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On the rise and fall of the AHI
A historical review and critical appraisal

"Study the past if you would define the future" - Confucius

RUNNING HEAD: Historic and critical literature review on the AHI

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Summary

The publication of '*The sleep apnea syndromes*' by Guilleminault et al. in the seventies of the previous century hallmarked the discovery of a new disease entity involving serious health consequences. Obstructive sleep apnoea (OSA) was shown to be the most important disorder among the sleep apnoea syndromes. In the course of time, it was found that the prevalence of OSA reached the proportions of a global epidemic with a major impact on public health, safety and the economy. Early on, a metric was introduced to gauge the seriousness of OSA, based on the objective measurement of respiratory events during nocturnal sleep. The apnoea index (AI) and later on the apnoea-hypopnoea index (AHI), being the total count of overnight respiratory events divided by the total sleep time in hours, were embraced as principle measures to establish the diagnosis of OSA and to rate its severity.

The current review summarises the historical evolution of the AHI, which has been subject to many changes and has been criticised for not capturing relevant clinical features of OSA. In fact, the application of the AHI as a continuous exposure variable is based on assumptions that it represents a disease state of OSA and that evocative clinical manifestations are invariably caused by OSA if the AHI is above diagnostic threshold. A critical appraisal of the extensive literature shows that both assumptions are invalid. This conclusion prompts a reconsideration of the role of the AHI as the prime diagnostic metric of clinically relevant OSA.

Key words: Sleep apnoea, apnoea-hypopnoea index, diagnosis, severity rating, bias, entanglement.

Introduction

In the second half of the previous century, medical attention was drawn to a new syndrome in which disturbances of sleep and breathing seemed to play an instrumental role. It had become evident from case reports that symptoms and signs such as hypersomnolence, obesity, respiratory failure and loud snoring could cluster and together constitute a distinctive but yet puzzling clinical picture. While other cases were published previously, and some of them already mentioned breathing pauses during sleep, a case report by Burwell et al. in 1958 was pivotal in describing the association between morbid obesity, hypersomnolence and respiratory failure. These authors gave a meticulous account of relevant clinical observations and coined the name 'Pickwickian Syndrome' to illustrate the striking resemblance between the patient's phenotype and the appearance of a character in a novel by Charles Dickens, i.e. '*The posthumous papers of the Pickwick club*' (Burwell, Robin, Whaley, & Bickelmann, 1956). While Burwell et al. did not mention episodes of breathing stoppage during sleep, they documented that most of the clinical characteristics, including hypersomnolence and hypercapnia, would disappear following substantial loss of body weight, and the Pickwickian syndrome, as described, likely represented a mixed syndrome of obesity hypoventilation and obstructive sleep apnoea.

Subsequent research on the Pickwickian syndrome involved respiratory and electro-encephalographic recording of sleep either at night or during daytime naps. Several investigators observed loud snoring and long interrupted breathing episodes during sleep in these obese patients but failed to attribute the causal role of these apnoeas in the pathogenesis of the clinical syndrome. It was not until the application of tracheostomy, and the striking improvement of both hypersomnolence and respiratory blood gas exchange following this intervention, that the fundamental significance of sleep apnoea became evident. The scientific journey of discovering sleep apnoea as a salient causative agent in the obesity-hypoventilation syndrome has been described elsewhere (Lavie, 2008).

The late Christian Guilleminault and his colleagues can be credited in establishing sleep apnoea as a mediator of disease in its own right. Their research group at Stanford University

was the first to point out that sleep apnoea, even in the absence of obesity, is not only associated with hypersomnolence but also with a wide array of daytime and night-time clinical findings. In their publication on 'The sleep apnea syndromes' in 1976, they wrote a detailed report of the constituting symptoms, signs and laboratory findings (Guilleminault, Tilkian, & Dement, 1976). Using strain gauge and thermistor recording techniques, these investigators were able to continuously monitor respiratory disturbances at night. Apnoeas were defined as a cessation of airflow at the nose and mouth lasting at least 10 sec. A sleep apnoea syndrome was diagnosed if during seven hours of nocturnal sleep at least 30 apneic episodes were observed. The publication by Guilleminault et al. has changed the face of medicine ever since, because formal proof was given that previously unexplained medical conditions actually originate in respiratory problems occurring during nocturnal sleep. It was the very start of the discovery of a global epidemic that accounts for a massive impact on public health, safety and the economy.

This review consists of two parts: a historical reconstruction of the creation and evolution of the AHI, followed by a critical appraisal of its significance in clinical medicine and research. The narrative not only addresses historical facts, but also the assumptions and evidence that underpin the AHI as a metric. The scope of this work is sleep apnoea in adults – the literature on children was not consulted. Papers were retrieved in which the AHI is used as a predictor variable (aka exposure variable) for the diagnosis and severity rating of obstructive sleep apnoea (OSA). Publications of special interest include those that assess correlations between AHI and clinical outcomes, as well as AHI cut-offs for defining disease severity. Various types of publications, e.g. clinical trials, reviews, editorials, guidelines and book chapters were selected based on relevance for the topic. Cross-references of publications were checked in a retrograde and anterograde way using PubMed and Web of Science. While publications may be missing, the authors believe that the current set of references largely covers the state of knowledge on the topic.

Part 1: Historical review

The present manuscript aims at providing insight into the history of the sleep apnoea syndromes as a clinical concept and into the use of the apnoea-hypopnoea index (AHI) as a key measure of disease severity. To this end, we have targeted publications that appeared since the naming of 'The sleep apnea syndromes' in 1976 until present. Publications are grouped by decade. The seventies and eighties of the previous century have been merged because the number of papers is small. **Table 1** presents a timeline with a selection of key publications over the years.

Publications from 1970 till 1989

Two years after the publication of their seminal paper describing 'The sleep apnea syndromes' (SAS), Guilleminault and Dement edited a book with the same title, reporting on the outcomes of a workshop held in July 1977 among international researchers in the field of sleep-disordered breathing (SDB). In the first chapter, Guilleminault et al. recapitulated the salient clinical features of SAS and for the first time introduced the term 'apnea index' (AI) (Guilleminault, van den Hoed, & Mitler, 1978). This measure denotes the number of apnoeic events per hour of sleep. The authors believed (literally: 'felt') that the AI better represented the seriousness of the disorder than the total amount of breathing stoppages. However, concerning clinical decision making, the reader was left in uncertainty regarding the potential superiority of the index over the absolute number of events, as formal comparative analyses were not carried out due to a lack of data. Nevertheless, a reference value was provided for the AI to differentiate disease from normalcy. A cut-off value of at least 5 apnoeic events/h (i.e. at least 30 apnoeic episodes in an overnight sleep period of seven hours) was derived from comparing a limited cohort of SAS patients with 20 control subjects. Thus, a metric implicitly conceptualizing SAS and its severity was created. This concept subsequently gained wide acceptance but was not reproduced or validated ever since.

Early on, both the AI and the absolute count of apnoeas were utilised for severity rating in epidemiological investigations. Peter et al. studied the occurrence of sleep apnoea activity

(SAA) in a sample from the community and samples of four different clinical populations (Peter et al., 1986). Rather than to use a cut-off score of 5 apnoeas/h, they defined clinically relevant SAA as an apnoea index of > 10/h and > 100 apnoea episodes per night as significantly high SAA. A very high prevalence of clinically relevant SAA was demonstrated in different outpatient groups (12.5 – 55%) and in individuals from the community (10%). Significantly high SAA was prevalent to a lesser degree in the outpatient groups (7 – 35%) and in members from the community (6%). The authors speculated that SAA might be a risk factor or a comorbidity of internal disturbances and observed the highest prevalence of sleep apnoea in the group of outpatients with congestive heart failure. This study was remarkable not only for showing unexpectedly high prevalence figures of sleep apnoea in different populations, but also for using two metrics in defining the severity of SAA.

At an early stage, criticisms arose regarding the application of the relative or absolute count of apnoeic events for the purpose of diagnosing SAS. There was a concern that these counts would inappropriately reduce the varied clinical picture of SAS – both in the number and type of events as well as in symptom scores – into one figure. It was anticipated that the use of the AI would lead to overdiagnosis of SAS in certain patient populations. Block et al. identified hypopnoeas and oxygen desaturation events in addition to apnoeas in asymptomatic male subjects. However, no hypopnoeas and no desaturation events were observed in females. Because an elevated number of respiratory events was found in some men without associated symptoms, the authors concluded that separation of SAS from normalcy may be spurious when using arbitrary AI cut-off values (Block, Boysen, Wynne, & Hunt, 1979). In another study by Berry et al., it was shown that AI increases with age and that an increased AI does not necessarily reflect clinically relevant disease in the elderly. This observation, which was replicated in several other studies, indicated that an AI > 5/h implies high false positive rates and does not reliably predict increased health risk or somnolence in aging subjects (Berry, Webb, & Block, 1984). Moreover, doubt was cast on the AI as a measure of clinical severity for sleep apnoea. It was recommended to evaluate the predictive validity of AI cut-off scores in future research. This note of caution was however ignored in subsequent clinical investigations. In fact, AI and later AHI have become established as surrogate markers for disease severity over the years.

The AI was also criticized for not capturing the heterogeneity of SDB in several early publications. Philipson commented on the first chapter of the book on SAS that the nature of respiratory events, their distribution among sleep states, and most importantly, their effects on symptoms vary considerably among patients (Guilleminault et al., 1978). The contraction of all breathing disturbances observed during an overnight sleep study into one term, "apnoea index", was deemed inappropriate (Hudgel, 1986). The AI only represents complete breathing stops whereas other – non-apnoeic – breathing disturbances complete the picture. Although hypopnoeas were described prior to the 1976 and 1978 publications by Guilleminault, and the term ‘apnoea-hypopnoea index’ (AHI) was already mentioned in the literature (Smallwood, Vitiello, Giblin, & Prinz, 1983), Gould et al. focused specific attention on the relevance of these particular respiratory events (Gould et al., 1988). They claimed that hypopnoeas were important because of the association with symptoms as seen in the "sleep apnoea syndrome", that may appear in the total absence of any apnoeas.

By the end of the eighties, the AI was embraced as a measure of the SAS by some investigators, while others still preferred the absolute count of events as a predictor of disease severity. Some investigators had already adopted the AHI, although the assessment of hypopnoeic events was still controversial. Also, the duration of apnoeic events was considered but not further quantified. Different cut-off scores were used. Intuitively, AI or AHI were assumed to be predictive for the importance of the clinical complaints, but validation was still to be carried out (Guilleminault, 1989). Already, doubts were expressed about the AI or AHI as the single metric of disease severity.

Publications from 1990 till 1999

The first edition of the International Classification of Sleep Disorders (ICSD) was published in 1990 by the American Sleep Disorders Association (ASDA, 1990). The diagnostic criterion for obstructive sleep apnoea syndrome (OSAS) did not include any count of respiratory events nor A(H)I, but only a qualitative description: 'frequent episodes of obstructed breathing'. The severity criterion was primarily based on the seriousness of symptoms, which was assumed would be reflected in the polysomnography (PSG) findings.

In 1993, Young et al. published the results of a large systematic survey on the occurrence of SDB among adults in the middle-aged work force (Young et al., 1993). The estimated prevalence of SDB, defined as an AHI ≥ 5/h, was found to be 24% in men and 9% in women. Based on the combination of hypersomnolence and SDB, it was estimated that 2% of women and 4% of men meet the minimal diagnostic criteria for SAS. While the study by Young et al. was widely cited with respect to the prevalence figures of SAS, it was largely ignored that in the vast majority of the population SDB was not associated with the characteristic symptom of hypersomnolence. Moreover, the likelihood of co-occurrence of hypersomnolence and SDB by mere coincidence was not addressed.

Early studies seeking to find a correlation between the AHI (or other PSG variables such as the arousal index) and severity scores of relevant clinical features such as hypersomnolence were disappointingly negative. This was the case for subjective sleepiness assessed by the Epworth Sleepiness Scale (ESS) (Kingshott, Sime, Engleman, & Douglas, 1995) as well as objective sleepiness measured by the multiple sleep latency test (MSLT) (Kingshott, Engleman, Deary, & Douglas, 1998). Although the correlations of some PSG variables with indices of daytime function were statistically significant, the correlation coefficients were very weak and in no case more than 12% of the observed variance was explained by these PSG variables. While these studies provided preliminary evidence that the AHI may be inadequate to capture disease severity, they did not lead to targeted studies further exploring the validity of this measure.

In a study seeking to identify clinical predictors of OSA (defined by an AHI ≥ 15/h), Deegan et al. found that prediction was not dependent on single factors (Deegan & McNicholas, 1996). However, by combining clinical features and oximetry data, approximately one third of patients could be confidently designated as having OSA. For the remaining two thirds, formal sleep studies would be required to reach a confident diagnosis of OSA.

Opinion papers started to surface pointing at the methodological issues surrounding the measurement of the AHI. In particular, the recording and scoring of hypopnoeas seemed enigmatic (Moser, Phillips, Berry, & Harbison, 1994; Redline & Sanders, 1997, 1999).

Furthermore, no clear cut ‘dose-response relationship’ had been demonstrated between the number of respiratory events and the occurrence of relevant clinical consequences.

In 1993, Guilleminault et al. described a subtype of obstructive SDB with features of sleep apnoea, but with a normal index of apnoeic and hypopnoeic events (Guilleminault, Stoohs, Clerk, Cetel, & Maistros, 1993). In 48 patients with hypersomnolence but without OSAS according to prevailing definitions, the application of oesophageal manometry and pneumotachometry demonstrated distinct respiratory events characterised by inspiratory flow limitation, an abnormal increase in respiratory effort and a cortical arousal. Such an event was called a ‘respiratory effort-related arousal’ (RERA). This OSA-like condition with normal AHI but with an elevated amount of RERAs was called ‘upper airway resistance syndrome’ (UARS). Symptoms of UARS proved responsive to continuous positive airway pressure (CPAP) therapy as for SAS (Guilleminault et al., 1993).

The relevance of UARS and the distinction between UARS and OSAS was subsequently criticised. In the nineties it was customary to use thermal sensors for recording ventilation. This technique, however, was rather insensitive to show reduced airflow. Yet, OSAS and UARS were very similar in terms of clinical picture and total amount of respiratory events (Loube & Andrada, 1999). With the introduction of nasal cannula pressure transducers, additional non-apnoeic events were recognized that were characterised by flow limitation. By applying this highly sensitive nasal flow monitoring, events that were previously missed by thermistors or thermocouples became apparent (Norman, Ahmed, Walsleben, & Rapoport, 1997). By the same token, previously scored RERAs would thereafter qualify as hypopnoeas. In later years, the application of nasal cannula pressure transducers became standard practice in clinical PSG. Although the distinction from obstructive hypopnoea would fade, and the total count of RERAs found in a sleep study would basically depend on the hypopnea definition used, the term ‘RERA’ had become firmly established.

A new framework for syndrome definition and measurement techniques was published by an American Academy of Sleep Medicine (AASM) task force in 1999 (AASM, 1999). This paper, often referred to as the ‘Chicago criteria’, envisaged to offer a standardised approach for clinical research in SDB, but was explicitly not intended to serve as a guideline for clinical

practice. The authors disclosed that evidence was not sufficient to corroborate several statements and recommendations in their paper. A classification for disease severity was formally introduced. While it was acknowledged that no data was available to indicate an appropriate distinction between mild and moderate degrees of obstructed breathing events during sleep, it was approved by consensus that an AHI ≥ 15/h would represent 'moderate disease'. This value is approximately in the middle between an AHI ≥ 5/h (discriminating between 'no disease' and 'mild disease') and an AHI ≥ 30/h representing 'severe disease'. The latter was derived from the Wisconsin Sleep Cohort data that showed an increased risk of systemic hypertension that becomes substantial at an AHI of approximately 30/h (Young et al., 1997). The cut-off for severe OSA was rated as 'level 2 evidence' in the Chicago criteria. The attribution of this evidence label was obviously inaccurate because level 2 signified evidence derived from prospective cohort studies, whereas the referenced study was cross-sectional at the time of publication.

The Chicago criteria are also noteworthy for having introduced new standards in the definition and scoring of respiratory events. While in previous literature conservative measures of hypopnoeas were used, the definition of hypopnoeas was now substantially broadened by introducing alternative measures of oro-nasal flow. In physics and other domains of science, the introduction of a new metric necessitates redefinition or recalibration of the measurement units. Yet, with the new classification of respiratory events, the cut-off for presence of disease (AHI ≥ 5/h) and the severity thresholds remained unchanged. This change in methodology would prove to hamper the future development of reliable benchmarks in determining the presence or absence of sleep apnoea as a disease and in gauging its severity (see below).

In summary, the nineties were remarkable for further characterisation of non-apnoeic respiratory events, although the methodological aspects of defining these events as well as their clinical relevance remained controversial. The first large scale epidemiological and clinical studies were performed and OSA, defined by an AHI ≥ 5/h, proved highly prevalent in the general population. By the end of the decade, the AASM had published new criteria for syndrome definition of sleep apnoea and measurement techniques in clinical research. These

criteria would subsequently shape the future not only of sleep apnoea research, but also of clinical practice.

Publications from 2000 till 2009

While the AHI became widely established as the principle predictor variable for OSA in the years after 2000, it became clear that different approaches for measuring the various respiratory events may contribute to substantial variability in identification and classification of the disorder (Redline et al., 2000). Especially the variant definitions of hypopnoea appeared to affect the magnitude of the AHI. Ruehland and colleagues calculated the AHI according to three standard hypopnoea definitions published by the AASM (Ruehland et al., 2009). These definitions were derived from the Chicago criteria published in 1999 (see above) and from the Manual for Scoring of Sleep and Associated Events published in 2007 (Iber, Ancoli-Israel, Chesson, & Quan, 2007b). The latter provided two separate definitions of hypopnoea, i.e. a 'recommended (Rec)' and an 'alternative (Alt)' version (see below). The resulting AHI figures, named AHI(Chicago), AHI(Rec) and AHI(Alt), varied considerably. The median AHI(Rec) was approximately 30% of the median AHI(Chicago), whereas the median AHI(Alt), was approximately 60% of the AHI(Chicago). Cut-off points for severity classification of OSA were similarly affected. Roughly speaking, there was a two- to threefold difference in OSA severity when the most liberal definition – AHI(Chicago) – was compared with the strictest definition – AHI(Rec). It was contended that failure to adjust cut-off points for the new criteria would result in approximately 40% of patients previously classified as positive for OSA using AHI(Chicago) being negative using AHI(Rec) and 25% being negative using AHI(Alt). However, the obvious implication of redefining cut-off points in line with changing metrics was not proposed by the AASM (**Figure 1**).

Scepticism about increasing precision in sleep studies was raised, as it was presumed that this would not necessarily lead to a greater precision in definition and management of the disease (Stradling & Davies, 2004). The importance of CPAP responsiveness as a potential diagnostic feature was suggested, because the AHI by itself proved to be a poor predictor of symptomatic improvement with CPAP therapy (Kingshott et al., 2000). The concept of

therapeutic efficacy was embraced by the American Centers for Medicare & Medicaid Services (CMS) as they favoured to de-emphasize diagnostic accuracy in lieu of strategies more apt to predict favourable outcomes for treatment of OSA with CPAP (Chediak, 2008). In fact, CMS changed their prior procedure to only accept diagnostic AHI results derived from full PSG. As of 2007, it was accepted that home sleep apnoea testing (HSAT) with respiratory but without neurophysiological monitoring could equally produce reliable diagnostic results for therapeutic decision making regarding OSA (Collop et al., 2007). This change in policy had a high impact on OSA health care in the USA, as it paved the way for HSAT to become a predominant part of standard practice.

Two prospective observational studies demonstrated that severe OSA (AHI ≥ 30/h) (Marin, Carrizo, Vicente, & Agusti, 2005) and moderate to severe OSA (AHI ≥ 15/h) (Buchner, Sanner, Borgel, & Rump, 2007) increase the risk of fatal and non-fatal cardiovascular events. It was shown that CPAP treatment reduced this risk. Because of the observational design, it was not possible to conclude from these investigations whether and to what extent OSA played a causal role in the natural course of the cardiovascular comorbidities. Formal proof would have required evidence from randomized and controlled interventional trials. Such studies were not available at that time but were to be carried out in the next decade.

In 2005, The AASM published the second edition of the International Classification of Sleep Disorders (ICSD-2)(AASM, 2005). The new version differed from the previous one in that – for the first time – AHI cut-off points were introduced for the definition of OSA. The cut-off points were retrieved from the previously mentioned Chicago criteria. However, this reference was not appropriate as the Chicago criteria were explicitly intended to be a resource for research and were not suitable for making disease classifications or clinical guidelines (AASM, 1999). It was stipulated in the ICSD-2 that the UARS is subsumed under OSA and should not be considered a separate clinical entity.

The first Manual for the Scoring of Sleep and Associated Events was published by the AASM in 2007 (Iber, Ancoli-Israel, Chesson, & Quan, 2007a). Formal guidelines for scoring of PSG had been long awaited and were much needed with the advent of digital sleep recording technology. Before the turn of the century, sleep studies had been mainly recorded on paper.

This procedure was exceedingly time and resource consuming. While cumbersome, this technique was apt to assess the AI and later on the AHI for the very severe patients that were seen early on. The digitisation of PSG opened up a vista for new analytic methods and possibly new insights into the nature of various sleep disorders, including OSA. However, many possibilities offered by modern technology were not taken. For example, the AASM manual required that digital filtering be used on raw signals to emulate the effects of analogue filters on paper recordings. Yet, analysis of unmodulated data could have produced different results that might have advanced the field at an early stage.

In the Respiratory Rules section of this scoring manual, it was acknowledged that the evidence for making rules to score respiratory events was scarce and that most of the conclusions were based on consensus (Iber et al., 2007b). As mentioned above, two definitions of hypopnoea were provided. The 'recommended' definition required a 30% or greater drop in flow for at least 10 seconds associated with ≥ 4% oxygen desaturation, whereas the 'alternative' definition involved a drop in flow ≥ 50% for at least 10 seconds associated with a ≥ 3% oxygen desaturation or an arousal. Obviously, the first definition resulted in much lower AHI values. It appeared that the idiosyncrasy of adopting two distinct definitions was in part determined by prevailing health insurance policies in the United States, as at that time the CMS only accepted the recommended definition for reimbursement of CPAP therapy (R. B. Berry et al., 2012). Thus, the first manual for scoring of sleep and associated events was a practical guideline inspired by consensus and prevailing rules in the USA, rather than an evidence-based document.

Finally, the AASM published a clinical guideline for the evaluation, management and long-term care of OSA in adults (Epstein et al., 2009). For evidence regarding the definition of OSA, a reference was made to ICSD-2. Since the ICSD-2 referred to the Chicago criteria, no additional evidence was brought forward for using the AHI in the diagnosis and severity rating of OSA.

At the end of the first decade of the 21st century, efforts had been made to standardise the scoring of sleep and respiratory events, clearly with the intention to reduce inaccuracy due to intra- and inter-observer variability. However, this endeavour was largely offset by

accepting various scoring criteria of hypopnoea, and also by introducing different recording methods without changing the disease cut-offs. HSAT, while less accurate than conventional PSG, was officially accepted as a valid means of assessing the AHI in the USA. Disparate results from these two measurement techniques would fuel further controversy in the following decade.

Publications from 2010 till present

Contemporary research has confirmed that the AHI, even if correlated with relevant disease outcomes in groups of OSA patients, is of limited clinical relevance. In the last decade, novel studies have been carried out focussing on systemic hypertension, and on clinical as well as pathophysiological phenotyping.

Earlier investigations have shown that the AHI and other indices of sleep-related respiratory disturbance may significantly correlate with figures of prevalent hypertension. Grote et al. as well as Lavie et al. have studied this association in large clinical OSA cohorts (Grote et al., 1999; Lavie, Herer, & Hoffstein, 2000). While using different methods for sleep testing, i.e. HSAT versus conventional PSG, both investigational groups found comparable dose-response relationships between respiratory event indices and odds for systemic hypertension. In a more recent study by Tkacova et al., data from the European Sleep Apnoea Database (ESADA) were mined to evaluate cardiovascular features associated with OSA (Tkacova et al., 2014). Multiple regression analysis was applied to evaluate relevant relationships. When both the AHI and the oxygen desaturation index (ODI) were included in the same statistical model, the ODI was, whereas the AHI was not, independently associated with prevalent hypertension in the cohort of OSA patients. The authors contended that the ODI provides a solid reflection of the degree of intermittent hypoxaemia during sleep. In contrast, the AHI is a more complex measure also reflecting respiratory effort and arousal from sleep, and therefore susceptible to variability in the clinical setting. So, evidence is accumulating that the oxygen desaturation aspect of respiratory events is more important regarding the causation of systemic hypertension than the mere count of events by itself. This premise is also congruent with previous observations in the general population that hypopnoeas scored in accordance with

an oxygen desaturation of at least 4% are independently associated with cardiovascular disease, whereas no such association can be detected when hypopnoeas are defined by milder desaturations or arousals (Punjabi, Newman, Young, Resnick, & Sanders, 2008). The relevance of ODI versus AHI as indicators of cardiovascular risk is further discussed in the second part of this review.

Lipford et al. examined the relationship between the AHI and subjective sleepiness, assessed by the ESS, to find that the ESS is not strongly correlated with SDB in both men and women (Lipford et al., 2019). While no reference was made to the seminal work published by the Edinburgh group in the nineties (Kingshott et al., 1995), these new results virtually replicated the earlier findings by demonstrating huge scatter of the data and very low R-square regression indices. As such, this investigation failed to further elucidate the enigmatic relationship between AHI and subjective sleepiness.

It is known for long that clinical manifestations vary among OSA patients. Some of them complain mainly about nocturnal sleep disturbances, while others are particularly troubled by daytime symptoms such as hypersomnolence. Yet others have no or only minimal symptoms. OSA proves to be a heterogeneous disorder composed by several phenotypes. It could be expected that the AHI may vary among subtypes and that – intuitively – hypersomnolence would be most prominent in the upper AHI range. Such anticipations have been disproved in recent research. Using a cluster analysis model it was found that the AHI has no discriminatory power to differentiate clinical subtypes from one another (Keenan et al., 2018). Keenan et al. replicated and expanded earlier findings in 215 Icelandic OSA patients in whom cluster analysis had revealed three distinct groups, characterized by disturbed sleep, minimal symptoms, and excessive sleepiness (Ye et al., 2014). They showed that these clusters could be generalized to a large sample of OSA patients from other countries. The three clusters had similar average AHI values in both the Icelandic and the international samples (on average between 40 and 50/h), suggesting that clinical subtypes could not be differentiated by respiratory event frequency. This would indicate that the AHI offers no added value to the characterisation of OSA stratified by symptom scores.

Although essential characteristics of sleep-related respiratory pathophysiology have been described a long time ago (Phillipson, 1978), results of new investigational work have recently been published. In addition to clinical phenotypes, pathophysiological causes of sleep-related respiratory disturbances are also variable among OSA patients (Eckert, White, Jordan, Malhotra, & Wellman, 2013). Several factors play a role, including an anatomical feature (passive critical closing pressure of the upper airway [Pcrit]) and non-anatomical traits (genioglossus muscle responsiveness, arousal threshold, and respiratory control stability – loop gain). For any given AHI value, the relative contribution of each of these factors can vary markedly. AHI is not an intrinsic marker of the pathophysiological profile of OSA.

The second version of the Manual for the Scoring of Sleep and Associated Events was published by the AASM in 2012 (R.B. Berry et al., 2012a). In this edition, the duplication of the hypopnoea definitions was undone. The new hypopnea definition matched the old 'alternative' version, with the exception that the required drop in the flow signal was reduced from ≥50% to ≥30% (R.B. Berry et al., 2012b). The editorial task force of the manual concluded in a companion paper that scoring of RERAs remained optional, as in the first version. By consensus, the term 'respiratory disturbance index' (RDI) was assigned to the sum of the AHI and RERA index (R. B. Berry et al., 2012). It was acknowledged that the literature on the RDI as a distinct metric had been very confusing at that point. Even before the introduction of RERAs, the RDI had often been used interchangeably for the AHI in many journal articles. For instance, publications produced from the Sleep Heart Health Study cohort had used RDI instead of AHI but still defined it as the number of apnoeas and hypopnoeas per hour of sleep (Boland et al., 2002). This semantic confusion, which also biased scoring and CPAP titration procedures, was later commented on in a historical review (Krakow, Krakow, Ulibarri, & McIver, 2014).

The observation that variant definitions of respiratory events strongly affect the resulting AHI, has been confirmed in recent publications. The effects of applying different scoring methods on relevant outcomes have been investigated in several studies (Arnardottir, Verbraecken, et al., 2016; Duce, Milosavljevic, & Hukins, 2015; Hirotsu et al., 2019; Ho, Crainiceanu, Punjabi, Redline, & Gottlieb, 2015; Jung, Rhee, Al-Dilaijan, Kim, & Min, 2019; Mansukhani, Kolla, Wang, & Morgenthaler, 2019; Won, Qin, Selim, & Yaggi, 2018). The use of calibration models (Ho et

al., 2015) and of uniform standards (Arnardottir, Verbraecken, et al., 2016) for the AHI has been advocated. Given the potential implications regarding cause-consequence relationships between OSA and cardiovascular morbidity (Won et al., 2018), prevalence figures (Hirotsu et al., 2019) as well as surgical outcomes (Jung et al., 2019), the need for a consistent hypopnoea definition has again been emphasized.

AHI as an important measure of OSA is not only hampered by complexity in scoring methods, but also by the use of surrogate measures that may compromise the precision of the test results. For instance, peripheral arterial tonometry (PAT), while gauging pulse, oxygen saturation and movement, does not monitor airflow or respiratory effort. Yet, devices based on this technology yield respiratory index values that seem to generally correlate well with and are potential substitutes for the AHI assessed by standard PSG (Weimin et al., 2013). Even though the test results of both systems would perfectly match, the term 'AHI' is inappropriate when derived from non-PSG devices, as the assessment technique does not comply with conventional recording and scoring prescriptions. The same argument holds for CPAP devices used to treat OSA. While these machines monitor airflow constantly, they do not record respiratory effort, arousals or oxygen desaturations. Certainly, nice correlations have been shown between reports from CPAP devices and standard PSG recorders regarding indices of respiratory disturbance (Li et al., 2015; Ueno et al., 2010), but these findings offer by no means any proxy for using the AHI indifferently. Finally, it is acknowledged in recent literature that standard PSG and HSAT yield different AHI values (because not only the scoring of hypopnoeas is different, but also because the former has the *total sleep time* in the denominator, whereas the latter figures the *total recording time*) (Escourrou et al., 2015). The AASM has suggested to use the term 'respiratory event index' (REI) instead of AHI when this measure is assessed by HSAT devices that lack an EEG montage for recording sleep (Collop et al., 2011; Kapur et al., 2017).

Ambiguity persists in the last decade as to the relationship between OSA and the AHI (Punjabi, 2016; Rapoport, 2016). It is still presumed that an AHI above cut-off essentially implies the presence of a clinically relevant disorder, regardless of any association with symptoms (Collop et al., 2011). Furthermore, the presence of comorbid disorders is implied in the clinical picture of OSA, especially at the severe end of the spectrum. The third edition of the International

Classification of Sleep Disorders (ICSD-3) has further expanded on OSA as a disease model, now including mental, metabolic and cardiovascular comorbidities as intrinsic components of the disorder (AASM, 2014). While the literature lends some support to the validity of the comorbidity concept as described in the ICSD-3, there is still a lack of evidence to support the distinction between severity categories. No additional arguments for severity classification of OSA have been brought forward since the publication of the Chicago criteria. Despite this knowledge gap, the ICSD-3 has been quoted as a reference for OSA severity rating in the most recent clinical guideline on diagnostic testing of OSA published by the AASM (Kapur et al., 2017).

Two recent European epidemiologic studies have demonstrated that the prevalence of OSA (defined as an AHI ≥ 15/h) is extraordinarily high in the general population (Arnardottir, Bjornsdottir, Olafsdottir, Benediktsdottir, & Gislason, 2016; Heinzer et al., 2015). Heinzer et al. performed demographic research in the community of Lausanne, Switzerland (the HypnoLaus study) (Heinzer et al., 2015). The prevalence of OSA in their population-based sample was 23.4% (95% CI 20.9-26.0) in women and 49.7% (46.6-52.8) in men, assessed with PSG studies and using the AASM 2012 hypopnoea scoring criteria requiring ≥3% desaturation or arousals (R.B. Berry et al., 2012b). It was suggested that this high rate might be attributable to the increased sensitivity of current recording techniques and scoring criteria. Arnardottir et al. found prevalence rates of 24.1% for mild OSA (AHI 5-14.9/h), 12.5% for moderate OSA (AHI 15-29.9/h), and 2.9% for severe OSA (AHI ≥ 30/h) in the Icelandic population (Arnardottir, Bjornsdottir, et al., 2016) using HSAT methodology and the stricter 2007 AASM hypopnea scoring requiring ≥4% desaturations (Iber et al., 2007b). In addition, 3.6% were already diagnosed and receiving OSA treatment. However, no significant relationship was found between AHI and subjective sleepiness or clinical symptoms. Both studies were remarkable for the finding that in only a small minority of subjects, identified with an AHI ≥ 15/h, any relevant symptoms such as excessive sleepiness could be demonstrated.

The prevalence of OSA in the HypnoLaus cohort was additionally assessed using to the AASM criteria of an AHI ≥ 5/h plus symptoms and comorbidities (Heinzer, Marti-Soler, & Haba-Rubio, 2016). The estimated prevalence was 79.2% in men and 54.3% in women. These implausible results demonstrated that the description of OSA as determined by the ICSD-3 is not tenable.

The astronomical prevalence rate (Benjafield et al., 2019) that is associated with the current definition of OSA may jeopardise the clinical relevance of the disorder in the eyes of patients, the medical community as well as the health care insurers. Although the AASM would recommend to treat subjects without any symptoms or signs but with an AHI ≥ 15/h, because they would suffer from an implied disorder, the US Preventive Services Task Force recently advised not to screen for OSA in asymptomatic adults (Bibbins-Domingo et al., 2017). This recommendation was based on insufficient current evidence to assess the balance of benefits and harms with respect to such screening procedure. Moreover, subjects identified with OSA have shown scepticism towards this diagnosis and its therapeutic implications because of an inherent aspect of improper medicalisation (Zarhin, 2015).

Although outcomes depended in part on compliance to treatment, and compliance was relatively low, three recent major randomised controlled trials found no significant effects of CPAP therapy on the incidence of cardiovascular complications in non-sleepy OSA patients (McEvoy et al., 2016; Peker et al., 2016; Sanchez-de-la-Torre et al., 2019). Neither was the incidence of cardiovascular events increased in the untreated control group of OSA patients in the latter study. In addition, two recent meta-analyses on cardiovascular outcomes of CPAP treatment in OSA patients showed overall negative results (Abuzaid et al., 2017; Yu et al., 2017). Certainly, cardiovascular outcomes may have been influenced by common confounders such as obesity, lifestyle and healthy adherer's behaviour, but no attention was given to the potential role of the AHI as a flawed predictor of disease severity. The fact that the inclusion of subjects was based on an AHI ≥ 15/h as the major selection criterion may explain to some extent the absence of beneficial treatment outcomes. As the AHI may not be a real marker of clinical disease, a substantial number of false-positively labelled OSA patients may have been included, thereby confounding compliance to CPAP treatment and blurring its clinical effects. Indeed, any relevant therapeutic effect in the subgroup of patients with real OSA disease will be masked by the lack of effect in the false-positive subgroup.

Conversely, treatment responsive OSA patients with an AHI < 15/h may be wrongly excluded from participation or may be included in control groups. A recent randomised controlled trial on therapeutic effects of CPAP showed robust improvements of quality of life indices in mild OSA (Wimms et al., 2019). CPAP would have been denied to these subjects in standard

practice, because an AHI < 15/h commonly constitutes an exclusion criterion. Adherence to therapy was high in the CPAP treatment arm and 81% of patients randomly assigned to this group elected to continue CPAP treatment after completion of the three months lasting trial. So, the evidence grows that CPAP may be an appropriate treatment option for symptomatic OSA patients, even at the lower end of the AHI spectrum (McNicholas, 2019). By extension, low AHI values may prove to be associated with relevant clinical outcomes. A recent analysis using data from the ESADA cohort showed that the AHI in the range of 5 to 15/h was significantly associated with prevalent hypertension (Bouloukaki et al., 2020). This finding indicates that even minor exposure to obstructive respiratory events may entail health risks in susceptible individuals.

Observations from the last decade on OSA and the use of the AHI are thus remarkable for increasing complexity and diversity regarding medical terminology, recording technology and scoring methodology. The quest for finding and applying clinically reliable diagnostic methods, including assessment of disease severity, has clearly taken the wrong path. Very recently, an ad hoc working group on sleep-disordered breathing of the European Respiratory Society and the European Sleep Research Society advocated to address the intricacies that hamper the assessment of the AHI and of clinical disease severity, and to further investigate underlying pathophysiological and clinical phenotypes that are not captured by this measure (Randerath et al., 2018). Furthermore, this group of opinion leaders advised to go beyond the AHI in finding relevant biomarkers that truly reflect the seriousness of the disorder, whereby systemic effects induced by respiratory events as well as individual susceptibility to these effects should be taken into account.

Part 2: Critical appraisal of the AHI

In this section, issues with the validity of the AHI are critically reviewed and the concept and working definitions of the SAS are addressed. Several aspects are relevant to the discussion. It is suggested to separate AHI as a test result from the clinical presentation of OSA. Alternative models for severity classification of clinical OSA are proposed. Opportunities for future developments are outlined.

Limitations of the AHI as a measure of sleep-disordered breathing

Interpretation of the AHI requires procedural information

In the course of time, the spectrum of sleep-disordered breathing has been expanded from apnoeas and hypopnoeas to various new types of respiratory events and has been modified by adopting new working definitions. Complexity has been further enhanced by using different time periods in the denominator of the AHI. Obviously, the rating of an apnoea-hypopnoea index will be affected by several factors, not only the applied methods and scoring criteria, but also the expertise of the evaluator. Any given OSA disease state may yield different AHI values depending on the characteristics of the assessment procedure. Therefore, the AHI as a single unequivocal metric does not exist – each time an AHI is produced the assessment protocol should be disclosed. Likewise, clinical outcomes of OSA that are based on the measurement of AHI are only suitable for comparison if similar definitions, methods and professional skills have been applied.

Semantic issues

Semantics is yet another aspect that has to be addressed. Currently, a kaleidoscopic array of definitions is in use. Although most terms have basically a different meaning, several of them are often used interchangeably (See **Table 2** for a list of terms). For instance, the AI has become the AHI, which then turned into the RDI to integrate RERAs, that are important for the diagnosis of the UARS. Furthermore, the AHI would have to be replaced by the REI if HSAT is the recording method of choice. Obviously, the sleep apnoea field would benefit from a simplification of terminology.

Methodological issues

The quest for a quantified index of respiratory events as a measure of clinically relevant OSA has left us with many unanswered questions. First, if – in spite of the aforementioned limitations – respiratory events are to be used as an exposure variable, what would be the best predictor: the burden of events (= total count or amount) or the rate of events (= index or amount/h)? The burden of events has never been seriously investigated in the past as a potential predictor of clinical outcomes. One obvious advantage of not using the index is to delete the denominator of the ratio and thus to remove the component of time, which is in part accountable for the discrepancy between the AHI assessed by standard PSG vs HSAT. Second, is there a difference between hypopnoeas (and by extension RERAs) and apnoeas in terms of biological effects (Campos-Rodriguez et al., 2016; Kulkas, Duce, Leppanen, Hukins, & Toyras, 2017)? If so, what criteria should be used to define hypopnoeas? Third, should the duration of events be taken into account? Event duration is an important aspect of SDB, and some argue that it should become a separate point of interest. However, event duration will materialize through augmentation of systemic effects and as such its relevance may be subordinate (see below). Fourth, should events without any downstream effects such as arousals and oxygen desaturations be taken into account? Fifth, if a rate of events over time is to be used, what denominator should define the index: total sleep time or the time in bed (Escourrou et al., 2015; Vat et al., 2015)? Sixth, how many consecutive nights must be monitored to yield a reliable AHI (Crinion et al., 2020; Le Bon et al., 2000; Prasad et al., 2016; Stoberl et al., 2017)? And, finally, should the procedure be performed in the sleep laboratory or at home (Pevernagie & Verbraecken, 2015)?

Limitations of the AHI as a measure of syndrome severity

The AHI cannot be interpreted outside the clinical context

While the AHI often bears a connotation of clinical relevance, this metric is actually the result of a diagnostic test that cannot be interpreted outside the clinical context. The exact performance characteristics of this diagnostic test are as yet unknown. From what epidemiological research has shown, we may anticipate that the test has high sensitivity but

low specificity, meaning that there is probably a high rate of false positive results, even in the 'high severity' range. Thus, this single test result should never be a proxy for a disease state. In doing so, an attempt is being made to capture a variable and heterogeneous condition into a monolithic disease construct suitable for 'one size fits all' therapeutic approaches and socio-economic inferences.

AHI cut-offs are not valid for clinical severity scoring

It is clear from the historical narrative above that the lack of evidence has become sufficiently robust to accept that clinically relevant OSA cannot be ruled in or out based on the sole use of the AHI. In fact, the AHI fails to indicate a disease state or its severity in the individual OSA patient. This conclusion is supported not only by the various trials showing a flimsy correlation of the AHI with symptom scores and associated comorbid conditions, but also because the AHI has been found to explain no more than 25% of the variance in relevant outcomes such as driving performance and sleepiness (George, Boudreau, & Smiley, 1996; Kingshott et al., 1998). This figure is too low for reliable prediction making at the individual level. Thus, the widely accepted severity cut-offs 5, 15 and 30/h, introduced in the Chicago criteria, are invalid. It has been emphasized over and over again that these severity categories are arbitrary and misleading for clinical decision making (Hudgel, 2016). Ergo, AHI should be abandoned as a "stand alone" exposure variable of clinically relevant sleep-disordered breathing in the individual OSA patient.

This is actually bad news for all the organisations that rely on AHI cut-offs for decision making. Currently, many official bodies use the AHI as a panacea in the assessment of medical fitness, ability to drive, indications for treatment and for granting reimbursement of health care costs. In some instances, the definition or recording methods of the AHI have been adapted to meet specifications issued by stakeholder parties (R. B. Berry et al., 2012; Chediak, 2008). The AHI is explicitly mentioned in national or international laws. For instance, the EU OSA Driving Directive requires both increased AHI and sleepiness to preclude driving until treated (Bonsignore et al., 2016). Strictly speaking, the AHI as a tool of convenience would have to be revoked from several prevailing regulations, but such endeavour would be very difficult to realise, given the ubiquity of this measure.

Merging a test result with a clinical condition

In the literature so far, the concepts OSA as a test result (i.e. AHI above threshold) on the one hand and OSA as a clinical disorder on the other, while being fundamentally different, have been merged inadvertently. The entanglement between the AHI and clinical manifestations of OSA has been a source of confusion in both clinical practice and clinical research. By using the term 'syndrome', this linking has been accentuated. The word 'syndrome' (from Greek language: συν-δρόμος meaning 'con-currence') denotes a clinical presentation of different phenomena that together invoke a common cause on which the eventual diagnosis is established. However, this expression may introduce a bias when a cause is inferred but cannot be proven. Causal inference may be spurious when clinical manifestations are non-specific, as in OSA. In that case, a gold standard reference test is needed to demonstrate that the presumed cause is present. If such test is not available, the 'syndrome' definition has no solid foundation and the disease construct may be nothing more than a black box. While the defective AHI is currently used to confirm the diagnosis, there is as yet no gold standard (or 'ground truth') to define the real disease state of OSA. Therefore, the causative role of OSA in provoking symptoms and signs is hard to ascertain, even in the presence of very high AHI values.

Assessment of OSA significance and severity beyond the AHI

Diagnostic therapy

To solve the enigma of causality, the effects of treatment have to be assessed. Durable symptomatic relief in OSA patients with CPAP (or other) treatment is proof of the principle that the clinical manifestations are partially or fully caused by the disorder (McNicholas, 2019; Stradling & Davies, 2004). A diagnostic therapeutic trial, i.e. attributing the cause of any symptoms by observing improvement under therapy, instead of the traditional syndromic approach, may be an alternative way to improve outcomes in the future. This method may be inspired by 'reverse engineering' known from industrial technology. The goal of this procedure is to identify factors that are involved in the composite outcome of a process and to assess the relative contribution of the components in a retrograde way. Subsequently, this

process may be reconstructed from the findings of the analysis. The analogy of reversed engineering with the management of OSA would consist of monitoring a wide array of biomarkers to observe any associations or alterations under causal therapy, the outcome of which will probably be influenced by variant underlying phenotypic traits. Relevant biomarkers may become anchor points for shaping novel targeted treatment in the context of precision medicine. An example from the recent literature is the identification of biomarkers with predictive value as to antihypertensive effects of CPAP in CPAP responsive OSA patients with refractory hypertension (Sanchez-de-la-Torre et al., 2015).

In contrast with the limited utility of the AHI as a predictor, this parameter may be properly used as an outcome measure (Shahar, 2014). Causal treatment of OSA is aimed to stabilise the upper airway, thereby reducing the AHI in the first place. If this goal is achieved, and compliance to treatment is adequate, then symptoms associated with OSA should abate. However, if no symptomatic improvement is obtained despite significant reduction of the AHI, other causes must be explored. In that case, the presence of OSA may be co-incidental to another disorder explaining the clinical picture. In this respect, the effect of treatment on the AHI is a relevant outcome parameter. Therefore, the AHI – in the sense of a dependent variable – can be used as an instrument to discern between true OSA disorder and co-incidental OSA. This concept is further discussed below.

Differentiation between frequency of respiratory events, their systemic effects and their bodily impact

The limitations of the diagnostic and prognostic value of the AHI pose challenges for future assessment procedures in OSA. These issues have been comprehensively addressed in a recent review (Randerath et al., 2018). The AHI (or its alternative – the absolute count of respiratory events) only represents an amount of events per hour of sleep (A). As such, and regardless of any improved quantification methodology, this figure will never be powerful enough to reasonably predict disease severity.

While the ODI may better explain the variance of relevant clinical outcomes than the AHI, this does not mean that the AHI can be replaced unconditionally by the ODI as a risk marker for cardiovascular disease. In fact, the pathophysiology of OSA-driven cardiovascular morbidity

is determined by several systemic effects, including not only hypoxaemia, but also sleep fragmentation, sympathetic excitation, blood pressure and intrathoracic pressure swings, among others. All these systemic effects (E) must also be taken into account. The magnitude of these systemic effects varies largely among OSA patients and in individual OSA patients according to sleep state and body position. The integration of the amount of events with the amplitude of the associated systemic effects (A•E) may better correspond with clinical disease severity. This has been demonstrated for indices of hypoxaemia such as the ODI (Punjabi et al., 2008; Tkacova et al., 2014), as well as for obstruction severity defined as a product of event duration and area of desaturation (Muraja-Murro et al., 2014).

Finally, there is clinical evidence to indicate that the impact of the systemic effects of OSA may differ among patients as well. Depending on constitutional factors, the end-organ strain or injury (O) may be variable among individuals for any given degree of systemic effect. Thus, the eventual clinical picture will be defined by the susceptibility (or its antonym, the tolerance) of the bodily organs. The complex interaction between A, E and O may be illustrated by a model of repetitive strain impact (**Figure 2**). Future research should preferably shift attention from measuring exposure in terms of number of events alone to measuring systemic effects and individual susceptibility as well. The study of biomarkers may be of special relevance in this respect.

Integration of clinical characteristics into the severity scoring of OSA

The observation that the AHI is defective for the purpose of estimating OSA severity and that necessarily clinical markers have to be taken into account, actually brings us back to the first publication of the ICSD in 1990, in which the severity of OSA was graded on symptom scores of disturbed sleep and daytime hypersomnolence. As yet, we know that cardiometabolic features are likewise important, meaning that composite scores should be devised for disease state assessment. An innovative model has recently been published featuring a dichotomous score of hypersomnolence or insomnia in the horizontal dimension and a dichotomous score of end-organ impact (or comorbidities) in the vertical dimension (**Figure 3**) (Randerath et al., 2018). Four outcomes A through D can be established based on a combination of mild versus severe symptoms and undetectable or well controlled versus recurrent or poorly controlled end-organ impact (or comorbidities). In this model it is assumed that AHI should be equal to

or above a threshold of 15/h, although this principle can be modified to patients with a lower degree of respiratory event frequency. This four-factor model would be appropriate to differentially classify subjective complaints versus objective findings and to clarify whether symptoms versus comorbidities would respond differently to causal therapy of OSA.

Another approach is to integrate several relevant aspects into one clinical score that also can be used for treatment follow-up. The Clinical Global Impression Scale for disease severity (CGI-S) was initially used in clinical trials of psychiatric diseases but has also appeared in recent OSA studies. The CGI-S allows a 7-step grading from normal to "one of the most severe cases ever seen". A recent multi-site study of 7864 patients referred for suspected OSA analysed the factors which determined the sleep physician's decision of 'overall OSA disease severity' at the end of the diagnostic process (Dieltjens et al., 2019). Variables like age, sex, BMI, cardiovascular and metabolic comorbidity, ESS score and the AHI independently influenced the CGI-S rating. This study demonstrated that, aside from the AHI, other factors determine the perception of OSA disease severity by the sleep specialist, and that a crude grading system like the CGI-S is capable of capturing the overall effect of these constituents.

Inferences and future perspectives

In summary, to have OSA is not necessarily the same as to suffer from OSA. To unravel the different meanings of OSA, on the one hand defined by the AHI and on the other hand characterised by clinical manifestations, there is a need for adaptation of definitions as well. To this end, a fundamental, unequivocal definition of 'OSA' is required. Because OSA signifies the occurrence of obstructive respiratory events during sleep, OSA can appropriately be defined as an AHI above a certain threshold (at least until a more suitable marker is found and validated). The choice of the threshold is admittedly arbitrary, but this working definition is suitable for both clinical practice and research for now. Next, it must be evaluated whether clinical manifestations that are compatible with OSA as a disorder are present or absent. To discriminate between the test condition and the clinical aspect, we propose the following terms, some of which are already being used in the current literature (**Figure 4**):

- OSA = AHI above threshold = test result

- Symptomatic OSA = AHI above threshold with relevant clinical manifestations
- Asymptomatic OSA = AHI above threshold without relevant clinical manifestations
- Coincidental OSA = AHI above threshold with relevant clinical manifestations that are not caused by the sleep-disordered breathing
- OSA disorder (also OSA syndrome) = treatment responsive symptomatic OSA
- Diagnostic therapy = proof of principle that the clinical manifestations are causally related to OSA

The meaning of clinical manifestations in this context encompasses both symptoms such as disturbed sleep and/or hypersomnolence, and comorbidities such as hypertension, insulin resistance, etc. In fact, there is a semantic aspect to this terminology as well, as some of these 'comorbidities' could be considered primary symptoms or signs of OSA.

The observation that OSA represents a heterogeneous disorder, both in terms of pathogenesis and clinical expression, prompts further differentiation into subgroups with certain phenotypic traits. Contemporary research focuses on the discovery and validation of biomarkers that hold unique information on particular disease processes and modifications of disease progression under therapy. In this relatively new scientific domain, already some interesting results have been produced that may help to understand the multifaceted appearance of OSA. The quest for surrogate markers that characterise OSA disorder extends into three areas of investigation, i.e. diagnostic biomarkers, morbidity biomarkers and indicators of favourable response to treatment (Khalyfa, Gileles-Hillel, & Gozal, 2016). As yet, mainly pro-inflammatory biomarkers have been studied. While promising results have been published in some meta-analyses, an unambiguous effect of CPAP therapy on these biomarkers has not been shown so far (Martinez-Garcia, Campos-Rodriguez, Barbe, Gozal, & Agusti, 2019). A particular challenge is to identify biomarkers, whether biochemical or derived from PSG, that reflect pathogenetic relevance of OSA in asymptomatic subjects, which would be indicative of subclinical disease. Conversely, specific markers may be helpful in clarifying the clinical significance of respiratory events in symptomatic OSA, as the clinical presentation may be determined by several factors, also including non-respiratory causes. A survey for clinically useful markers will require prospective follow up of large multi-centre patient cohorts, thereby recording a wide array of symptom scores and cardiovascular outcomes as

well as several metabolic indicators. Validation of candidate biomarkers will necessarily involve diagnostic therapy, because as yet this is the only method to confirm the presence of OSA as a disorder.

Conclusions

From the present historical review and critical appraisal, it is concluded that the introduction of the AHI in the previous century was appropriate and has served a purposeful role in the establishment of OSA as disease in its own right. This approach was pivotal in differentiating the clinical picture of OSA from other disorders such as obesity hypoventilation syndrome and narcolepsy. Moreover, it was instrumental for developing and assessing effective treatment modalities including CPAP therapy. However, in the course of time, the AHI has become a proxy for the existence and severity rating of OSA, construed as a uniform disease concept. This conception has instigated controversy in the scientific literature and has been a source of uncertainty regarding the clinical relevance of OSA, given the fact that several clinical trials yielded unclear results. At present, the traditional role of the AHI as a diagnostic marker and severity indicator of clinically relevant OSA is on the retreat. The observation that OSA covers a large spectrum of clinical and pathophysiological features necessitates new paradigms not only for the overall diagnosis of clinically relevant OSA, but also for allowing precision medicine to focus on various treatable traits that constitute this heterogeneous disease. We believe it is time to release the AHI as a mainstay for OSA diagnosis and to start using more precise clinical markers, many of which still remain to be discovered.

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TABLES

Table 1. Timeline with a selection of key publications over the years

YEAR	AUTHORS	SUMMARY OF CONTENT
1956	Burwell et al. *Am J Med*	Description of the 'Pickwickian syndrome': a case report on the combination of morbid obesity, loud snoring, hypercapnia and hypersomnolence.
1976	Guilleminault et al. *Annu Rev Med*	Description of the sleep apnoea syndromes: sleep-disordered breathing is recognised as an autonomous cause of disease manifestations.
1978	Guilleminault et al. *Sleep apnea syndromes*	Recapitulation of the previous paper as a chapter in a new book. The 'apnea index' is introduced as a metric to define the presence and seriousness of sleep apnoea syndromes.
1979	Block et al. *New Engl J Med*	The use of arbitrary cut-off values for AI for the separation of SAS from normalcy is criticised.
1984	Berry et al. *Chest*	It is demonstrated that the AI increases with age and that an increased AI may be present in asymptomatic elderly subjects.
1988	Gould et al. *Am Rev Respir Dis*	The importance of hypopnoeas is highlighted. These respiratory events may cause similar symptoms as apnoeas.
1990	ASDA. *International Classification of Sleep Disorders (ICSD -first edition)*	The first nosological catalogue of sleep disorders published by the ASDA. The obstructive sleep apnoea (OSA) syndrome is characterised by symptom severity. There is no mentioning of the AI or the AHI.
1993	Young et al. *New Engl J Med*	First epidemiological study on the prevalence of OSA in middle-aged employed subjects. The prevalence of an AHI > 5/h is reported to be 24% in men and 9% in women. Hypersomnolence is present in only a minority.
1996	Deegan et al. *Eur Respir J*	This study aimed at identifying clinical predictors of OSA. A combination of clinical features and oximetry data produced the best results.
1998	Kingshott et al. *Eur Respir J*	Correlations between the arousal index or AHI and results from the MSLT prove not statistically significant. So, hypersomnolence cannot be predicted from the AHI at the group level or in the individual patient.
1999	AASM Task Force. *Sleep*	In these so-called 'Chicago criteria' new standards for the definition and scoring of respiratory events are introduced. The statements are largely founded on expert opinion. The standards are intended for clinical research purposes, not for clinical practice.
2000	Redline et al. *Am J Respir Crit Care Med*	Different approaches for measuring the various respiratory events leads to substantial variability in the diagnosis and severity classification of OSA as a disorder.
2004	Stradling and Davies. *Thorax*	In this review article, the importance of CPAP responsiveness is emphasized, because results from sleep testing have only limited predictive value as to symptomatic improvement with CPAP treatment in OSA patients.

2005	Marin et al. *Lancet*	A large observational study showing the deleterious consequences of untreated severe OSA on the incidence of cardiovascular disease.
2005	AASM. *International Classification of Sleep Disorders, second edition (ICSD-2)*	The second edition of the ICSD. In this version, OSA is defined as a combination of nocturnal or diurnal symptoms in combination with an AHI above threshold (i.e. ≥ 5/h) or an AHI ≥ 15/h, even in the absence of relevant symptoms.
2007	AASM. *The AASM manual for the scoring of sleep and associated events. Rules, terminology and technical specifications*	The first manual for scoring of sleep and associated events, published by the AASM. Respiratory events are described in detail. Remarkably, two versions for the scoring of hypopnoeas (recommended and alternative) are provided.
2007	Collop et al. *J Clin Sleep Med*	Clinical guideline produced by an AASM task force for the use of unattended portable monitors in the context of HSAT.
2008	Chediak. *J Clin Sleep Med*	Background information on the approval of HSAT by the CMS. Previously, only results from conventional PSG were allowed for reimbursement of CPAP therapy.
2009	Ruehland et al. *J Clin Sleep Med*	Different approaches for measuring the various respiratory events leads to substantial variability in the diagnosis and severity classification of OSA.
2009	Epstein et al. *J Clin Sleep Med*	Clinical guideline drafted by an AASM task force for the evaluation, management and long-term care of OSA in adults.
2012	AASM. *The AASM manual for the scoring of sleep and associated events. Rules, terminology and technical specifications, second edition.*	The second version of the scoring manual. In contrast with the previous version, only one set of criteria for hypopnoea scoring is provided.
2013	Eckert et al. *Am J Respir Crit Care Med*	Landmark publication on the different phenotypic causes of OSA. The AHI is not specifically related to any of the underlying pathophysiological traits and there is a widespread relationship between Pcrit and AHI.
2014	Tkacova et al. *Eur Respir J*	The prevalence of systemic hypertension is assessed in OSA patients registered in the ESADA cohort. When both the AHI and the ODI are included in the same statistical model, the ODI is, whereas the AHI is not, independently associated with prevalent hypertension.
2014	AASM. *International Classification of Sleep Disorders, third edition (ICSD-3)*	The third edition of the ICSD reports a definition of OSA similar to the second edition, although an addition is made regarding potential associations with comorbid disorders.
2015	Escourrou et al. *J Sleep Res*	This study suggests that HSAT results in underdiagnosis and misclassification of OSA. AHI values tend to be lower when obtained from HSAT as compared with standard PSG.
2015	Heinzer et al. *Lancet Respir Med*	The prevalence of OSA, as defined by and AHI ≥ 15/h according to the 2012 AASM scoring criteria, is assessed in a large group of urban dwelling subjects. High prevalence figures are demonstrated for both male and female individuals in the community. The need for revision of the diagnostic criteria of OSA is advocated.
2016	Arnardottir et al. *Eur Respir J*	This study confirms that OSA, defined by an AHI above threshold, is highly prevalent in the general population, but that the majority of individuals with observed OSA have no symptoms.

2016	McEvoy et al. *New Engl J Med*	In this large clinical population study, secondary prevention of cardiovascular disease is not enhanced by CPAP therapy in OSA patients with an AHI >= 15/h. Better compliance to treatment, however, improves the outcome.
2016	Peker et al. *Am J Respir Crit Care Med*	Prescription of CPAP to non-sleepy OSA patients with coronary artery disease does not significantly reduce long-term adverse cardiovascular outcomes in the intention-to-treat analysis.
2017	Kapur et al. *J Clin Sleep Med*	Clinical practice guideline drafted by an AASM task force for diagnostic testing of OSA in adults.
2017	Bibbins-Domingo et al. *JAMA*	The US Preventive Services Task Force advises not to screen for OSA in asymptomatic adults.
2017	Abuzaid et al. *Am j Cardiol*	Systematic review and meta-analysis showing that, compared with medical therapy alone, utilization of CPAP in patients with OSA is not associated with improved cardiac outcomes except in patients who are sufficiently compliant to therapy.
2017	Yu et al. *JAMA*	Systematic review and meta-analysis showing that the use of CPAP, compared with no treatment or sham, is not associated with reduced risks of cardiovascular outcomes or death for patients with sleep apnea. These results do not support CPAP treatment intended to prevent cardiovascular disease.
2018	Keenan et al. *Sleep*	Previously identified clinical clusters of OSA in the Icelandic population are confirmed and expanded to populations in other countries. While AHI values are similar across groups these clusters provide an opportunity for a more personalized approach to the management of OSA.
2018	Randerath et al. *Eur Respir J*	Opinion paper in which the diagnosis and management of OSA is critically reviewed. A poor correlation between AHI and daytime symptoms such as sleepiness is acknowledged. Management decisions should be linked to the underlying phenotype and outcomes beyond the AHI are to be considered.
2019	Sanchez-de-la-Torre et al. *Lancet Respir Med*	Large multicentre trial by the Spanish Sleep Network assessing the recurrence of cardiovascular events in non-sleepy OSA patients with acute coronary syndrome. The presence of OSA is not associated with an increase of cardiovascular events and treatment with CPAP does not significantly alter the outcome.
2019	Wimms et al. *Lancet Respir Med*	The results of this study lend support to treating patients with mild OSA, as favourable effects on quality of life and adequate compliance to treatment with CPAP can be obtained in subjects with low-level AHI.

Table 2. List of terms

TERM	MEANING
AASM	American Academy of Sleep Medicine. The AASM is the principal professional society in the US dedicated to the medical subspecialty of sleep medicine, comprising health care, education, and research.
AI	See apnoea index.
AHI	See apnoea-hypopnoea index.
Apnoea	A cessation of airflow at the nose and mouth lasting at least 10 sec.
Apnoea index	The total amount of apnoeas recorded in an overnight sleep study divided by the total sleep time.*
Apnoea-hypopnoea index	The total amount of apnoeas and hypopnoeas recorded in an overnight sleep study divided by the total sleep time.*
Arousal index	The total amount of arousals recorded in an overnight sleep study divided by the total sleep time. The arousal index cannot be assessed with HSAT.
ASDA	American Sleep Disorders Association. The predecessor of the AASM.
CMS	Centers of Medicare and Medicaid Services. A federal agency within the US Department of Health and Human Services involved in the insurance of public health care.
Continuous positive airway pressure	A therapeutic intervention aimed at securing a patent upper airway by increasing the intraluminal airway pressure. This treatment prevents the occurrence of obstructive respiratory events during sleep.
CPAP	See continuous positive airway pressure.
Epworth sleepiness scale	A questionnaire consisting of 8 questions probing the tendency to fall asleep in different situations. Results may range from 0 to 24 and a result >10 indicates hypersomnolence.
ESS	See Epworth sleepiness scale.
Home sleep apnoea testing	Performing a diagnostic test for sleep apnoea in the home environment. The montage includes respiratory signals, but not EEG. As such, sleep and arousals cannot be assessed with this technique, thereby excluding the possibility of detecting cortical arousals and limiting the possibility of identifying hypopnoeas.
HSAT	See home sleep apnoea testing.
Hypopnoea	A decrease (but not complete cessation) of airflow at the nose and mouth lasting at least 10 sec.
ICSD	See International Classification of Sleep Disorders.
International Classification of Sleep Disorders	Nosological classification system of sleep disorders published by the ASDA and later on the AASM. There are three editions: ed. 1 appeared in 1990, ed. 2 in 2005 and ed. 3 in 2014.
MSLT	See multiple sleep latency test.
Multiple sleep latency test	A standardised test for the objective measurement of sleepiness. Typically, 5 naps of 20 minutes are recorded with an interval of 2 hours. A mean sleep latency of < 8 min is an objective indicator of hypersomnolence.
Non-apnoeic events	Other events than apnoeas. These include hypopnoeas and RERAs.
Obstructive sleep apnoea	A condition whereby most sleep-related respiratory events are obstructive in nature. Respiratory events include apnoeas, hypopnoeas and RERAs.
Obstructive sleep apnoea syndrome	OSA typified by an AHI above threshold and characteristic symptoms, signs and comorbidities.
ODI	See oxygen desaturation index.
OSA	See obstructive sleep apnoea.
OSAS	See obstructive sleep apnoea syndrome.

Oxygen desaturation index	The total amount of oxygen saturation dips recorded in an overnight sleep study divided by the total sleep time.* These dips may vary in amplitude and are expressed as % decrease from baseline (e.g. ODI ≥ 3% or ≥ 4%).
PSG	See polysomnography
Polysomnography	Standard procedure for recording sleep. The following biological signals are included: electro-encephalography (EEG), electromyography (EMG), electro-oculography (EOG), airflow through nose and mouth, respiratory movements of thorax and abdomen, electrocardiography (ECG) and body position, among other signals.
RDI	See respiratory disturbance index
REI	See respiratory event index
RERA	See respiratory effort-related arousal
Respiratory disturbance index	A nonspecific term meaning the total number of respiratory events recorded overnight divided by the total sleep time.* According to some definitions the RDI equals the AHI. In the context of UARS, the RDI is used to also include the total number of RERAs.
Respiratory effort-related arousal	A respiratory event characterised by inspiratory flow limitation, increased respiratory effort and a terminating arousal. These events are similar to obstructive hypopnoeas identified by the arousal criterion. With more sensitive monitoring techniques, the difference between the two may be hard to tell.
Respiratory event index	The total amount of respiratory events recorded with HSAT divided by the total recording time.
Respiratory events	Disturbed breathing events during sleep, usually lasting more than 10 sec. Respiratory events include apnoeas, hypopnoeas and RERAs, among others.
SAA	See sleep apnoea activity
SAS	See sleep apnoea syndrome.
SDB	See sleep-disordered breathing.
Sleep-disordered breathing	An umbrella term for respiratory sleep disorders, comprising obstructive sleep apnoea (including snoring and UARS), central sleep apnoea and alveolar hypoventilation.
Sleep apnoea activtiy	An obsolete term used in some early epidemiological studies to quantify the incidence of apnoeas in an overnight sleep study.
Sleep apnoea syndrome	A clinical condition originally defined as the occurrence of at least 30 apneic episodes during seven hours of nocturnal sleep. Later on, a discrimination was made between central and obstructive sleep apnoea syndromes (see above).
UARS	See upper airway resistance syndrome
Upper airway resistance syndrome	A clinical condition similar to obstructive sleep apnoea syndrome but hallmarked by RERAs instead of apnoeas and hypopnoeas. This clinical entity is subsumed under OSA in the ICSD-2 and ICSD-3.

*If sleep is not recorded (as in HSAT), total sleep time is replaced by total recording time.

FIGURES

Figure 1. Hypothetical effect of transforming the Metric System of Measurement (cm) into the Imperial System of Measurement (1 inch = 2.54 cm) without changing the measurement units. A factor 2.5 difference, which corresponds approximately with the difference between AHI(Chicago) and AHI(Rec), substantially affects the size of the outcome. Obviously, changing metrical systems requires recalibration.

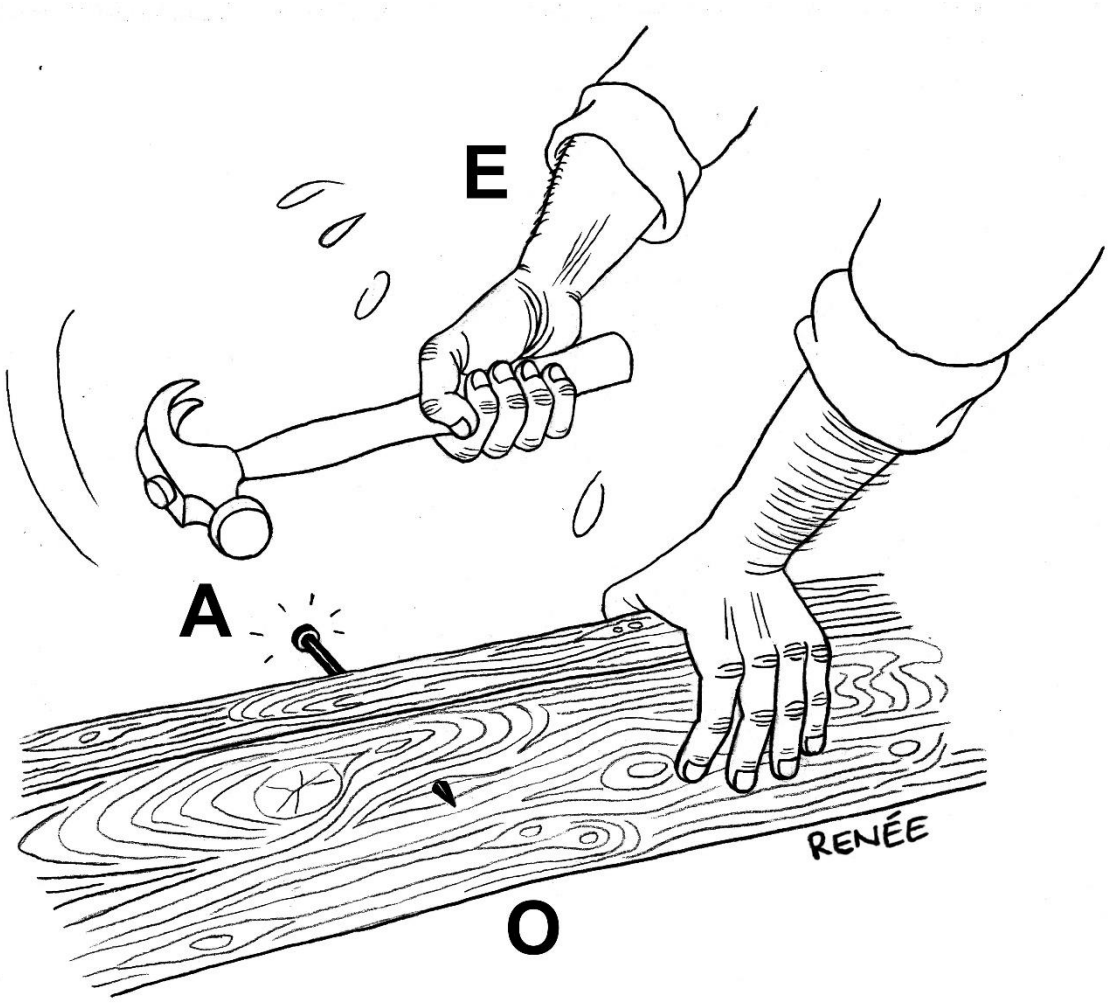

Figure 2. Model of repetitive strain impact. Driving a nail into a medium with a hammer. The number of hits = A, whereas E would represent the applied force. Factor O, the quality or firmness of the medium, will finally determine whether and to what extent the nail penetrates the medium. In OSA research, especially the equivalent of factor A (i.e. the number of events) has been considered. The equivalent of factor E (i.e. systemic effects associated with the events, e.g. the degree of hypoxaemia) is gaining increased interest. However, the equivalent of factor O (i.e. the susceptibility of end-organs to the impact of the systemic effects) has been left unexplored so far.

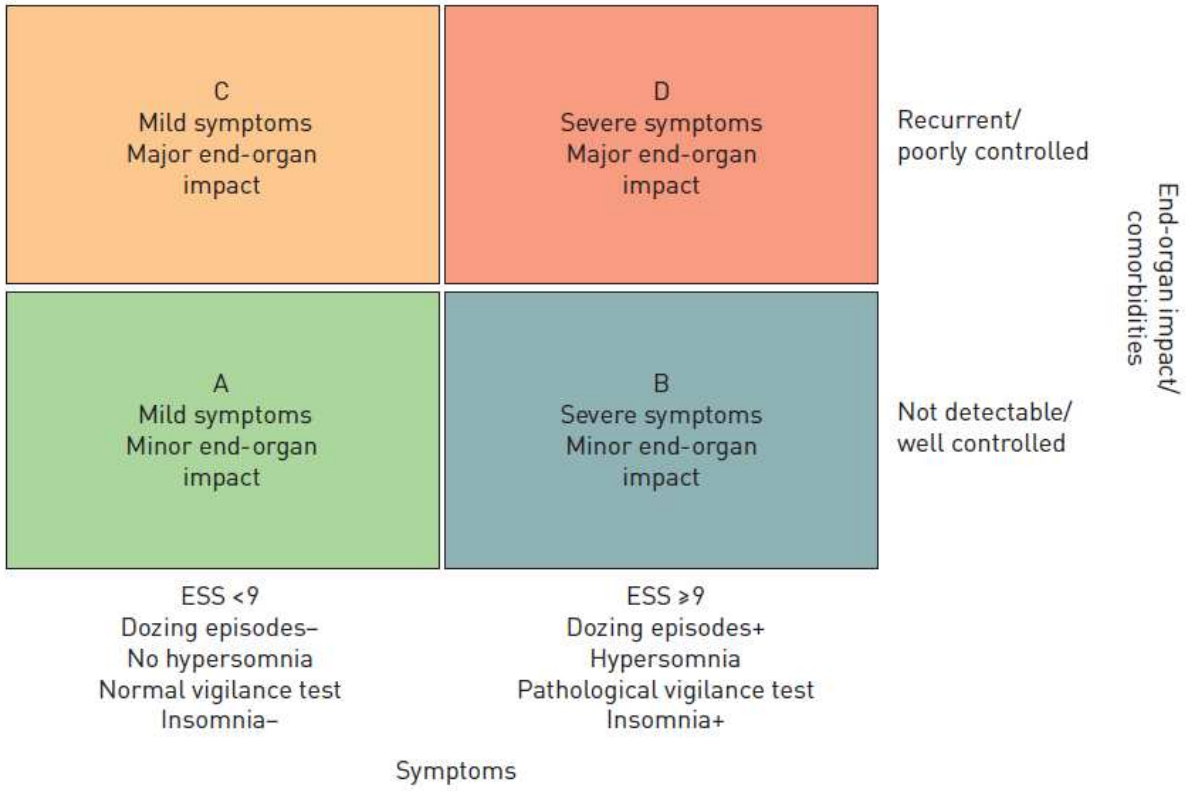

Figure 3. Proposal of a multicomponent grading system for obstructive sleep apnoea (OSA) severity in subjects with an AHI ≥ 15/h. ESS: Epworth Sleepiness Scale. Prerequisite for the following grading system is the evidence of obstructive sleep-related breathing disturbances (AHI ≥ 15/h). The proposal combines the symptomatology with the impact of OSA on the cardiovascular system and metabolism or any other accompanying comorbidities. Four categories (A-D) are defined.
Reproduced from (Randerath et al., 2018) with permission from the publisher (ERS).

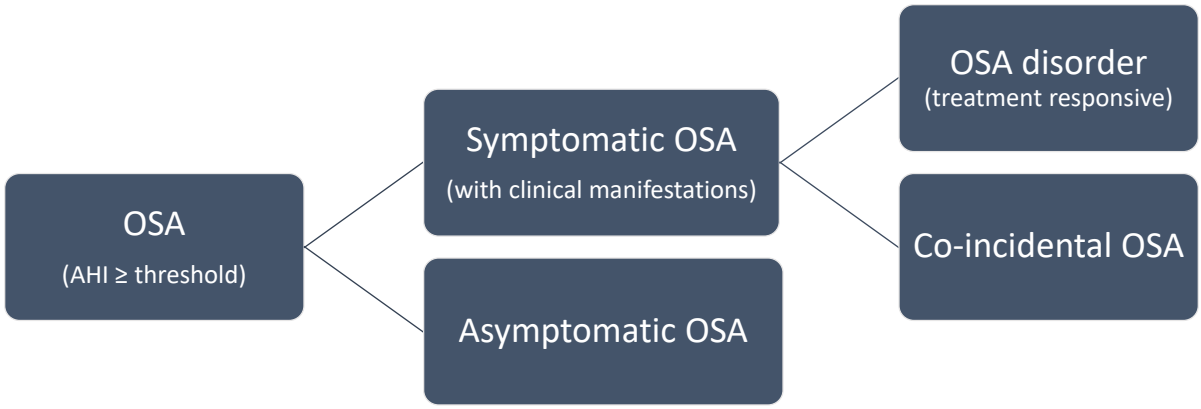

Figure 4. Different meanings of OSA. OSA basically means that an AHI ≥ 5/h is demonstrated by a sleep test. If there are no associated clinical manifestations, the condition is asymptomatic. Symptomatic OSA means that this elevated AHI is associated with clinical manifestations that are consistent with OSA as a disorder. OSA as a disorder is confirmed by durable symptomatic relief induced by causal treatment. If no relief is obtained despite adequate treatment, the presence of clinical manifestations is assumed to be caused by other factors and is co-incidental as such.