep apnea severity by the apnea-hypopnea index (AHI) assumes that all events are equal in terms of their duration and depth. However, as shown in this figure, there is substantial variability in the duration and depth of the respiratory events and their ensuing desaturations for any given AHI.

1. The oxygen saturation signals resulting from respiratory events (**Figure 2A**) were synchronized with respect to the end of the events (**Figure 2B**).
2. These time-aligned SpO_2 episodes were then ensemble-averaged, resulting in a subject-specific average oxygen saturation curve associated with apneas and hypopneas. The interval between the pre-event and post-event maximum oxygen saturation values defines a subject-specific search window (**Figure 2B**).
3. The area under an event-related baseline saturation (maximum SpO_2 around the event) was restricted to the search window obtained for each respiratory event (**Figure 2C**). Total HB (%minute/hour) was defined as the sum of individual areas (%minute) divided by total sleep time (hours).

HB can be conceptually estimated from average desaturation area per event (**Figure 2D**). For example, assume a subject has 20 events/hour and each event, on average, has a triangular-shaped desaturation area with an 8% height (desaturation depth, **Figure 2D**) and a 0.5-minute base (desaturation duration, **Figure 2D**). For this case, the desaturation area for each event is 2 %minute (area of the desaturation triangle= ½ × 0.5 minute × 8%). The total HB will be 40 %minute/hour (20 event/hour × 2 %minute/event).

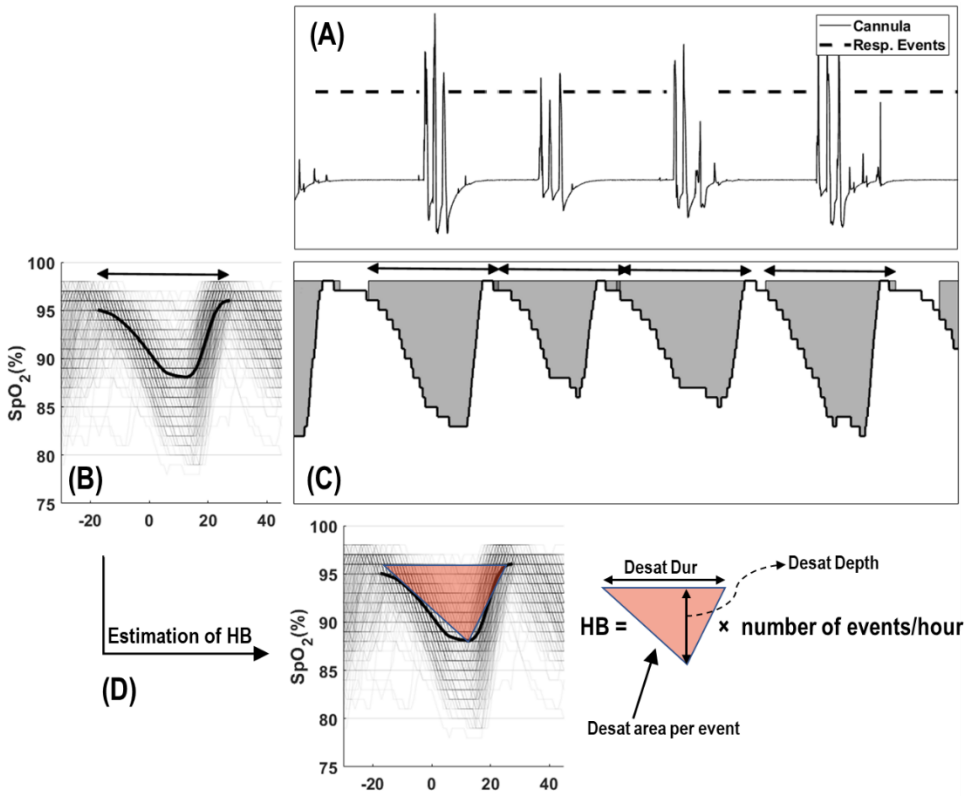

Figure 2: Calculation of hypoxic burden (HB) is based on scored respiratory events **(A)** and a subject-specific search window (B). The search window is obtained by aligning local SpO_2 curves with respect to the end of scored respiratory events. All aligned event-related curves are then ensemble averaged **(B)**. The interval between the pre-event and post-event maxima (solid black line on the bottom-left panel) is the search window used to define the boundaries for area calculation **(C)**. The summation of all individual areas divided by total sleep time is the total hypoxic burden. Conceptually, hypoxic burden can be estimated from the average desaturation area (copper triangle) per event times the number of events per hour **(D)**. The average desaturation area per event is a function of desaturation duration ("Desat Dur") and desaturation depth ("Desat Depth").

ASSOCIATIONS OF HYPOXIC BURDEN WITH HEALTH OUTCOMES

Past studies have shown a strong association of hypoxic burden with several cardiometabolic outcomes in both cross-sectional and longitudinal studies (**Table 1**).

Cardiovascular Morbidity and Mortality: In the first study, the relationship between hypoxic burden and cardiovascular mortality was examined in two large community-based cohort studies, including the Osteoporotic Fractures in Men Study (MrOS; age:76.3±5.5 years; male only) and the Sleep Heart Health Study (SHHS; age 63.7±10.9 years; 52.8% female). In an overall sample consisting of more than 7500 middle-aged or older adults, hypoxic burden predicted cardiovascular-related mortality after adjusting for multiple covariates and confounders[12]. In the fully-adjusted model when compared with individuals in the lowest quintile those in the highest quintile had a cardiovascular mortality hazard ratio of 1.96 (95% CI: 1.11-3.43) and 2.73 (95% CI:1.71-4.36) in SHHS and MrOS, respectively. In contrast, in the same model, the AHI did not predict these outcomes. In secondary analyses, to compare the effect of deep versus shallow desaturations on CVD mortality, a higher weight was assigned to deeper desaturations (using a square power transformation) and the area was recalculated. While, this additional analysis did not seem to meaningfully change our main findings[12], the impact of short/deep desaturations versus long/shallow ones should be evaluated in future studies.

Heart failure (HF): Similar to cardiovascular mortality, HB was strongly associated with incident HF in middle-aged or older men. Data from the SHHS (4,881 adults; 45.6% male; follow-up of 10.4 ± 3.4 years; 543 incident HF events) and MrOS (2653 men; follow-up of 8.8 ± 2.8 years; 145 incident HF events) studies were used to test the association of HB with incident HF[13]. HB predicted incident HF in men in both SHHS [HR, 1.18 (95% CI, 1.02-1.37)] and MrOS [HR, 1.22 (95% CI, 1.02-1.45)] cohorts, while the AHI did not[13]. In secondary analyses, excluding individuals with central sleep apnea or those with coronary heart disease at baseline did not meaningfully alter these findings[13]. It is worth noting that the association of HB (and AHI) with incident HF was null in women in the SHHS study. A potential explanation may be lack of adequate statistical power due to the small number of women with severe OSA and/or short follow-up period. To examine whether the association of HB with incident HF differed by the AHI level, in a subgroup analysis, men from both cohorts were divided into low AHI/low HB, low AHI/high HB, high AHI/low HB, and high AHI/high HB. Compared to the low AHI/low HB subgroup, the risk of incident HF was significantly higher in individuals with high HB regardless

of the AHI level (i.e. low AHI/high HB and high AHI/high HB), while those in the high AHI/low HB subgroup had a non-significant decreased risk of HF (adjusted HR 0.84 [95% CI, 0.47-1.51)[13].

Stroke: The association of HB and incident stroke was examined in a longitudinal clinical cohort (*Pays de la Loire Sleep Cohort*), linked to the French health administrative data (N=3597; follow-up of 5.9[3.5-8.4] years; 83 incident cerebrovascular events). In the fully-adjusted model, HB predicted incident stroke while AHI did not[17]. The association appeared to be stronger in the non-obese subgroup. A major limitation of this study was the small number of incident events and therefore, the findings need to be replicated in larger samples.

Major adverse cardiovascular events (MACE): In a recent article, Trzepizur et al. examined the association of HB and major adverse cardiovascular events in the *Pays de la Loire* longitudinal clinical cohort study, including 5,358 individuals with OSA and without preexisting cardiovascular disease. Over a median follow up of 78 months, 592 cardiovascular events were observed. In the fully-adjusted model, HB predicted the incidence of MACE (adjusted HR: 1.21 [95% CI, 1.07-1.38]) while AHI did not[18]. Important limitations of this study include lack of information on potential confounding variables and linkage with health administrative data.

Blood pressure and chronic kidney disease: OSA is strongly associated with prevalent and incident hypertension[1]. The association appears to be stronger in poorly controlled, drug resistant hypertension[19, 20]. Intermittent hypoxia has been implicated as an important mechanism linking OSA to hypertension[21]. Cross-sectional analyses using data from the Multi-Ethnic Study of Atherosclerosis (MESA) cohort study revealed a significant association of hypoxic burden with increased diastolic blood pressure in the fully-adjusted model[22]. In individuals who were not on hypertension medications, one standard deviation increase in HB was associated with a .1% increase in SBP (95% CI: 0.1% to 2.1%) and 1.9% increase in DBP (95% CI: 1.0% to 2.8%). Data from the same MESA cohort study also demonstrated a significant association between HB and increased prevalence of moderate to severe chronic kidney disease[23]. Compared to the first quintile of the HB, the adjusted prevalence of moderate to severe chronic kidney disease was 36% higher in fifth quintile[23].

Table 1: Studies that examined the relationship between hypoxic burden and health outcomes

Author (year)	Cohort	Age Sex Follow-up	Outcomes	Findings
Azarbarzin et al (2019)[12]	MrOS (n=2,743) Population-based	76.5 (5.5). 100% men 10.0 years	CVD mortality (n=440) All-cause mortality (n=1270)	HR: 1.81 [95% CI, 1.25-2.62] [HB: 53-88 %min/h] vs. [HB<20%min/h] HR: 2.73 [95% CI, 1.71-4.36] [HB>88 %min/h] vs. [HB<20%min/h]
Azarbarzin et al (2019)[12]	SHHS (n=5,111) Population-based	63.7 (10.9). 47.2% men 10.9 years	CVD mortality (n=313) All-cause mortality (n=1142)	HR: 1.61 [95% CI, 1.00-2.61] [HB: 43-71 %min/h] vs. [HB<16%min/h] HR: 1.96 [95% CI, 1.11-3.43] [HB>71 %min/h] vs. [HB<16%min/h]
Blanchard et al (2020)[17]	Pays de la Loire Sleep Cohort (n=3,597) Clinical-based	58 [48-67]. 63% men 5.9 years	First incident stroke (n=83; 70 ischemic including TIA)	HR: 1.28 [95% CI, 1.05-1.57] per 1 point increase in natural log-transformed HB
Azarbarzin et al (2020)[13]	SHHS (n=4,881) Population-based	63.6 (11.1) 45.6% men 10.4 years	Incident heart failure (n=543)	HR [overall]: 1.05 [95% CI, 0.95-1.17] HR [men only]: 1.18 [95% CI, 1.02-1.37] per 1SD increase in HB
Azarbarzin et al (2020)[13]	MrOS (n=2,653) Population-based	76.2 (5.4) 100% men 8.8 years	Incident heart failure (n=145)	HR: 1.22 [95% CI, 1.02-1.45] per 1SD increase in HB
Kim et al (2020)[22]	MESA (n=2,055) Population-based	68.4 (9.1) 46% men Cross-sectional	%change in SBP and DBP	SBP: 0.5 (-0.3 to 1.3); p=0.21 DBP: 1.1 (0.4-1.8); p=0.002 per 1SD increase in HB
Jackson et al (2021)[23]	MESA (n=1,895) Population-based	68.2 (9.1) 46% men Cross-sectional	Prevalent moderate-to-severe CKD	Prevalence rate of CKD: 1.36 [95% CI, 1.00-1.18] [HB>84.4 %min/h] vs. [HB<16.24 %min/h]
Trzepizur et al (2021)[18]	Pays de la Loire Sleep Cohort (n=5,358) Clinical-based	60 [51-69] 63.7% men 6.5 years	MACE (n=592)	HR: 1.21 [95%CI, 1.07-1.38] per 1 point increase in natural log-transformed HB

MrOS, the Osteoporotic Fractures in Men Study; CVD, cardiovascular disease; HR, hazard ratio; HB, hypoxic burden; SHHS, the Sleep Heart Health Study; SD, standard deviation; SBP, systolic blood pressure; DBP, diastolic blood pressure; MESA, the Multi-Ethnic Study of Atherosclerosis; CKD, chronic kidney disease; MACE, Major adverse cardiovascular events. Table adapted from *Nat Rev Cardiol*. 2023

HYPOXIC BURDEN VERSUS CONVENTIONAL METRICS OF HYPOXEMIA IN OSA

Conventional metrics of hypoxemia that are often reported on sleep studies include the oxygen desaturation index (ODI), percent sleep time with SpO_2 below 90% (T90), and nadir SpO_2. These metrics share similar limitations to those of AHI. For example, ODI only measures the frequency of transient desaturation that exceed a threshold of 3% or 4%. However, the information on the desaturation severity (depth/duration) is lost beyond these arbitrary thresholds. T90 is the percent sleep time with SpO_2 below 90%. A major limitation of T90 is its dependence on the baseline SpO_2 level that may be influenced by non-OSA-related factors, including hypoventilation, lung diseases, and noise/artifacts. Inaccurate estimation of arterial oxygen saturation by pulse oximetry tends to influence T90 substantially more than hypoxic burden. For example, if baseline oxygen saturation is near 90%, a 2%-error in pulse oximetry reading could alter the value of T90 from 0 to 100% in either direction. However, this is less of an issue for the hypoxic burden as the change from a pre-event baseline is measured in the hypoxic burden calculation. Finally, minimum SpO_2 during sleep has been considered a measure of hypoxemia severity in OSA. However, in addition to having limitations similar to T90, this metric is only a single value that fails to capture the overall OSA-related drops in SpO_2. Assuming that artifacts and baseline drifts are not an issue, two individuals with a very different OSA severity could have similar minimum SpO_2 values.

HYPOXIC BURDEN THRESHOLD FOR INCREASED RISK OF CVD

Hypoxic burden ranges from 0 to >1000 %minute/hour in very severe forms of OSA. The threshold above which the hypoxic burden is “abnormal” remains incompletely understood. Further studies are needed to identify a threshold for HB above which a treatment should be prescribed to control daytime symptoms and reduce intermediate and long-term risk of adverse cardiovascular and neurocognitive outcomes. Based on past observational and clinical-based studies, an hypoxic burden of 50-75 %minute/hour appeared to be associated with increased risk of major adverse cardiovascular outcomes (**Table 1**). Additionally, a hypoxic burden of >60 %minute/hour identified individuals who had treatment-related improvement in Epworth Sleepiness Scale[24]. Furthermore, although some small experimental studies argue for a

therapeutic benefit (i.e. lowing blood pressure) with the treatment of mild intermittent hypoxia[25], larger studies are needed to confirm these findings and identify the dosage of intermittent hypoxemia indicating possible beneficial effects[26]. Therefore, the diagnostic and risk stratification threshold for the HB in the context of OSA warrants further investigation in larger studies.

HYPOXIC BURDEN MEASUREMENT FROM IN-LAB AND IN-HOME POLYSOMNOGRAMS

While it is challenging for most clinicians and investigators to calculate the hypoxic burden, manufacturers of sleep apnea test devices have started to integrate hypoxic burden values into their reporting systems (Sleepware G3). In addition, an online web application (https://hypoxicburden.thesiestagroup.com/) has recently been created that allows the users to upload their raw EDF files to obtain the hypoxic burden values. Currently, this system automatically scores the sleep stages[27] and respiratory events[28] using the Somnolyzer Scoring system[27, 28]. Therefore, there may be some differences resulting from the automatic scoring of the respiratory events and sleep time.

CONCLUSIONS AND FUTURE DIRECTIONS

Conventional measures of OSA severity have several limitations that have partly contributed to inconsistent associations of OSA, as quantified by the AHI, with adverse health outcomes. By oversimplifying the severity of individual apneas and hypopneas into their overall count per hour of sleep, these metrics are unable to precisely quantify the magnitude of exposure to OSA and its downstream physiological consequences. By integrating all three dimensions of OSA-related nightly hypoxia exposure (frequency, depth, and duration), hypoxic burden has shown promise to better identify individuals with OSA who were at increased risk of cardiovascular morbidity and mortality. In addition, hypoxic burden is a more appropriate metric to evaluate the true effect of a treatment because all three dimensions can be evaluated simultaneously. For example, a treatment could be appealing (and may improve symptoms and health outcomes) if it makes the individual respiratory events less severe (e.g. by converting apneas to hypopneas with less severe desaturation) but does not reduce the overall AHI at all.

Therefore, hypoxic burden should be considered as an alternative metric to inform clinical therapeutic decisions in OSA patients.

While HB can now be added as an alternative measure of OSA severity and treatment effectiveness, future considerations in the field of sleep apnea include: 1) addition of non-oximetric aspects of OSA, including cortical and cardiovascular responses to respiratory events and measures of sleep depth, 2) examination of short/deep desaturations versus long/shallow ones and how they modify the association of hypoxic burden with cardiovascular outcomes, 3) investigation of how non-OSA-related factors, such as obesity and lung function, influence hypoxic burden and modify its association with health outcomes, 4) prospective evaluation of hypoxic burden in larger cohort studies and randomized controlled trials of OSA treatment, and finally 5) assessment of hypoxic burden's association with daytime symptoms and neurocognitive outcomes.

REFERENCES

1. Javaheri S, Barbe F, Campos-Rodriguez F, Dempsey JA, Khayat R, Malhotra A, et al. Sleep Apnea: Types, Mechanisms, and Clinical Cardiovascular Consequences. *J Am Coll Cardiol*. 2017; **69**(7): 841-58.
2. Gottlieb DJ, Punjabi NM. Diagnosis and Management of Obstructive Sleep Apnea: A Review. *JAMA*. 2020; **323**(14): 1389-400.
3. Netzer NCC, Ancoli-Israel SC-C, Bliwise DL, Fulda S, Roffe C, Almeida F, et al. Principles of practice parameters for the treatment of sleep disordered breathing in the elderly and frail elderly: the consensus of the International Geriatric Sleep Medicine Task Force. *Eur Respir J*. 2016; **48**(4): 992-1018.
4. Garvey JF, Pengo MF, Drakatos P, Kent BD. Epidemiological aspects of obstructive sleep apnea. *J Thorac Dis*. 2015; **7**(5): 920-9.
5. Osorio RS, Martinez-Garcia MA, Rapoport DM. Sleep apnoea in the elderly: a great challenge for the future. *Eur Respir J*. 2022; **59**(4).
6. Baldwin CM, Griffith KA, Nieto FJ, O'Connor GT, Walsleben JA, Redline S. The association of sleep-disordered breathing and sleep symptoms with quality of life in the Sleep Heart Health Study. *Sleep*. 2001; **24**(1): 96-105.
7. McEvoy RD, Antic NA, Heeley E, Luo Y, Ou Q, Zhang X, et al. CPAP for Prevention of Cardiovascular Events in Obstructive Sleep Apnea. *N Engl J Med*. 2016; **375**(10): 919-31.
8. Peker Y, Glantz H, Eulenburg C, Wegscheider K, Herlitz J, Thunstrom E. Effect of Positive Airway Pressure on Cardiovascular Outcomes in Coronary Artery Disease Patients with Nonsleepy Obstructive Sleep Apnea. The RICCADSA Randomized Controlled Trial. *Am J Respir Crit Care Med*. 2016; **194**(5): 613-20.
9. Sanchez-de-la-Torre M, Sanchez-de-la-Torre A, Bertran S, Abad J, Duran-Cantolla J, Cabriada V, et al. Effect of obstructive sleep apnoea and its treatment with continuous positive airway pressure on the prevalence of cardiovascular events in patients with acute coronary syndrome (ISAACC study): a randomised controlled trial. *Lancet Respir Med*. 2020; **8**(4): 359-67.
10. Karhu T, Myllymaa S, Nikkonen S, Mazzotti DR, Toyras J, Leppanen T. Longer and Deeper Desaturations Are Associated With the Worsening of Mild Sleep Apnea: The Sleep Heart Health Study. *Front Neurosci*. 2021; **15**: 657126.
11. Hietakoste S, Korkalainen H, Kainulainen S, Sillanmaki S, Nikkonen S, Myllymaa S, et al. Longer apneas and hypopneas are associated with greater ultra-short-term HRV in obstructive sleep apnea. *Sci Rep*. 2020; **10**(1): 21556.
12. Azarbarzin A, Sands SA, Stone KL, Taranto-Montemurro L, Messineo L, Terrill PI, et al. The hypoxic burden of sleep apnoea predicts cardiovascular disease-related mortality: the Osteoporotic Fractures in Men Study and the Sleep Heart Health Study. *Eur Heart J*. 2019; **40**(14): 1149-57.
13. Azarbarzin A, Sands SA, Taranto-Montemurro L, Vena D, Sofer T, Kim SW, et al. The Sleep Apnea-Specific Hypoxic Burden Predicts Incident Heart Failure. *Chest*. 2020; **158**(2): 739-50.
14. Berry RB, Gamaldo CE, Harding SM, Brooks R, Lloyd RM, Vaughn BV, et al. AASM Scoring Manual Version 2.2 Updates: New Chapters for Scoring Infant Sleep Staging and Home Sleep Apnea Testing. *J Clin Sleep Med*. 2015; **11**(11): 1253-4.

15. Berry RB, Budhiraja R, Gottlieb DJ, Gozal D, Iber C, Kapur VK, et al. Rules for scoring respiratory events in sleep: update of the 2007 AASM Manual for the Scoring of Sleep and Associated Events. Deliberations of the Sleep Apnea Definitions Task Force of the American Academy of Sleep Medicine. *J Clin Sleep Med*. 2012; **8**(5): 597-619.

16. Martinez-Garcia MA, Sanchez-de-la-Torre M, White DP, Azarbarzin A. Hypoxic Burden in Obstructive Sleep Apnea: Present and Future. *Arch Bronconeumol*. 2023; **59**(1): 36-43.

17. Blanchard M, Gerves-Pinquie C, Feuilloy M, Le Vaillant M, Trzepizur W, Meslier N, et al. Hypoxic burden and heart rate variability predict stroke incidence in sleep apnoea. *Eur Respir J*. 2021; **57**(3).

18. Trzepizur W, Blanchard M, Ganem T, Balusson F, Feuilloy M, Girault JM, et al. Sleep Apnea-Specific Hypoxic Burden, Symptom Subtypes, and Risk of Cardiovascular Events and All-Cause Mortality. *Am J Respir Crit Care Med*. 2022; **205**(1): 108-17.

19. Navarro-Soriano C, Martinez-Garcia MA, Torres G, Barbe F, Sanchez-de-la-Torre M, Caballero-Eraso C, et al. Long-term Effect of CPAP Treatment on Cardiovascular Events in Patients With Resistant Hypertension and Sleep Apnea. Data From the HIPARCO-2 Study. *Arch Bronconeumol (Engl Ed)*. 2021; **57**(3): 165-71.

20. Pengo MF, Soranna D, Giontella A, Perger E, Mattaliano P, Schwarz EI, et al. Obstructive sleep apnoea treatment and blood pressure: which phenotypes predict a response? A systematic review and meta-analysis. *Eur Respir J*. 2020; **55**(5).

21. Bosc LV, Resta T, Walker B, Kanagy NL. Mechanisms of intermittent hypoxia induced hypertension. *J Cell Mol Med*. 2010; **14**(1-2): 3-17.

22. Kim JS, Azarbarzin A, Wang R, Djonlagic IE, Punjabi NM, Zee PC, et al. Association of novel measures of sleep disturbances with blood pressure: the Multi-Ethnic Study of Atherosclerosis. *Thorax*. 2020; **75**(1): 57-63.

23. Jackson CL, Umesi C, Gaston SA, Azarbarzin A, Lunyera J, McGrath JA, et al. Multiple, objectively measured sleep dimensions including hypoxic burden and chronic kidney disease: findings from the Multi-Ethnic Study of Atherosclerosis. *Thorax*. 2021; **76**(7): 704-13.

24. Labarca GP, Op De Beeck S, Vena D, Sands SA, White DP, Redline SS, et al. Effect of Hypoglossal Nerve Stimulation on Hypoxic Burden and Sleepiness: Secondary analysis of the STAR trial. C98 DEEP PHENOTYPING FOR SLEEP APNEA THERAPY SUCCESS: *American Thoracic Society*; 2022. p. A4818-A.

25. Panza GS, Puri S, Lin HS, Badr MS, Mateika JH. Daily Exposure to Mild Intermittent Hypoxia Reduces Blood Pressure in Male Patients with Obstructive Sleep Apnea and Hypertension. *Am J Respir Crit Care Med*. 2022; **205**(8): 949-58.

26. Eckert DJ, Sands SA. Hypoxia and Sleep-disordered Breathing: Friend or Foe? *Am J Respir Crit Care Med*. 2022; **205**(8): 869-72.

27. Anderer P, Moreau A, Woertz M, Ross M, Gruber G, Parapatics S, et al. Computer-assisted sleep classification according to the standard of the American Academy of Sleep Medicine: validation study of the AASM version of the Somnolyzer 24 x 7. *Neuropsychobiology*. 2010; **62**(4): 250-64.

28. Punjabi NM, Shifa N, Dorffner G, Patil S, Pien G, Aurora RN. Computer-Assisted Automated Scoring of Polysomnograms Using the Somnolyzer System. *Sleep*. 2015; **38**(10): 1555-66.