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Obstructive Sleep Apnea (OSA): Diagnostic and Therapeutic Challenges

Literature Review

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Abstract – Obstructive sleep apnea (OSA) is a prevalent condition with known impacts on cardiovascular and neurocognitive health, affecting nearly 1 billion individuals globally. While the apnea-hypopnea index (AHI) is the most commonly used metric to gauge OSA severity, its effectiveness in evaluating treatment response remains uncertain. This review explores the history and predictive capabilities of the AHI in various clinical scenarios and considers alternative metrics such as hypoxic burden, arousal intensity, odds ratio product, and cardiopulmonary coupling. Future research directions include utilizing genetics, blood biomarkers, machine learning, and wearable technologies to identify distinct OSA endophenotypes. The aim is to enhance diagnostic accuracy, prognostic insights, and patient care strategies in managing OSA-related consequences.

Keywords – Sleep, Apnea, Hypoxia, Cardiovascular, Lung, Hypopnea.

I. INTRODUCTION

Obstructive sleep apnea (OSA) is a prevalent chronic condition linked to cognitive impairment, high blood pressure, and the onset of heart and brain diseases [1]. Current estimates suggest that OSA affects around 1 billion individuals globally, with many cases going undiagnosed [2]. The conventional method of diagnosing OSA by measuring the frequency of breathing pauses during sleep (apnea-hypopnea index, AHI) has faced challenges and limitations [3]. This research aims to address the shortcomings of AHI in predicting the impact of OSA and responses to treatment [4-6]. Considering the various health issues associated with OSA, the ideal measure of OSA severity may vary depending on specific outcomes [7,8]. This review explores the evolution of apnea and hypopnea definitions, evaluates the strengths and weaknesses of AHI, and discusses the potential benefits of new metrics derived from polysomnography. It serves as a guide for research to enhance OSA diagnostic methods and severity assessment, rather than as a practice standard or exhaustive literature review. Central sleep apnea and hypoventilation are beyond the scope of this research.

1. Defining Metrics

A metric is a system for measuring something or a standard of measurement. A metric is a system for measuring something or a standard of measurement. In medicine, metrics assist differentiate ailment states from ordinary and categorize the severity of illnesses. The use of metrics in healthcare has become increasingly important to define disease states, measure outcomes, and improve care continually. According to Blumenthal and McGinnis, [9]"If something cannot be measured, it cannot be improved." The traditional metrics used to define sleep-disordered breathing syndromes are based on the number of breathing events during

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sleep. In the 1970s, healthy subjects were studied to establish a threshold for defining "disease" as <5 apneas per hour. Apneas were not initially differentiated by type [10]. Lugaresi et al. proposed that more than 30 apneas during the night was the best discriminator of normal vs. abnormal [11,12,]. The concept of hypopneas was introduced to identify episodes of reduced breathing due to drops in oxygen saturation or arousal [13-15]. Inconsistency in defining sleep-disordered breathing events, especially hypopneas, has been a significant concern. The threshold to define disease may evolve based on interventional studies, similar to cholesterol and blood pressure. History of Polysomnography (PSG) evolved from electroencephalography (EEG) first described by Berger in 1929 and applied to the study of sleep by Loomis in 1937 [16-17].In 1957, Dement and Kleitman described sleep cycles and proposed a sleep classification schema[18-19]. Breathing sensors were introduced in the 1960s, with Gastaut describing obstructive breathing events in patients with the Pickwickian Syndrome[20]. Cardiac signals were later incorporated, leading to the term "polysomnography." Thermal sensors were initially used to measure airflow in a semiquantitative manner. Norman et al. in 1997 reported using a standard nasal cannula connected to a pressure transducer to detect airflow more sensitively[21]. Respiratory effort measurement has evolved from mercury strain gauges to respiratory inductance plethysmography (RIP), which is now the standard methodology. Additional measures like carbon dioxide sensors and esophageal pressure transducers have been used to assess ventilation and respiratory effort. Pulse oximeters are commonly used to measure oxygen saturation, with thermal sensors and nasal cannula-pressure transducer devices being the recommended standard for airflow measurement.

2. Defining Respiratory Events

The term obstructive sleep apnea syndrome (OSAS) was introduced in 1976 after discovering daytime sleepiness and polysomnographically proven obstructive apneas[22]. An apnea is defined as a cessation of airflow at the nose and mouth lasting at least 10 seconds, based on a study from 1975[23-25]. This rule helps differentiate pathological apneas from normal breathing in adults. Hypopneas were first described as shallow breathing events causing oxygen desaturation. Desaturations are considered clinically significant when there is a 4% or greater fall from the preceding baseline[26,27]. The first case of sleep hypopnea syndrome, with frequent hypopneas but no apneas, was described in 1988. Initially, OSA was defined by 30 apneas during the night, which later evolved into the apnea index, where a cut-off of 5 apneas/hour was set to diagnose the disease. Variability in hypopnea definitions became evident as hypopneas were recognized in sleep-disordered breathing[25]. The Wisconsin Sleep Cohort study defined hypopneas as clear decreases in signal amplitude accompanied by a 4% oxygen desaturation[28]. The Sleep Heart Health Study acknowledged the variability in hypopnea definitions and demonstrated the impact of varying definitions on calculated AHI[29,30]. In a move to standardize event definitions, an American Academy of Sleep Medicine (AASM) task force in 1999 recommended that apnea and hypopnea be considered equivalent and defined the apnea/hypopnea event as a clear decrease from baseline in breathing amplitude during sleep. The task force also introduced the respiratory event-related arousal (RERA) ,including the following: “These events must meet the following criteria:

(1) a technique that generates progressively negative esophageal pressure, with a sudden change in pressure to a suboptimal level and end with the stimulus .

(2) the action lasts 10 seconds or more ”. It was also recommended that severity be graded by sleep patterns and the frequency of respiratory events, with the following severity ratings based on the number of respiratory obstructions per hour.

1. Easy: 5 to 15 events per hour

2. Moderate: >15 to 30 events per hour

3. Significance: More than 30 events per hour

Note that these recommendations were based on expert opinion, acknowledging that the data used to base these event definitions and severities are limited and ultimately subject to limited flexibility these types are refined as data from intervention studies help characterize patients most likely to benefit from treatment. Additional variables beyond estimating events alone are likely to be needed, consistent with the use of C reactive protein (hsCRP) as a guideline for glycemic control definitions of respiratory events continue to evolve. The AASM Manual for the Scoring of Sleep and Associated Events was published in 2007 [32] with a redefinition of the code for respiratory events. Relaxation was scored as a decrease in maximum thermosensor rotation to 90% of baseline, an event lasting at least 10 seconds and meeting amplitude reduction criteria for at least 90% of the event duration and then averaged as lungs by presence or absence of inspiratory energy. The recommended rule of thumb for hypopnea is to reduce

nasal pressure signal transport to ≥30% of baseline for at least 10 seconds with desaturation ≥4% from prevent onset, and 90% of the event's duration satisfies the amplitude reduction criteria of breathing. Lungs were then classified by the presence or absence of motivational effort. The recommended rule of thumb for hypopnea was to reduce nasal pressure signal transport to ≥30% of baseline for at least 10 seconds with ≥4% desaturation from preevent onset, and should reach 90% amplitude reduction over event duration 3% were associated with desaturation or arousal RERA was defined as an episode of at least 10 seconds that did not meet the definition of hypopnea and was characterized by an increased respiratory effort or a flattening of the nasal pressure waveform, it stimulates arousal from sleep [33, 34]. Although RERA is best defined by the esophageal panometer, nasal pressure and induction plethysmography are newer measurement tools [33-35] AASM Scoring Manual Version 2 in 2012 with significant changes in the definition of recommended hypopnea were removed have demonstrated a delay of ≥30% of the 10 second flow signal associated with ≥3% oxygen desaturation or stimulation, with optional co-reporting of hypopnea by definition requiring association with ≥4% desaturation [27]. This modification reflected the acknowledgment that some patients whose events were not associated with 4% desaturations had symptoms and would benefit from OSA treatment.

This alternative definition of two events acknowledged divergent findings each absolutely characterizing the severity of OSA, and "to determine the presence and severity of OSA , and the criteria for calculating the health-related consequences of OSA and the definition of hypopnea of use corresponds to [27,36]".However, the AASM does not recommend such changes in recommended severity based on frequency of occurrence. As developments and changes in respiratory monitoring technology and inconsistencies in event interpretation lead to confusion and difficult comparisons between studies, the terminology used in respiratory frequency occurrence of events is also inconsistent at the same time as the term (AHI), the term respiratory distress index (RDI) is also being used as a synonym [27] . The 2007 AASM scoring manual defined RDI as including hypopnea and apnea plus RERA, which refers to sleep per hour, and thus formally distinguishes it from AHI [27, 36] Commonly used in early PSG while measuring ventilatory and respiratory effort decreases, it is still frequently reported today, the Oxygen Desaturation Index (ODI) is defined as the rate at which oxygen saturation temporarily falls per hour of sleep Should specifying a percentage used to characterize a desaturation event (usually 3% or 4%).

3. Sleep Apnea Testing at Home

Technological advances in measuring sleep reliability in recent years aim to reliably assess OSA in an unsupervised home setting because of greater patient convenience and cost which is lower for the patient as a result of self-administered and recorded sleep and cardiopulmonary symptoms at home .A home sleep apneas test used to diagnose and/or assess OSA (also known as portable / ambulatory monitoring) from devices with 1–2 sensors (e.g. pulse oximetry or ventilation) with sleep heart and lung indicators more to multichannel devices [37–40]. The definitions used for these devices to score breathlessness in sleep disorders vary widely depending on the technology used and the symptoms recorded comparable making it difficult to compare data across devices [41] Although that the Home Sleep Apnea Test (HSATs) full PSG do not record the same symptoms, however, both provide an index of OSA severity with the AHI derived from the PSG for the use of the AASM definition of hypopnea with EEG stimulation is not possible due to EEG recording on most HSAT devices. However, some HSAT devices use surrogates for EEG stimuli such as changes in pulse, heart rate, or movement to detect hypopnea [42] . Most HSAT devices use time recording or normal signal time as an indicator rather than total sleep (TST) in the calculation of AHI because EEG sensors are not included to distinguish between sleep and awake. [43] To distinguish between indices that use recorded time (including sleep and wake time) and total sleep time (EEG only describes sleep time), the AASM recommends the term Respiratory Event Index (REI). However, an increasing number of HSATs are able to distinguish between sleep and awake using limited EEG or other technologies (such as a combination of muscle tonometry and other physiological parameters) and allow TST measurements to approximate [40, 44–46] .

Despite the differences, validation studies comparing HSAT with in-laboratory PSG data suggest reasonable OSA severity indices and adequate diagnostic sensitivity/specificity for OSA [47-50] because HSATs do not interfere much, Patients take notes in a natural setting and have the ability to take notes on several nights (combined with the night to night physiological changes of OSA), these notes can lead to severe dyspnea if a more theoretically reliable measure of sleep disturbance than one night in the laboratory. Although most portable sleep testing devices are equipped with sensors to measure airflow, some new technologies, such as peripheral arterial tonometry (PAT), have been used to detect respiratory events that cause sleep disturbance without use airflow .[45,51] The severity of residual OSA when the therapy is measured by the airflow of the PAP devices. Without the ability to measure sleep, PAP device measurements can use recording time as the denominator for AHI based on airflow changes alone

[52] .Strengths and Weaknesses of the AHI In this section we address the ability of the AHI to identify clinically relevant correlates of OSA, including patient-reported outcomes such as daytime sleepiness and quality of life, motor vehicle and industrial accidents , hypertension, diabetes, CHD , stroke , heart disease . In addition to the limitations of the AHI due to the methodological inconsistency described above, there has been concern that the AHI cannot capture the physiological abnormalities that underlie its neuropsychological, metabolic, and under cardiovascular influence equally. In considering the limits of AHI as predictors of this outcome, it is important to recognize three factors that may lead to limited predictive power :

1. The accuracy with which the AHI reflects OSA-related etiology with negative consequences, due to inability to accurately characterize physiologic pathology or measurement error due to night-to-night variability or the they cannot be said properly because of scoring inaccuracy.

2. Individual differences in response to OSA, including genetics, age, medications, and co-occurring conditions such as obesity and others. These differences in OSA of this response would limit the outcome even if the accurate measurement of the obstructive airway. Thus, where there is a comparison of the predictive power of the AHI with other established risk factors for daytime sleepiness, excessive daytime sleepiness (EDS) has long been recognized as the primary symptom of OSA, as early reports in the 1970s explained by early reports, [26,53] Proposed mechanisms for EDS in OSA include sleep fragmentation [54], increased sleep-induced cytokines and intermittent nocturnal hypoxemia [55-58], possibly intermittent to is caused by nerve injury affecting the waking regions of the brain, . It also induces apoptosis [59, 60] . However, EDS is not universal in OSA patients, as some also report fatigue or lack of energy [61], and others have no symptoms at all in fact, most OSA patients do not report EDS, according to how prevalence is about 40% . EDS in OSA Has been observed in several multicenter studies [62, 63] The prevalence of EDS in OSA may vary with comorbidities, with the prevalence of heart disease [64] and atrial fibrillation [65] being much lower than compared to its prevalence in asthma[66], epidemiological data from Sleep Heart Health Study (SHHS) and Wakefulness-Sleep Cycle (WSC) [67–70]

Support monotonic associations of higher OSA severity as defined by the AHI and higher percentages of those with EDS, associations that were also present at mild OSA levels however these studies differ in specific sex differences in sleep symptoms in OSA. Although the SHHS did not support differences, the WSC showed higher rates of EDS in men versus women--specifically, 22.6%of women and 15.5% of men with AHI-4% >5/hour [70] . However, in these epidemiological studies, less than half of those with moderate to severe OSA (defined as AHI-4% ≥15/hour) were excessively sleepy [defined as Epworth Sleepiness Scale Score(ESS) ≥11/24] [68, 71] . All clinical-based studies appear to be consistent in their significant association with EDS, primarily resolved by ESS, but in some cases by objective multi-day delayed testing and observational testing dependence on sleep, with high rates of OSA as defined by the AHI [72–78].Several clinical trials have shown that treatment of OSA leads to improvements in objective measures of self-reported sleepiness. Although OSA severity as assessed by the AHI has been associated with sleep improvement in some studies, initial sleep severity is a good predictor of improvement, demonstrating its importance as an individual respond to OSA as an indicator of disease severity.

4. Quality of Life

Few studies have examined the relationship between OSA scales and quality of life; Nevertheless, there appears to be an association between AHI and quality of life(QoL). In a study of 737 individuals with community-based WSC, a higher AHI-4% was associated with significantly lower scores on 6 of the 8 SF-36 health status scores (mental health, energy, physical functioning, social, physical functioning, overall health), in a dose-response manner [80]. For example, relative to subjects without OSA (AHI = 0) and after adjusting for confounders including BMI, the general health perception AHI (in group is 72.5). The decrease in general health perception is similar for moderate and severe OSA is similar to other common diseases such as rheumatoid arthritis (7.3 reduction), hypertension (3.5 reduction), and back problems (4.4 reduction), although the values are lower than those seen in diabetes or angina using (12.8 and 13.2) respectively [81]. These results were generally consistent with those of the SHHS group, with participants with severe OSA (AHI-4% ≥30/hour) showing significantly better quality of life across settings but within SHHS was reported, only SF-36 energy scores showed a consistent linear relationship with AHI [82–84] . CPAP therapy may improve some aspects of overall QoL, particularly with regard to physical function. However, the effect of CPAP appears to be stronger for day-specific quality of life instruments such as the Sleep Apnea Quality of Life Index (SAQLI) or Functional Outcomes of Sleep Questionnaire (FOSQ) [85] .

5. Motor Vehicle Crashes and Occupational Industries

A putative relationship between OSA and motor vehicle crash occurrence (MVC) [86], is due to the effect of sleep separation on severity and reaction time although many other factors also contribute to MVC, e.g., circadian factors , and age, however, several studies have documented an increased rate of MVC in patients with OSA In a meta-analysis of 10 studies [87], a significantly higher rate of MVC in patients with OSA (as measured by standard indices such as AHI measured) than those without OSA were higher (RR = 2.43, 1.21-4.89, p = 0.01). Evidence for the relationship between disease severity (measured by AHI) and accident rates is inconclusive. Three studies had sufficient data to yield pooled estimates of the association between AHI and MVC risk in patients with OSA. In all three of these studies, patients with OSA who had an accident tended to have higher AHI, up to about 10/h (standardized mean difference in AHI between groups = 0.27, p = 055). Of the 8 reviews not included in the study, 3 found OSA severity to be associated with accident risk, but 5 did not. However, a recent community-based study (SHHS) reported a significant increase in MVC risk with increasing AHI-4% (OR 1.15, 95% CI 1.07–1.26 1.07–1.26 per 10 events/4). for the hourly increase in AHI-4%), after adjustment for age, sex, driving distance, usual sleep duration, and sleepiness (based on score ≥11/24 on the Epworth Sleepiness Scale). [88] . The MVC risk associated with a 10-unit increase in AHI was slightly higher than the MVC risk associated with one hour of practice Depends on job type/responsibilities. Nevertheless, reviews have consistently showed an increased risk of occupational injuries in patients with OSA, as studied lately [89] . In this analysis of 7 studies, patients with OSA had an increased risk of occupational injury (OR = 2.18, 1.53– 3.1). In four studies, OSA was defined according to PSG or polygraphs; OSA was diagnosed based on threshold AHI (5–10/ hour). Considering only these studies, the OR = 1.78 (1.03–3.07), again consistent with the high risk associated with OSA as documented by the AHI. In a subsequent study of 1109 workers referred for sleep study (PSG), severe sleep apnea (log (AHI+1)) was significantly associated with the occurrence of occupational injury (OR = 1.31, 95% CI 1.02–1.73, p = 0.04), controlling for confounding factors [90]. Patients with moderate and severe OSA were twice as likely as patients without OSA (OR 1.99, 95% CI 0.96–4.44 and 2.00, 95% CI 0.96–4.49 to moderate and severe OSA groups, respectively). This increase in OR factors /was similar to an increased odds ratio of workers in craft-related occupations versus those not (OR = 2.28). Patients with OSA who are dependent on continuous positive airway pressure (CPAP) have similar MVC rates as individuals without OSA [91]; The extent to which CPAP therapy can reduce the risk of occupational injury is unclear. However, there is no evidence that the AHI metric by itself predicts a reduction in accident risk with treatment.

6. Hypertension

OSA is strongly associated with a prevalence of asthma and hypertension, although this effect appears to be weaker in older populations [92-98] . Between WSC and SHHS, after adjustment for age, sex, and anthropometric characteristics, systolic and diastolic blood pressure (among non-users of antihypertensive drugs); and prevalence of hypertension increased linearly as measured by AHI-4% The magnitude of these associations with OSA severity was significant: SHHS At the median, despite a 43% prevalence of hypertension on the baseline, an AHI-4% ≥30 was associated with an adjusted OR of 1.47 compared with those with an AHI-4% <1.5. were 1.75 and 3.07, respectively, and there was also a dose-dependent association between OSA measured with AHI in WSC compared with no AHI, and hypertensive episodes. Compared with an AHI of zero, the AHI-4% after adjustment for age, sex, and body type was 2.03 for 5–14.9 and the AHI-4% was 2.89 for ≥15/hour [95] However, none had developed hypertension in the SHHS group No significant association was found [98]. A recent meta-analysis of observational studies showed that the prevalence and incidence of hypertension increased with greater severity of OSA as measured by AHI [99] Although AHI is rarely compared to other blood pressure risk factors reported although multivariable regression in a study of 372 adults aged 68 years (SD 1) showed severe OSA (AHI-3% defined as >30 /hour) is more strongly associated with incident hypertension or BMI ≥ 30 than male sex [96] . Several studies have shown that CPAP therapy for OSA reduces blood pressure [100–102] . Few studies have looked at the PSG predictor in detail rather than high blood pressure or cholesterol. Mooe et al., They found that in males, AHI ≥14/hour was associated with CHD with an aOR of 4.5, which was almost equal to the effect of hypertension (aOR 4.2), diabetes (aOR 4.3), or BMI (aOR) 4. 8), was significantly more severe than a positive smoking history (aOR 1.6 for current or former smoking). In women, AHI ≥5/hour was, although not, associated with CHD with an aOR of 4.1, greater than hypertension (aOR 3.4), smoking history (aOR 2.4), or BMI (not significant). as severe as diabetes (aOR 6.8) . In a cross-sectional analysis of baseline data from the community SHHS, a significantly weaker association between AHI and CHD was observed, with an aOR of 1.2 after significant covariate adjustment for AHI-4% >4.4/hour,1. high time There was no increased risk AHI levels [114].

7. Coronary Artery Disease

Community-based studies of the association between OSA and incident CHD do not yield consistent results. Using a non-traditional sample group of participants with AHI = 0, the Wisconsin Sleep Group study showed age, sex, BMI-, and smoking-adjusted hazard ratio (aHR) for incident CHD in participants not using CPAP was 2.4 (95 %). CI 1.0–6.0) for those with AHI-4% ≥30/hour [115]. For the groups with AHI >0–<5, 5–<15, and 15–<30, the AHR ranged from 1.6 to 1.8, and all trends were not statistically significant in SHHS, the age of OSA manifestation of CHD occurrence. The adjusted associations for ethnicity, BMI and smoking were significant only in men, and the excess risk was limited to those with an AHI-4% ≥30/hour [116] The association between OSA and incident CHD this was significant only in those younger than 70. In the Busselton Health Study cohort, using the MESAM IV device (a version of the HSAT) to measure respiratory events, moderate to severe OSA occurred in CHD (AHI ≥15/hour duration compared AHI <5/hour, aHR 1.1, 95% CI 0.24–4.6) [117]. Clinical-based prospective studies have also yielded mixed results regarding recurrence of OSA or CHD, and many are difficult to interpret due to different studies in CPAP-dependent and nonadherent patients CPAP , including the healthy user therefore the results are a high risk of bias due to side effects. Recently, several randomized clinical trials in insomnia patients with significant AHI have failed to demonstrate a reduction in CHD, stroke or mortality with PAP therapy [118-120]

8. Stroke

A recent meta-analysis of 86 studies including 7096 stroke patients (which included both 3% or 4% desaturation criteria) found 71% AHI >5/h and 30% AHI >30/h Extension was similar to a 1-month evaluation >30 months after stroke. OSA has also been associated with event depression in community-based treatment units [117, 122–129] . In reviews that have studied both outcomes, the association between OSA and incident trauma is significantly stronger than that of CHD. WSC, found that AHI-4% ≥20/hour was associated with an increased risk of first stroke in the 4-year follow-up period (OR 4.3, 95% CI 1.3–14.2) The effect size was slightly smaller and so BMI was normal (3.1, 95% CI 0.74–12.8). was not statistically significant after adjustment for, and had a wide confidence interval because of the relatively low incidence of stroke in this young group [122] SHHS found that the risk having seizure events was higher in men with moderate-to-severe OSA in adjusted analyses (aHR = 2.9, 95% CI 1.1–7.4) [123]. This effect was not noticed in women. One of the first hospital-based studies designed to screen for OSA and stroke found an approximately 2-fold increase in stroke incidence and mortality (HR 1.97, 95% CI 1.12–3.48) with an AHI >5 in In a study of 392 CHD patients with OSA , the presence of AHI-3 Na % ≥5 was associated with an adjusted HR of stroke events of 2.9 (95% CI 1.4–6.1), which was more severe than the risk associated with type 2 DM, hypertension, current smoking or atrial fibrillation 127] . However, a clear dose-response relationship between AHI and stroke risk is often not observed. Although prospective studies have shown a decreased risk of stroke in patients treated with CPAP compared to untreated patients [128, 130, 131] though, these studies have a high risk of bias when comparing CPAP-dependent and non-CPAP-dependent patients .

Randomized clinical trials in stroke patients have not shown a reduction in stroke risk, although they were modest and limited power. No reduction in stroke risk was found with CPAP in large randomized trials of patients with cardiovascular disease and OSA, although these studies were also not powered to find out changes in actual stroke risk [119, 120, 128, 132, 133] traditional OSA criteria for mortality and AHI Hypoxemia measures are also significantly associated with mortality risk in the general population. In the WSC, Busselton Health Survey, and SHHS, mortality risk increased with AHI after adjustment for age, sex, BMI, and prevalent medical conditions [134–136] Although not there was always a clear monotonic increase in AHI though it did change with increasing OSA severity as measured by AHI. The risk of mortality was generally higher in WSC e.g. Among participants not treated with positive airway pressure, mild (AHI-4% 5.0–14.9/hour), moderate (AHI-4% 15.0) OSA –29.9/hour), severe (AHI-4% ≥30.0/hour) was 1.4, 100. normal (95% CI was 0.7–2.6), 1.7 (95% CI 0.7–4.1), and 3.8 (95% CI 1.6–9.0), with an AHI- 4%. <5 Percentage of time with SpO2 <90% in SHHS was also associated with increased mortality, although less strongly than AHI, while arousal index was not predictive of mortality Mortality has been predicted an increased in OSA patients not treated in group-based sleep clinics have been reported over time [137, 138] there are]. where contemplated, the risk of death in these groups increases with greater severity of OSA as measured by the AHI [130, 139, 140]. The mortality risk associated with OSA compared with other causes of death has been reported in a few studies. In the Busselton Health Survey, AHI ≥15 had an unadjusted HR of 5.0 (95% CI 2.0–12.2), similar to diabetes (HR 4.0), ten years of age (HR 3.6), and current smoking (HR 3.8) and more than 10 mmHg increase in mean arterial pressure (HR 1.7) [136] . Two hospital-based studies from Spain reported anthropogenic adjusted for OSA comparable to other important causes of mortality, although these studies report risk for OSA in treatment-naïve patients and therefore must be interpreted with caution Martinez Garcia et al. reported that compared with those

with AHI-4% <15, the aHR was 1.4 for untreated moderate OSA (AHI-4% 15–<30/hour) and 2 for severe OSA untreated (AHI-4% ≥30/hour). whereas smoking ≥30 pack-years was associated with an aHR of 1.5, diabetes aHR of 2.3, and older age of aHR of 1.8 per decade [140] .

Similarly, Campos-Rodriguez reported that compared with those with AHI-4% <10, those with AHI-4% untreated in the range of 10–29 had an AHR of 1.6, those with AHI ≥30 untreated had an AHR of 3.5, while diabetes had an AHR of 1.4 per decade, hypertension 2 .4 AHR, with an age-related AHR of 1.6 [139]. Both community-based treatment groups show a stronger association between OSA and mortality in older adults less than 70 years [135, 141] It is unclear whether this reflects factors exhibiting increased competing mortality or distinct physiological responses to OSA in the elderly. There are no adequately powered randomized clinical trials of OSA treatment to reduce mortality have been performed, and no significant reduction in mortality was reported in cardiovascular secondary prevention trials involving CPAP therapy [119, 120]. Another study AHI has been a widely used metric of sleep depth for decades, but the methodological problems described above are widely acknowledged Furthermore, mechanisms that compel OSA pathophysiology under the poorly quantified may contribute to limit the ability of AHI itself to predict or respond to OSA clinical outcome OSA therapeutic nomenclature Based on the basis, it has been suggested that alternative methods for measuring disease severity [142] We summarize here some of these alternative methods, acknowledging that many have been proposed, and no ideal metric has yet emerged. Indeed, because OSA is currently considered a heterogeneous disease in terms of both underlying mechanisms (endotypes) and clinical manifestations (phenotypes] [1, 143, 144], it is most likely that no single metric will be able to predict it OSA and all its components well associated risk factors.

8.1 Hypoxic Burden

It is recognized that hypoxia, especially in acute phase, adversely affects cardiac and metabolic function. The degree of desaturation and frequency of desaturation are usually expressed, but recently researchers have adopted the area under the oxyhemoglobin saturation curve as a metric of hypoxic load, Azerbarzin et al., reported that a load with this hypoxic level could easily be achieved by sleeping overnight studied mortality from cardiovascular disease in two community-based cohorts [145, 146]. Both the SHHS and the bone fracture study in men [147] found a progressive increase in cardiovascular mortality with increasing hypoxic load, an effect that was not attenuated by adjustment for AHI or conventional polysomnographic measures plays a large role in relation to hypoxia, including very low saturation or percentage time full <90%. The adjusted HR for cardiac death in the upper quintile of hypoxic burden in SHHS was 1.96 (95% CI 1.11–3.43). In contrast, AHI did not significantly predict mortality from cardiovascular causes in these groups. Findings indicate that not only the frequency and duration of sleep-related upper airway obstructions, are important disease features And previous authors have prescribed T90 (duration a prevalence lower than 90%), a non-OSA-specific measure of hypoxic burden, with important outcomes including platelet aggregation and predicted overall mortality [148] In contrast , a recent follow-up study of the SAVE (Sleep Apnea Cardiovascular Endpoints) study has shown little predictive value of desaturation indices for event composite cardiovascular outcome [149] Notably, pulse oximeters has developed over many years but varies in sensitivity and time stability .

8.2 Stimulus Strength

Amatoury et al., quantified stimulation intensity as a potentially important physiological variable [150] . The authors hypothesized that sleep-deprived arousal may vary in intensity with some stimuli being more subtle (and not captured by traditional EEG parameters), whereas Others are more robust allowing complete awakening from sleep [151]. Increased stimulus intensity was unrelated to the magnitude of the preceding respiratory stimulus but was negatively correlated with stimulus duration, stimulation time, rapidly changing epiglottic pressure, and body weight index ($R2 > 0.10{,}000$). $p \leq 0.006$). The respiratory response of pharyngeal muscles increases with stimulus intensity. Thus, highly motivated patients may be more susceptible to respiratory control instability. Previous work on 'subcortical arousal' noted a sleep dissociation that significantly influenced diurnal activity but was not captured by conventional EEG parameters Azerbergine et al compared stimulus intensity to changes in incidence heart rate associated with disturbing events in 20 PSG samples performed in patients attending a sleep laboratory Correlation (average reported r: 0.95 ± 0.04), which is consistent with the concept of stimulus intensity a marker of autonomic activation [152] Heart rate response prevention of fatal events in the upper quartile of the population (HR 1.68, 95% CI 1.22–2.30). it was nonfatal (HR 1.60, 95% CI 1.28). – 2.00) was associated with an increased risk of both cardiovascular events in the Sleep Heart Health Study, and this risk was particularly high in those who also had the greatest hypoxic burden [153] . Notably, motivation can also be highly variable, depending on inter- and intra-observer variability. Self-response to stimulation is perhaps the most

important underlying Pathophysiology of OSA complications [154]. However, the prognostic value of this parameter for acute cardiovascular events has not been tested and will require further investigation.

8.3 The Odds Ratio Product (ORP)

The odds ratio product (ORP) is a recent metric of sleep depth [155]. Derived from quantitative data performs EEG analysis using power spectral meters. ORP values can range from 0 to 2.5 with values of 0 to 1.0 indicating sleep and 2.0 to 2.5 indicating wakefulness. Although ORP can vary significantly in any particular sleep phase, ORP values and between sleep phases are similar. Like any metric of sleep quality, there is considerable night-to-night variability in ORP values [156] . ORP values have also been shown to be effective in CPAP therapy in patients with OSA. ORP sleep time has also been associated with excessive wake time and deep sleep in those with OSA and/or *Periodic Limb Movement* (PLM)[157].Correlations between right and left hemisphere ORP measures (interhemispheric sleep depth consistency) may be a measure of sensitivity to negative neurocognitive effects in sleep beliefs. Those who were they had a 57% lower risk of falling compared with the lowest quartile, according to the AHI. Thus, ORP measures may subjectively predict OSA outcome. However, the relationship between cardiovascular outcomes remains untested.

8.4 Cardiopulmonary Coupling (CPC)

Thomas and others, developed an automated method for measuring CPC during sleep using a single-lead EKG signal [159] . From the continuous, single-lead electrocardiograms, the authors extracted both normal to normal sinus interpulse interval series and the corresponding respiratory signal from an electrocardiogram. Using Fourier-based methods, which the cross-correlation and potential effects of these two simultaneous signals with cardiopulmonary coupling motion during sleep of character. This method designed to generate spectrographic representations implies that eyes non rapid sleep in adults exhibits spontaneous and abrupt changes between high and low cardiopulmonary coupling regimes, including characteristic electroencephalograms in health and disease. Agreement with standard sleep staging using kappa statistics with respiratory and heart rate signatures was poor (training group 62.7%, test group 43.9%) but high with cyclic alternating pattern scoring (training group). 74%, the experimental-group was 77.3%). The authors concluded that the sleep spectrum image obtained from the data in the single-lead electrocardiograph could be used to dynamically monitor cardiopulmonary synchrony, this technique may provide a complementary method to the traditional characterization of the sleep phase characterized by visual inelasticity. The CPC derived measure is correlated with conventional metrics derived from PSG including AHI [160] . Several studies have correlated measures of CPC with outcomes including prediction of early response in patients with dementia, improved sleep on CPAP therapy, upper airway surgery, and MAD [161-164] Although these data suggest potential benefits from CPC, AHI and other available time points/ frequency analyzes (e.g. cardiovascular entropy) further investigation is needed to determine whether they add value.

8.5 Apnea-hypopnea Event Duration

The duration of the process has been quantified by Butler et al. [165] ,the authors found a significant potential association between the outcome of SHHS and the duration of respiratory events and the overall mortality rate observed in SHHS. Theoretically, brief episodes of inspiration may reflect low arousal (wake) but in addition may be a person with unstable ventilatory control (high loop gain), also respiratory events are released faster than someone with a lower loop gain. Regardless, the authors suggested that shorter respiratory times predicted mortality for both sexes. After correction for demographic factors (mean age : 63 yrs.; 52% women), apnea-hypopnea index (average, 13.8/h; SD, 15.0), smoking, and prevalence of cardiovascular disease so followed by an important all-cause mortality in individuals with a short event duration of 1.31 (1). 95% confidence interval, 1.11– 1.54) and risk levels. The authors hypothesized that individuals with micro respiratory issues may have more respiratory instability and/or increased autonomic nervous system responses that increase the risk of adverse health outcomes. Notably, however, shorter respiratory episodes are associated with lower hypoxic burden compared with longer respiratory episodes, leading to some discrepancy or complexity in the predictive value of different factors given the interest in personalized medication in OSA .

9. Current Opinion on Co-morbid Insomnia and Sleep Apnea (COMISA) Treatment

Lack et al., according to , the presence of concomitant OSA does not appear to interfere with insomnia. After an insomnia treatment program, the magnitude of improvement in sleep-wake function variables in COMISA patients was in fact comparable to that observed in patients without OSA [166] The correct treatment strategy for patients presenting with complaints of OSA and

insomnia appears to be the treatment of both disorders, although there are no clear specific guidelines for the order of treatment sequence or sequence at the time of writing .

9.1 Positive Airway Pressure Device

Continuous positive airway pressure (CPAP) is the first-line treatment for moderate-to-severe obstructive sleep apnea syndrome (OSAS) [167] . Although CPAP offers many health benefits in the treatment of OSA, it is unlikely to also improve insomnia in patients with OSA and insomnia [168] Bjornsdottir et al., showed that successful CPAP use was associated with a 50% reduction in insomnia success, but early insomnia symptoms were still common at two-year follow-up .

Patients with OSA and insomnia are less reliant on PAP than those without insomnia , as previously reported [169] . Mendes et al., investigated the effect of nocturnal respiratory support. In this study, nocturnal ventilation proved effective in the treatment of insomnia secondary to OSAS, with favourable outcomes in patients who did not meet criteria are associated with PAP.

Moreover, analysis by insomnia subtype in the same study showed that most mixed insomnia patients could overcome insomnia symptoms so despite improved apnea-hypopnea index (AHI), sleepiness scale and time [170].

9.2 Oral Appliances and Surgery

Other treatment options for OSA include the use of mandibular advancement devices (MAD) , postural training, and surgery. These therapies are often recommended based on specific features of sleep reliability (e.g., mild OSA, condition-dependent episodes, and dilated tonsils) [168] A recent review of MAD/CPAP treatment in patients with OSA concluded that, despite higher PAP on AHI, daytime sleepiness, cognitive function, reduced alertness; There was no significant difference between the two treatments for blood pressure and quality of life. Furthermore, a randomized cross-sectional study of veterans diagnosed with OSA reported higher patient preference and adherence to PAP therapy than MAD [171]. According to Guilleminault et al., this procedure significantly improved total sleep time (TST), (slow wave and rapid eye movement (REM) sleep time, sleep duration, and respiratory disturbance index (RDI) in selected patients with insomnia and mild OSA. has been improved. , AHI, minimum oxygen saturation and daytime sleepiness scores.

9.3 Cognitive-behavioural Therapy for Insomnia

Although CBTI is generally considered safe and effective in comorbid conditions, some aspects remain controversial. For example, sleep restriction has been shown to increase daytime sleepiness through longer periods of time in bed, and may improve sleep quality in individuals with insomnia associated with OSA In systematic reviews in a recent study by Bahr et al. focused on treating patients with the clinical entities of comorbid insomnia and OSA (COMISA) and used a combination of PAP and CBTi, or just separate treatments .The authors suggested that the presence of concomitant OSA did not interfere with insomnia in COMISA patients. Furthermore, insomnia in COMISA patients could be treated with CBTI [169] . The authors' overall conclusion was that both CBTI and PAP therapy are necessary even though different treatment strategies may be beneficial in different COMISA phenotypes.

9.4 Benzodiazepines

Although hypnotic pills can be used for patients with insomnia, benzodiazepine-based treatments are generally not recommended for patients with OSA [172]. Dolly et al. We tested the effects of fluorazepam on nocturnal oxygen desaturation and sleep-disordered breathing . In their double-blind, placebo-controlled, randomized trial, although the degree of desaturation increased after taking fluorazepam, the number of episodes of hypopnea and desaturation did not increase significantly. Additionally, total sleep time was significantly increased in patients treated with fluorazepam ($p = 0.04$) [173]. Similar results were reported by Camacho et al. Accomplished. A large randomized trial examining the effects of temazepam on breathing in older adults with insomnia and mild sleep apnea. In this study, no increase in the total number of events (i.e., apneas and hypopneas, RDI) was detected in older adults with mild OSA who received temazepam 15–30 mg [174]. Other authors have reported unexpected effects of drug treatment for insomnia. Hanly et al. In patients with central sleep apnea, hypnotics not only improve sleep but also reduce the frequency of apneas, possibly by decreasing alertness and increasing arterial PCCO2, thereby reducing respiratory depression. reported that it improves sleep quality without causing symptoms. As a result, the authors changed the statement "hypnotics should not be used in patients with sleep apnea" to "hypnotics may be used in patients with sleep apnea." [175]. Two years later, Barry et al., investigated the effects of triazolam (0.25 mg) on apnea duration during sleep and wakefulness response

to airway obstruction in patients with severe OSA. The authors concluded that triazolam increased the arousal threshold to airway closure, but the result was only a small increase in event duration and increased desaturation [176]. Considering the moderate effect of benzodiazepines on OSA, Ong et al., recommended that these drugs should be used with caution in COMISA patients [168].

9.5 Non-Benzodiazepine Agents

In recent years, new non-benzodiazepine sedative-hypnotics (NBSH), such as zolpidem, zaleplon, and eszopiclone, have been developed and are being studied in patients with insomnia with or without OSA. These compounds refer to non-benzodiazepine (non-BDZ) sedatives that act as BDZ receptor agonists and have generally been shown to have fewer adverse effects on the airways. Luyster et al., non-benzodiazepines have similar hypnotic and sedative effects as benzodiazepines, but some drugs, particularly those selective for the gamma-aminobutyric acid (GABA) receptor, Medications may have less muscle-relaxing effects and are therefore a more preferred treatment approach to Insomnia in OSA [177]. When evaluating the acute use of eszopiclone in patients with mild to moderate OSA, a pilot study by Rosenberg et al. found that respiratory events, total alertness, apnea duration, and hypopnea. No significant differences were found in the mean values of respiratory episodes, oxygen saturation - treated patients It is possible to determine which patients received treatment. Patients treated with eszopiclone experienced improved sleep duration and sleep efficiency, as well as decreased wake time during sleep and wake time after sleep onset [176]. Given the strong bidirectional association between OSA and insomnia and the observation that zolpidem is one of the most commonly prescribed sedative and hypnotic drugs, recent studies have shown that the drug attempts are being made to determine whether sleep-disordered breathing may affect the severity of pre-existing sleep-disordered breathing. In a study by Cirignotta et al., doses of zolpidem 20 mg above the recommended hypnotic dose increased the apnea index and oxygen desaturation, suggesting that the usual therapeutic of zolpidem should not be exceeded in the treatment of patients with OSA [178]. Berry et al., investigated zolpidem treatment during her PAP therapy in patients with OSA. Administration of 10 mg of zolpidem to 16 patients with severe OSA treated with effective levels of CPAP did not increase AHI or oxygen saturation index. There were no differences in sleep structure between zolpidem and placebo nights, except for a decrease in sleep latency and mean arousal index on zolpidem nights, indicating that zolpidem does not interfere with the effectiveness of CPAP in patients with severe OSA. It has been suggested [179]. An interesting recent meta-analysis by Nigam et al., When evaluating the effects of benzodiazepine-free sedative-hypnotics on apnea-hypopnea index, the majority of patients taking NBSH had lower baseline AHI values (mild, moderate, severe or no OSA). On the contrary, in many cases, the use of NBSH slightly improved baseline AHI compared to the placebo group [180].

9.6 Anti-Depressive Agents

Other authors investigated the effects of antidepressants prescribed to OSA patients with insomnia. Kreiger et al., evaluated the efficacy and safety of ramelteon in people with mild to moderate HER OSA. Ramelteon is a selective melatonin MT(1)/MT(2) receptor agonist for the treatment of insomnia. The potential effects of ramelteon on apnea and hypopnea events and arterial oxygen saturation in patients with OSA were investigated in a randomized, double-blind, crossover study in which this antidepressant was administered to subjects with mild sleep apnea. It was concluded that it does not worsen sleep apnea syndrome even when administered to patients mild to moderate OSA [181]. Reduced serotonergic facilitation of upper airway motor neurons during sleep has been suggested as a risk factor for upper airway obstruction in patients with OSA. Serotonin reuptake inhibitors have been shown to modestly reduce AHI during non-rapid eye movement (NREM) sleep and sleep fragmentation [182]. Curley et al., showed that 4.5 to 15 mg of mirtazapine, a mixed 5-hydroxytryptamine receptor antagonist (5-HT2/5-HT3) that promotes serotonin release in the brain, reduced AHI by half. In their study, mirtazapine was also associated with sedation and weight side effects in OSA patients [182]. An emerging theme is that a decreased respiratory arousal threshold may be involved in the development of OSA. In this context, a randomized crossover study by Smales and Malhotra [183] showed that when trazodone, one of the most commonly prescribed drugs for the treatment of insomnia, was administered to patients with OSA, alertness index and AHI was shown to be significantly reduced without worsening. Hypoxemia. Systematic reviews consistently found no difference in sleep efficiency or discontinuation rates due to adverse events between trazodone (bedtime dose range 50-150 mg) and placebo in patients diagnosed with chronic insomnia. . Trazodone was more effective in improving subjective sleep quality, but there were no differences in sleep onset latency, total sleep time, or wakefulness after sleep onset [184].

9.7 Sleep Hygiene Education

Sleep hygiene education and medication are the most commonly offered treatments for chronic insomnia disorders. Sleep hygiene education typically includes information about caffeine, alcohol, and nicotine intake, exercise, sleep environment, sleep-wake regularity, nap avoidance, and stress management [185]. A late study by Jung et al., Among the factors associated with sleep hygiene-related disorders, including those with sleep apnea, inappropriate temperature and humidity, alcohol consumption before bedtime, and emotional arousal and excitement are associated with symptoms of mild to moderate OSA. It turned out that This study supports the hypothesis that patients with mild to moderate OSA can experience symptom relief if they are taught to modify their lifestyle habits to maintain adequate conditions related to sleep hygiene. [186]

9.8 Melatonin and Herbal Therapy

A meta-analysis on the use of melatonin to treat primary sleep disorders found that sleep latency was reduced by approximately 7 minutes, total sleep time increased by 8 minutes, and 10 out of 15 showed little improvement in sleep quality. Side effects were not discussed [187]. Similarly, the use of valerian or chamomile to treat insomnia is also not supported by evidence. Of note, a systematic review found no differences in daytime function or insomnia severity between valerian or chamomile compared to placebo [188]. Melatonin may be a potential treatment option for COMISA, which is associated with circadian rhythm sleep-wake disorders [189].

10. COMISA and Other Sleep Disorders

10.1 Patients with Restless Legs Syndrome (RLS)

A sleep-related movement disorder, may exhibit characteristics characteristic of insomnia, such as sleep-disturbing habits and cognition [190], and similar data suggest that sleep apnea It has also been found in patients with the syndrome [191]. Compared to patients suffering solely from sleep apnea, patients with OSA and RLS have been shown to exhibit higher levels of insomnia-specific psychiatric symptoms, which may suggest the benefits of cognitive behavioural therapy in these populations. [192] Previous studies have shown that the arousal index, periodic leg movement index (PLM), and PLM arousal index are more pronounced in OSA and RLS patients, indicating that RLS is an independent risk factor for sleep maintenance difficulties in OSA patients. [192,193] Furthermore, CPAP therapy may affect her PLM index in OSA patients [194]. The question of whether disturbed sleep quality in these patients is caused by restless legs syndrome, OSA, or insomnia is not easily resolved. However, the fact that insomnia associated with other sleep disorders should be treated with insomnia-specific methods is an important feature of insomnia management [195].

10.2 Epilepsy and Parasomnias

There is increasing evidence that obstructive sleep apnea syndrome is associated with insomnia symptoms in epilepsy (10% of unselected adult patients with epilepsy and up to 30% of patients with drug-resistant epilepsy). Continuous positive airway pressure treatment for OSA in epilepsy improves seizure control, cognitive performance, and quality of life [196]. Parasomnias and epileptic seizures can occur together in the same person, making differential diagnosis particularly difficult. REM sleep behaviour disorder (REM sleep parasomnia) co-occurs in 12% of older patients with epilepsy and has been found to have specific patterns of association. between nocturnal frontal lobe epilepsy (NFLE) and NREM wake parasomnia [197]. People with epilepsy often complain of poor sleep and feeling unrefreshed. However, insomnia in epilepsy is poorly understood and sleep hygiene interventions in epilepsy need to be more comprehensive and consider the various pathologies that may underlie sleep disturbances in epilepsy patients [198].

10.3 Central Failure

Narcolepsy OSA is common in narcolepsy and can delay diagnosis and prevent appropriate treatment of narcolepsy. Patients with OSA should be aggressively screened for cataplexy (an important narcolepsy feature) to rule out the presence of narcolepsy. OSA and narcolepsy are associated with poor sleep quality and excessive daytime sleepiness (EDS). Treatment with CPAP usually does not improve her EDS in narcolepsy patients with OSA [199].

Although sleeping pills can be used for patients with insomnia, benzodiazepine-based treatments are generally not recommended for patients with OSA [172]. Dolly et al., We investigated the effects of fluorazepam on sleep-disordered breathing and nocturnal oxygen desaturation. In their double-blind, placebo-controlled, randomized trial, although the degree of desaturation increased

after taking fluorazepam, the number of episodes of hypopnea and desaturation did not increase significantly. Additionally, total sleep time was significantly increased in patients treated with fluorazepam (p = 0.04) [173]. Similar results were reported by Camacho et al. Accomplished. A large randomized trial examining the effects of temazepam on breathing in older adults with insomnia and mild sleep apnea. In this study, no increase in the total number of events (i.e., apneas and hypopneas, RDI) was detected in older adults with mild OSA who received temazepam 15–30 mg [174]. Other authors have reported unexpected effects of drug treatment for insomnia. Hanly et al. In patients with central sleep apnea, hypnotics not only improve sleep but also reduce the frequency of apneas, possibly by decreasing alertness and increasing arterial PCCO2, thereby reducing respiratory depression. reported that it improves sleep quality without causing symptoms. As a result, the authors changed the statement "hypnotics should not be used in patients with sleep apnea" to "hypnotics may be used in patients with sleep apnea." [175]. Two years later, Barry et al. investigated the effects of triazolam (0.25 mg) on apnea duration during sleep and wakefulness response to airway obstruction in patients with severe OSA. The authors concluded that triazolam increased the arousal threshold to airway closure, but the result was only a small increase in event duration and increased desaturation [176]. Considering the moderate effect of benzodiazepines on OSA, Ong et al. recommended that these drugs should be used with caution in COMISA patients [168].

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10.4 Circadian Rhythm Disorders

Circadian rhythm sleep-wake disorders are a group of disorders that can occur when a patient's typical sleep times are out of sync. Many people suffer from jet lag, travel across at least three time zones, or sleep phase disorders from shift work. This affects people with unconventional work schedules, resulting in lack of sleep and fatigue during waking hours. It is important to consider whether you may be experiencing another sleep disorder, such as: B. Sleep apnea syndrome may worsen and new insomnia may develop. Treatment options include CBTi with progressive circadian rhythm delay through phototherapy, exposure to natural light, and strategic use of melatonin [189].

11. Meaning of Results

OSA is the most common type of sleep apnea and is characterized by collapse of the upper airway during sleep, with repeated apneas and hypopneas and decreased oxygen saturation. As demonstrated in our retrospective observational cohort, it is associated with a number of other diseases, including heart failure, hypertension, stroke, arrhythmias, and decreased renal function [206], and may have a negative impact on long-term survival. be. A recent study [207]. At the same time, OSA may be associated with sleep disturbances, a very common comorbidity of insomnia. Both OSA and insomnia are common in the general population. Because they have some common clinical features and can exacerbate each other through mutually detrimental pathogenic mechanisms, COMISA has become a clinically relevant disease that requires an integrative and multidisciplinary approach. [208] The definitions of insomnia and OSA in the available studies vary, making it difficult to determine whether these disorders actually overlap. Symptoms of insomnia may be present in OSA patients from the beginning or may develop during treatment. In patients with insomnia who have difficulty maintaining and are less effective on CBTi or sleeping medications, evaluation for signs and symptoms of OSA is recommended [171]. This optic requires more precise phenotypic analysis of clinical and polysomnographic features. Among drug treatments, newer non-benzodiazepine drugs, such as zolpidem and eszopiclone, appear to have fewer adverse effects on the airways. A randomized trial appears to show that zolpidem does not affect the effectiveness of CPAP in patients with severe OSA [179]. Therefore, clinical judgment should be used to decide whether to initiate PAP therapy, or another appropriate option for OSA, or her CBT for insomnia, or both [168, 208]. In this regard, a recent randomized trial

demonstrated that combined treatment of COMISA patients with CBTi and CPAP more effectively improved CPAP use and insomnia symptoms than treatment with CPAP alone [209]. Treatment of insomnia and her OSA gives the best results for COMISA patients [210]. Therefore, a multidisciplinary patient-centred approach is recommended to optimize the clinical management of COMISA [211].

12. Future Prospective

Our goal the laboratory-based AHI, derived from his PSG, is considered the gold standard measure of OSA severity [212], but financial constraints and the magnitude of the problem prohibit its use at home. Reliance on sleep apnea testing is increasing. This change has been accelerated by the coronavirus pandemic, with many patients seeking the convenience and safety of at-home testing [213]. Although OSA assessed by the AHI is strongly associated with neurocognitive, metabolic, and vascular outcomes, the AHI as a single measure is not adequate to define the presence of OSA or characterize its severity. It's clear that it's not enough. This assumption is based on the fact that many patients with severely elevated AHI have no reported symptoms and that her AHI is not used alone to identify patients with cardiovascular disease who would benefit from her PAP therapy. is supported by. Therefore, we strongly support the development of new techniques to detect the occurrence of her OSA and predict its complications. Given that the underlying biology of each organ system is different, the ideal measure of OSA severity is expected to vary depending on the comorbidity of interest. Such severity metrics include:

[1] Measurement of the intensity of OSA stimulation (e.g., using measurements of gas exchange abnormalities such as hypoxic stress to account for obstructive and central apnea mechanisms)

[2] A combination of individual responses may be required. responses to stimuli (such as autonomic nervous system assessments and EEG)

[3] and individual responses to treatment (such as improved sleepiness and lower blood pressure) [214]. There are many approaches to better quantify the severity of sleep apnea. Regardless of the limitations of the AHI, as new metrics are developed, it is important that their ability to improve the AHI as a prognostic marker or predictor of response to treatment is formally tested and replicated in all populations of interest.

Several strategies have been proposed:

1.Assessment of symptom subtypes. Severity of sleepiness was considered in his 1999 AASM recommendations for classifying OSA severity. However, because there were no reproducible criteria for assessing sleepiness, this severity indicator was not retained in subsequent recommendations. However, it may be particularly important to consider an individual's symptom response to OSA treatment. Ye et al. used cluster analysis to show three distinct groups of OSA patients: a group with minimal symptoms, a group with sleep disturbances, and a group with EDS [174]. In SHHS, an increased risk of developing overall cardiovascular disease, coronary artery disease, and heart failure was observed only in the cluster characterized by excessive sleepiness [215]. Similarly, another study found an increased risk of death only in OSA patients who reported excessive sleepiness [216]. In recent clinical trials, he speculated that the failure to demonstrate reduced cardiovascular risk with PAP therapy may be due to the exclusion of sleepy patients from these trials. Therefore, sleepiness may be a marker of an individual's response to her OSA, which also reflects her susceptibility to the cardiovascular effects of OSA. This idea justifies further investigation of symptoms as a measure of OSA severity or as a measure of susceptibility to OSA complications.

2. Genetics. Genetic factors likely play an important role in these individual differences, as suggested by trait-like behaviour in individual susceptibility to sleep deprivation-induced cognitive impairment [217-219]. Although OSA has long been recognized as a complex genetic trait, research investigating the genetic causes of OSA and its endotypes has only recently begun. This situation reflects the unavailability of sleep testing in many longitudinal cohort studies. This approach is likely to help explain interindividual differences in susceptibility to OSA and its clinical outcome, and further investigation of the genetic architecture of OSA is highly recommended.

3. Blood biomarkers. Panels of biomarkers have the potential to identify causal pathways affected in OSA, thereby providing important prognostic and predictive information [220]. Kaplan-Meier survival curves across apnea-hypopnea index categories (AHI-4%). The association between OSA and mortality was 15 to 29.9 (HR 1.20, 95% CI 1.00 to 1.44) for AHI-4% and 30 (HR 1.38) for AHI-4%, adjusting for age, sex, and race. significant, 95% CI 1.08 to 1.75). Malhotra et al., oxidative stress pathways aim to provide information on OSA-related cardiovascular disease risk. Evaluation of microRNAs and exosomes has also led to

important insights in terms of both OSA biomarkers and potential therapeutic targets for the treatment of OSA complications [221-224]. In addition to such hypothesis-driven biomarker panels, hypothesis-independent methods for discovering sleep biomarkers are also becoming increasingly available. Metabolomics, lipid omics, proteomics, and gene expression profiling, enabled by advances in mass spectrometry, microarrays, and other technologies, are being investigated and have the potential to identify new biomarkers for OSA [225-229]. In theory, these technologies could lead to diagnostic tests for OSA, prognostic markers for sleepiness and other sequelae of OSA, new therapeutic targets to prevent complications of OSA, and markers that can be tracked to monitor treatment success. may be identified.

4. Machine learning. Machine learning and other hypothesis-free deep learning techniques that identify complex patterns in empirical data are gaining traction in a variety of medical applications. In addition to applications in biomarker discovery, these methods can also be applied to advanced signal processing of polysomnography and other data to identify previously unrecognized patterns and to be used in the Alternative Indicators section above. It has the potential to complement the hypothesis-based approach to identifying the described alternative indicators. Although such methods require appropriate validation and training sets, they greatly facilitate the use of big data [230-234].

5. Wearable technology. Wearable technology is becoming more prevalent and offers new opportunities to gain insight into the pathophysiological abnormalities associated with sleep and sleep disorders. For example, data from one device supports its role compared to PSG [233–235].

Ongoing studies are comparing different simple techniques for OSA diagnosis, but there is still no alternative to PSG. Wearable technology provides the ability to record multiple nights of data over extended periods of time in a cost-effective manner. Future studies should evaluate the value of these longitudinal data (with variable parameters from each device) to improve prediction of OSA-related morbidity, including cardiovascular risk. New interventions that improve AHI in OSA diagnosis and severity classification will be particularly transformative if they help capture the variability of OSA endophenotypes. This approach may enable the development of robust, adaptive, randomized clinical trials that allow detailed evaluation of patients at risk for specific complications and suitable for specific interventions. New OSA metrics should be developed with the goal of making complex measurements available to clinical practitioners, allowing them to easily translate scientific advances into practice that improves patient care.

II. Conclusion

The findings summarized in this review suggest that the association between insomnia and OSA is an important unexplored research area that needs to be deeply investigated. Recent research interests have focused on the idea of better treatments through multidisciplinary approaches and simultaneous treatment of the two diseases. Although this appears promising, additional data are needed to determine the efficacy of combination treatment in this population. Globally, it is recommended that patients with OSA be screened for comorbidities if their symptoms persist despite appropriate treatment. Another important aspect of our study is that the occurrence of OSA symptoms may be independent of the occurrence of other co-occurring sleep disorders. Given this complex comorbidity profile in patients with OSA, physicians should investigate the possibility of co-occurring other sleep disorders, diagnose them as comorbidities, and treat them accordingly to maintain sleep integrity and improve daytime It is highly recommended to improve the quality of life of people.

Conflict of Interest

All authors declare no conflicts of interest.

Author Contribution

Authors have equally participated and shared every item of the work.

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ABBREVIATIONS

AHI: Apnea- hypopnea index

PSG: Polysomnography

RIP: Respiratory inductance plethysmography

AASM: American Academy of Sleep Medicine

RERA: Respiratory event-related arousal

TST : Total sleep time

RDI: Respiratory distress index

ODI: Oxygen Desaturation Index

HSATs: Home Sleep Apnea Test

PAT: Peripheral arterial tonometry

EDS: Excessive daytime sleepiness

SHHS: Sleep Heart Health Study

WSC :Wakefulness-Sleep Cycle

QoL: Quality of life

SAQLI: Sleep Apnea Quality of Life Index

FOSQ :Functional Outcomes of Sleep Questionnaire

MVC : motor vehicle crash occurrence

CPAP: Continuous positive airway pressure

MESAM IV: A system measures arterial oxygen saturation (Sa,O2), heart rate, snoring sounds and body position, and allows both automatic and manual scoring of the recordings.

OR: Odds ratio

SAVE : Sleep Apnea Cardiovascular Endpoints

ORP : Odds ratio product

PLM*: Periodic Limb Movement*

CPC: Cardiopulmonary Coupling

MAD: Mandibular advancement device

CBTI: Cognitive therapy of insomnia

COMISA : Comorbid insomnia and OSA

RLS: Patients with restless legs syndrome

EDS: Excessive daytime sleepiness