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Review and perspective on sleep-disordered breathing research and translation to clinics

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ABSTRACT

Sleep-disordered breathing, ranging from habitual snoring to severe obstructive sleep apnea, is a prevalent public health issue. Despite rising interest in sleep and awareness of sleep disorders, sleep research and diagnostic practices still rely on outdated metrics and laborious methods reducing the diagnostic capacity and preventing timely diagnosis and treatment. Consequently, a significant portion of individuals affected by sleep-disordered breathing remain undiagnosed or are misdiagnosed. Taking advantage of state-of-the-art scientific, technological, and computational advances could be an effective way to optimize the diagnostic and treatment pathways.

We discuss state-of-the-art multidisciplinary research, review the shortcomings in the current practices of SDB diagnosis and management in adult populations, and provide possible future directions. We critically review the opportunities for modern data analysis methods and machine learning to combine multimodal information, provide a perspective on the pitfalls of big data analysis, and discuss approaches for developing analysis strategies that overcome current limitations. We argue that large-scale and multidisciplinary collaborative efforts based on clinical, scientific, and technical knowledge and rigorous clinical validation and implementation of the outcomes in practice are needed to move the research of sleep-disordered breathing forward, thus increasing the quality of diagnostics and treatment.

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1. Introduction

Sleep-disordered breathing (SDB) comprises disorders ranging from obstructive sleep apnea (OSA) and central sleep apnea to sleep-related hypoventilation disorders and habitual snoring [1]. SDB, and particularly OSA have become a global health burden with remarkably high prevalence with OSA alone affecting up to a billion individuals globally [2,3]. Besides disrupting nocturnal respiration and fragmenting sleep [4], SDB predisposes the afflicted individuals to several life-threatening conditions such as neurodegenerative diseases, heart failure, stroke, and arrhythmias [5–7] and increases the risk for traffic and occupational accidents [8]. Overall, untreated or suboptimally treated SDB has been associated with direct healthcare costs, decreased productivity, and decreased quality of life [3–7,9,10]. While there have been advancements in the diagnostic process, for example, the increase of home-based recordings and semi-automatised scoring, the main parameters used to classify the SDB severity leading to clinical decision-making and treatment eligibility, have not significantly evolved in decades [11,12].

The current diagnostic practice of SDB mostly relies on complex recordings, either in-laboratory polysomnography (PSG) or a home sleep apnea test, over a single night despite significant night-to-night variability in SDB severity [13,14]. Overall, the current measurement protocols are suboptimal for long-term monitoring or screening more individuals with symptoms of SDB mostly limiting their availability only to individuals with a strong clinical suspicion of sleep disorders. This can explain why, for example, OSA often remains undiagnosed [2,15–17], and why the SDB severity is sometimes misdiagnosed. Moreover, despite using complex diagnostic recording setups and possibly spending up to a few hours of manual labour analysing the recordings, most information in the recordings is completely overlooked. Most notably, the diagnostic decision-making and treatment eligibility are based on arbitrary and simplistic metrics, such as the apnea-hypopnea index (AHI), shown to be poorly correlated to treatment outcomes, daytime symptoms, and physiological effects [12]. Moreover, the assessment of sleep quality relies on manually segmenting sleep in 30-s epochs instead of considering it as a continuum of different levels of neuronal and physiological activity [11,18]. Overall, the diagnostics rely on pioneering work in sleep research developed in an era with analogue recordings and limited knowledge of sleep disorders [12]. However, with modern medical technology and precision medicine, there is substantial motivation to fundamentally re-evaluate these diagnostic methods to achieve more individualized, patient-centered care.

With current technology, sleep recording data is digitally stored enabling access and analysis in both real-time as well as retrospectively. The biosignals comprising a sleep recording, such as electroencephalography (EEG), electrocardiogram (ECG), and blood oxygen saturation (SpO_2), may be analyzed efficiently by various methods to highlight the most relevant characteristics and physiological patterns. Moreover, with constantly increasing computing power [19], it is possible to dive deeper into the combined information content of all recorded signals and to study them as an inter-correlating ensemble. The increased computing possibilities alongside innovative applications of data analytics and machine learning could provide a more detailed and comprehensive representation of the sleep recordings, as demonstrated previously in multiple studies [20–24].

There have been previous, thorough reviews in more detailed sleep recording analytics [25–28]. However, these have mostly focused on clinical practices and alternate parameters to replace or complement the AHI without considering the shortcomings and factors hindering research or the discrepancies in the current scoring practice. In this review, we will discuss state-of-the-art research focused on novel approaches to SDB assessment in adult populations and its translation to clinical care while focusing on overcoming the factors hindering sleep research and the possibilities of multi-centre, multi-disciplinary, and multi-scorer datasets not dictated by outdated clinical practices. We will emphasize possible pathways to broaden the evaluation of SDB severity beyond the conventional epoch-by-epoch sleep staging and respiratory event counting. We will review modern digital signal analysis methods and machine learning techniques as well as the effectiveness of combining multimodal information for personalized SDB diagnostics. We will further discuss both possible solutions for utilizing the full complexity of overnight signals as well as the possibility of using simplified measurement and diagnostic setups to achieve accurate SDB monitoring. This review is written within the context of awarded major European Union Horizon 2020 grant "Sleep Revolution" focused on novel approaches to SDB assessment [29].

2. Current practices in research and diagnostics

2.1. Historical overview

Sleep architecture is currently analyzed by classifying sleep into rapid-eye-movement (REM) sleep and three stages of non-rapid-eye-movement (NREM) sleep (N1–N3). This classification comes from the American Academy of Sleep Medicine (AASM) recommendations [18,30,31], derived mostly from the Rechtschaffen & Kales scoring rules introduced in 1968 [32]. The most notable evolution has been the reduction of the NREM stages from four to three. However, the Rechtschaffen & Kales rules were derived mostly from studies conducted on healthy individuals making the generalization to sleep-disordered populations questionable, and segmenting sleep into 30-s epochs was chosen mostly for convenience rather than scientific evidence [32,33]. Yet a half-century later, the rules still form the cornerstone of sleep architecture assessment, both in research and in diagnostic practice.

Similarly, the quantification of respiratory events by discrete scoring rules is the foundation of SDB research and diagnostics. While OSA was recognized during the '60s with some features even before, the characterization of OSA severity by frequency metrics such as the AHI was first introduced in the '70s [34]. From that moment on, there has been a debate on how to count respiratory events, how to define hypopneas, and whether hypopneas should even be considered. The first criticism towards the AHI was set practically immediately after its establishment, focusing on the AHI being too simplistic and not capturing all the essential elements to describe the severity of SDB [12]. However, the AHI remains the main metric for treatment decisions in OSA and is the main parameter used in SDB research. Moreover, OSA severity is still conventionally graded by arbitrary 5/15/30 events/hour AHI thresholds and the hypopnea definition still sparks controversy with many coexisting hypopnea scoring rules. Under the surface, the physiological effects and even the length and type of respiratory events remain overlooked [35,36].

2.2. Research aspects

The current directions in SDB research aim to connect the measurable characteristics and patterns of SDB to physiological deficits and daytime symptoms which attribute to a lowered quality of life. Simultaneously, researchers explore links and pathways between SDB and different comorbidities. For example, while obesity has a well-established connection to the development of SDB, there are multiple other pathways to developing SDB [37]. Conversely, a wide body of evidence has been achieved, for example, stating that SDB is independently linked to different cardiovascular, cerebrovascular, and metabolic diseases [38–40]. Yet the underlying pathophysiological mechanisms contributing to the development of comorbid conditions remain unclear, likely due to current SDB metrics failing to fully capture the SDB characteristics and physiological effects. Furthermore, there is evidence of a bidirectional relationship between SDB and many linked comorbidities such as heart failure, stroke, and renal failure, which further complicates the assessment of causality [41].

The AHI may not be an optimal parameter to assess SDB severity and connections to symptoms and comorbidities [12], despite remaining not

only the main clinical parameter but also dictating almost all scientific publications in the field as the primary outcome parameter. For research purposes, the AHI is an important starting point to define the disease condition in the study population. However, it fails as an ultimate benchmark [12,36,42,43], thus diminishing the value of, for example, grouping the patient population conventionally to mild, moderate, or severe categories based on AHI thresholds of 5, 15, and 30 events/hour. Moreover, there have been slight modifications to the scoring rules over the years with different practices coexisting between different clinics, hindering the generalizability of the methods [44]. Still, the arbitrarily chosen group with AHI <5 events/hour is used as the "healthy" reference group which can cause bias in the results and lower the correlation to disease characteristics and outcomes. Similar issues appear in the analysis of sleep patterns and architecture which are usually quantified with percentages of sleep stages, arousal index, and sleep efficiency. These only capture limited parts of the sleep architecture and more detailed methods should be used when focusing on analyzing sleep.

Machine learning and big data applications in sleep research have gained widespread interest and have shown outstanding results in automatizing PSG scoring [21,24,45,46] and providing the same or even more detailed diagnostic yield from simpler, more comfortable, or surrogate recordings [20,22,47–51]. Traditionally, methods aiming for automatizing PSG scorings relied on pre-defined rules or simple classifiers operating on carefully selected PSG signal features. While these have arguably assisted in reducing the time spent for scoring, the more recent methods have surpassed these relying on supervised learning approaches with deep learning and different variations of artificial neural networks. Overall, these have often reached the human-level accuracy in scoring, comparable to the inter-rater reliability [21,22,45,52,53]. Still, clinical trials investigating the generalizability and reliability of the methods across individuals and different centres remain an essential study direction that could move their adaption to daily practice further. Furthermore, the robustness of the methods may be further illustrated by providing metrics that also reflect the certainty of the scoring as well as moving towards explainable and interpretable methods that provide the reasoning behind the decisions. The application of different realms of machine learning including representation learning, active learning, and other unsupervised or semi-supervised methods have a high potential and could provide breakthroughs in the coming years to fully utilize the potential of all the collected medical and overnight data.

Sleep quality and sleep monitoring have also gained widespread interest in the general population with the emergence of various wearable devices for self-monitoring [22,54,55]. Wearable devices (wearables) is an umbrella term for all non-invasive body-worn sensors. Smartwatches and activity watches are examples of wearables that capture information by relying on measurements such as accelerometers, photoplethysmography, and temperature sensors. Nearables on the other hand refer to sensors located in close proximity to the body, for example, in a mattress. Both wearables and nearables can arguably have their downsides due to inaccuracy, excessive monitoring, and placing unwarranted trust in devices with limited validation studies. However, these technological advancements hold great potential for sleep research when utilized properly. If validated in collaboration with sleep scientists and medical experts, wearable self-trackers with sufficient reliability can enable long-term monitoring of sleep in a home environment and supplement the information gained from traditional single-night sleep studies, both in diagnostics and in research [56].

3. Utilizing the full potential of PSG - pathways between physiological effects, symptoms, and comorbidities

Even though the AHI is the most frequently used parameter in clinical work related to SDB, a variety of alternative approaches have already been proposed [42,57–60]. In the next paragraphs, we will not focus on the ways to replace the AHI but instead enhance and add value to the gained information to move towards a more precise and individualized diagnosis and research. We review the most novel and informatic ways to analyze PSG data and focus on the future directions: (1) by emphasizing the evaluation of SDB-related physiological effects and their characterization; (2) by discussing possibilities for more detailed EEG and sleep architecture analysis; (3) by focusing on the novel methods and newest research on phenotyping SDB patients based on sleep recordings, and; (4) by presenting novel data analytics and machine learning applications in sleep medicine.

3.1. Physiological effects

The pathophysiology of SDB is multifactorial with multiple aspects remaining unknown [4,61–64]. In OSA, the typical fundamental abnormality reflects the inability of the upper airway (UA) dilating muscles to withstand the negative forces generated within the UA during inspiration. Factors that increase this negative pressure or diminish the efficacy of dilating muscle contraction upset this balance and promote UA obstruction [37]. Narrowing of the UA, which is a typical feature of OSA, increases negative pressure during inspiration, thus promoting collapse.

The UA dilator muscles contract in a phasic manner coordinated with inspiration. In OSA, a narrowed UA generates greater collapsing forces requiring stronger dilating muscle contraction to prevent closure. Factors further limiting dilator muscle efficacy include instability of ventilatory control during sleep, similar to periodic breathing, and UA obstruction is most likely when muscle activity is at the lowest point of the cycle. Apnea termination is followed by hyperventilation for several breaths, after which UA muscle activity decreases, predisposing to further obstruction [37]. Pathophysiological factors behind the cyclicity of hypo-and hyperventilation have been described as critical closing pressure of the upper airway, muscular compensatory activity, ventilatory loop gain, and arousal threshold [4,65]. Additional factors include the apnea threshold, which relates to oscillations in the respiratory drive that is critically dependent on carbon dioxide (CO_2), and amplified by post-apnea hyperventilation, resulting in CO_2 reduction and predisposition to further apnea [64]. These recurring cycles of hyper- and hypoventilation during sleep vary with ventilatory loop gain and a high loop gain increases ventilatory instability, predisposing to apnea [64]. Arousal at the end of apnea further enhances post-apneic hyperventilation, which represents a further apnea-promoting factor. While habitual snoring may not lead to apneic events and cyclic alternation of hypo- and hyperventilation, it is independently associated with sleep fragmentation, excessive daytime sleepiness, and the development of comorbidities such as hypertension [66].

Intermittent hypoxia and arousals are important stimuli that increase sympathetic activation and promote UA reopening [4,64]. However, these will result in hemodynamic consequences including cardiac acceleration, central and peripheral arterial vasoconstriction, and blood pressure surges. Vascular effects include increased inflammation triggered by reactive oxygen species, endothelial dysfunction, and increased vascular stiffness [68–70]. Jointly, these pathophysiological mechanisms have been linked to the development of hypertension and atherosclerotic disease in SDB patients. The amount of intermittent hypoxia is also related to adverse cardiovascular outcomes [28,72,83,84].

Techniques to quantify the physiological effects in more detail are gaining interest in the sleep community. For example, longer apneas and hypopneas lead to increased short-term heart rate variability (HRV) [71] and more severe oxygen desaturations [72]. Meanwhile, the severity of desaturations is associated with increased risk for cardiovascular mortality, daytime sleepiness, and impaired vigilance more strongly than the AHI [42,60,67,73–76]. Additionally, severe hypoxemia leads to distortions in cardiorespiratory coupling (CRC) [77] which has also been illustrated to act as a biomarker for unstable sleep [77,78]. Furthermore, characterizing the photoplethysmographic pulse wave signals has

revealed promising surrogates for arterial stiffness and sympathetic tone, serving as a direct link to the cardiovascular system [79,80] and helping to explain the connections behind cardiovascular morbidity and mortality [79,81,82]. Finally, there have been several promising methods to quantify the arousal threshold [83], upper airway collapsibility [58], and ventilatory loop gain [84] based on physiological modelling which could provide further insight into the physiological effects without the need for invasive studies. Overall, connecting the physiological effects and measurable characteristics with underlying pathophysiology while translating these to individualized treatment approaches remains an essential study direction [85,86].

3.2. Sleep architecture and quality

The analysis of sleep architecture is conventionally based on the percentage of sleep stages from the total sleep time as well as counting the number of arousals from sleep. However, these approaches may be regarded as oversimplifications of an extremely complex phenomenon. The sleep scoring practice was devised mostly based on recordings from healthy individuals [32,33] and may therefore not accurately reflect those with SDB. For example, the presence of sleep disorders and sleep deprivation affects spindle and slow-wave characteristics in N2 and N3 sleep [87–89]. The current parameters aimed to represent sleep fail to explain the variations in daytime sleepiness and impaired vigilance in sleep-disordered populations [59,74,90–93]. Similarly, only the number of arousals is usually considered despite the fact there is a large variation in the length and magnitude of arousals [94,95].

The scoring of sleep stages suffers from unreliabilities [96–101]. One major issue is the scoring of N1 sleep. It has repeatedly been shown that scoring of N1 sleep is highly unreliable with large variations existing between scorers, between centres, within centres, and within a single scorer, with agreement varying from 0.19 to 0.46 [96–99]. N1 can easily be mixed with either N2 or wake epochs causing uncertainties in detecting sleep/wake transitions but it also affects the total number of scored sleep epochs and thereby distorts total sleep time which is an important parameter directly affecting other parameters such as AHI, oxygen desaturation index, and arousal index. The question remains whether there should be two distinct light sleep stages or a single one, and how this stage should be scored. However, more studies are warranted on optimal scoring methodology to detect abnormal sleep and its connection to daytime symptoms. It could be argued that the current manual sleep staging practice, possibly with a limited number of stages, should be used only as a simple starting point to get a general idea of the sleep macrostructure.

There have been attempts to overcome the limitations of the current sleep scoring practice. For example, the cyclic alternating pattern (CAP) has been used to describe periodic EEG patterns in NREM sleep [102]. The CAP has been successfully used to act as a biomarker for sleep instability and can be used to investigate sleep microstructure [103–105]. However, CAP still requires manual scoring of the recordings and is therefore labour-intensive. There have been attempts to better characterize sleep depth without relying on additional manual scoring and moving beyond the artificial division of sleep into discrete stages [106–108]. For example, the Odds Ratio Product (ORP), assessing sleep depth as a continuous variable based on the EEG frequency content, has demonstrated variability across the night as well as within sleep stages, has been associated with arousability, and it has been shown that ORP-measured sleep quality increases with CPAP treatment [108–110]. Moreover, approaches to present sleep stages with a better temporal resolution relying on deep learning have been introduced [20,23,24]. Similarly, methods to analyze the continuity of sleep without relying solely on the number of arousals or sleep-wake transitions have also been developed [20,23,111].

Finally, the identification of arousals is important for recognizing sleep fragmentation but the current arousal scoring is hampered by several factors. Most notably, the agreement between scorers is poor for arousal scoring with a reported intra-class correlation of 0.54 [112,113]. Hypopnea scoring rules may also influence the arousal scoring. As a hypopnea must be associated with an arousal if a desaturation is not present, it may be tempting to score an arousal that otherwise might not fulfil the scoring criteria for the sake of scoring a visible hypopnea. Moreover, the information on arousals is mainly used for hypopnea scoring and for simply counting the number of arousals; hence, their lengths and start and endpoints may be scored ambiguously, as demonstrated by the studies on arousal scoring agreement [112]. As the accurate identification of arousals could greatly help in assessing sleep architecture, microstructure, and fragmentation, the arousal scoring rules and definitions may require revision and a paradigm shift.

Aside from rationalizing the assessment of sleep based on the electrophysiological activity of the brain, incorporating the physiological phenomenon visible in other biosignals could better represent the restorativeness of sleep. While EEG forms the basis for sleep staging and scoring of arousals, sleep is a phenomenon that extensively affects the body and assessment should not be based on EEG activity alone. A possible biomarker for the restorativeness of sleep could be the coherence or dissonance between the electrical activity of the brain and the physiological effects. For example, HRV differs in OSA patients compared to the normal population across all sleep stages [114]. One interesting possibility would be the photoplethysmography (PPG) signal as its characteristics have been linked to not only cortical activity [115] but also the autonomous nervous system and sympathetic activation [115,116]. PPG characteristics have also been used to explain, to some extent, the impaired vigilance seen in OSA patients [93] and sleep fragmentation [117]. PPG is also easy to record with a pulse oximeter, which is included in many wearables, and thus validated PPG-based methods have great potential for sleep evaluation also in long-term monitoring setups. Thus, it could be argued that enhancing the assessment of sleep by considering the autonomous nervous system activity and other physiological effects could provide benefits in better explaining the daytime effects related to OSA and other sleep disorders; however, more studies are warranted.

3.3. Phenotyping and endotyping SDB

A future direction to improve the assessment of SDB severity involves endotyping and phenotyping of patients based on a variety of characteristics, such as anatomical, demographical, anthropometrical, and PSG data [84,118–122]. Phenotyping delineates patient groups according to clinically observable characteristics using a broad variety of parameters, usually without assessing a direct link to underlying pathophysiology. Endotyping, on the other hand, describes the approach of grouping patients that share common pathophysiology and ultimately facilitating targeted and individualized treatment based on these characteristics.

Phenotyping of SDB is often performed by using unsupervised learning methods, such as clustering, to group the patients based on the characteristics and features from the available parameters derived from clinical investigation together with results from sleep recordings [119–121]. Phenotypes may be assessed by separating SDB patients based on their symptoms, comorbidities, clinical examination, and sleep quality measures [123–126]. For example, phenotyping has been conducted based on comorbidities and daytime symptoms [125] with differences appearing in positive airway pressure (PAP) treatment outcomes between the groups [127]. However, the currently discovered phenotypes are still relying on conventional parameters with their known shortcomings. In the future, cluster analyses could benefit from including features such as microstructure of sleep architecture [23,128], spindle and k-complex morphology [88,129,130], frequency domain information and intensity of arousals [95], breath-by-breath upper-airway flow-limitation [131], and detailed characterization of desaturations [60,74].

However, as the scoring practices differ, and sleep staging and arousal detection suffer from a low inter-rater agreement, the clusters

found in different studies are not directly comparable. It must be acknowledged, that the highly differing ranges of used parameters, the normalization methods, and the method chosen for clustering for a specific set of data influence the performance of the model and the results of the clustering [132,133]. In general, the usage of ratio parameters in sleep medicine has been questioned [36], as they do not represent total or absolute exposure. A practical example of this is the sleep stage percentage: a proportion of 15 % of stage N3 sleep can be vastly different in minutes between individuals sleeping e.g. total of 5 or 9 h. Furthermore, as it has been shown that N3 sleep affects the metabolic waste clearance from the brain [134,135], the proportion or ratio metrics related to total sleep time may not be the optimal choice when neurocognitive deficits are the target outcome.

Simply utilizing data-driven methods to discover clusters within a single dataset will not be enough to reach significant clinical benefits and will not easily generalize across populations. Usually, the identified clusters can only be used for describing the current data and by definition, only describe the data-specific differences between the groups. Thus, mechanisms and pathways linking the identified clusters back to measurable characteristics and classifying new datasets with these are needed. These classifications and characterizations need to undergo stringent multi-centre validation to determine their generalizability and the possibility to explain SDB severity and link to comorbidities and symptoms.

The endotyping of SDB aims to explain the pathophysiological origin of the SDB and the reasons leading to the visible phenotypes. For example, the anatomical collapsibility and neuromuscular recovery of the upper airways, the arousal threshold, and ventilatory control have been suggested to explain the phenotypes and be possible pathways guiding treatment decisions in the future [124,136,137]. However, the assessment of these mechanisms often requires invasive measurements such as using an esophageal pressure catheter, electrodes, and a pneumotachograph [65,138]. However, modelling of the ventilatory control system has provided promising surrogates of these traits relying only on signals recorded during conventional clinical PSGs [58,84,139,140]. These surrogates have been assessed in recent randomized controlled trials to investigate drug mechanisms [141–143] and to explain compliances in OSA treatment to support clinical decision-making [136].

Currently, the AHI together with subjective symptoms, clinical examination, and comorbidities guide the treatment decisions instead of the pathophysiological endotypes or more distinct measures of the overnight pathology such as the degree of desaturations or cardiovascular functionality. Novel diagnostic approaches may better characterize the underlying mechanisms of SDB or the most predictive diagnostic parameters. This could lead to more personalized treatment approaches specifically targeting the endotypes or the causes of adverse health outcomes. However, most of these concepts and approaches are still in a research state, and only a few fully released analysis tools or commercial products exist for phenotyping and endotyping. It is therefore of high priority to conduct further large-scale and multicenter studies to bring forward the validation of these methods, make them accessible to clinicians, and show their applicability in guiding therapeutic decision-making. Ultimately, more detailed phenotyping and endotyping may move the diagnostic decision-making and treatment pathways forward through two different approaches: (1) phenotyping can assist in identifying the characteristics most associated with

Table 1
New technological solutions for sleep-disordered breathing (SDB) diagnosis and assessment and their potential applications in care.

Technology	Metrics and Methods	Associated Evidence	Potential Application in Care
Machine learning algorithms	Analysis of multimodal data, deep learning-based methods to analyze respiratory events and sleep stages	Studies show improved accuracy in SDB diagnosis and automation of scoring [21,45,46,51,53]	Enhances diagnostic accuracy while reducing the manual workload
Wearable/nearable sleep monitors	Heart rate, oxygen levels, movement, snoring, radar technologies, sleep mattresses, smartwatches, wearable electroencephalography	Studies show a correlation between wearable and nearable data-derived sleep stages and respiratory events and can provide useful information on respiration and heart-rate-variability [20,47,50,55]	Helps in the initial assessment, screening and monitoring of sleep patterns and SDB symptoms, potential for SDB diagnosis
Smartphone apps	Patient follow-up, questionnaires, cognitive testing, snoring detection	Capability to collect various metrics and data from patients, decent snoring detection and potential for simplified screening for SDB [168]	Easily implementable methods to collect patient-reported outcomes during treatment and to gain other subjective metrics and other relevant information (e.g. sleep diaries and cognitive functioning)
Portable polysomnography devices	Comprehensive sleep studies	Substantial correlation with in-lab polysomnography [22,159,160]	Comprehensive sleep studies in a familiar environment, possibly over multiple nights with a reduced first-night effect
Analysis of sleep microstructure	Deep learning-based analysis of sleep conventionally and with a better temporal resolution, Odds Ratio Product (ORP), cyclic alternating pattern (CAP)	Studies show increased capability to differentiate fragmented sleep architectures and better quantify the sleep depth on a continuous scale [20,23]	Deeper understanding of fragmented sleep and SDB-specific microstructural changes as well as normal sleep, the possibility for targeted interventions
Quantifying physiological effects	Hypoxemia, respiratory events, electrocardiography (ECG)-based quantifications, pulse transit time, vascular stiffness, cardiorespiratory coupling	Hypoxemia-based metrics better correlate to various comorbidities, the length of the respiratory events differs between patients, SDB patients have differing ECG morphologies [59,60,74–77,93]	Better understanding of underlying effects of SDB and potential for targeted interventions
Phenotyping and endotyping	Clustering, classifiers, machine learning-based methods (e.g. unsupervised learning)	SDB patients express differing phenotypes and endotypes regardless of conventional severity assessments [84,118–122,140]	More detailed and individualized diagnosis potentially leading to more targeted treatment pathways

deleterious outcomes and help focus on the treatment for those who require it while avoiding unnecessary treatment of individuals with a low likelihood of benefits; and (2) endotyping enables identifying individual pathophysiological causes which facilitates the development of new therapies and individualizes and targets the optimal treatment pathway for the individual. Table 1.

4. Future directions

4.1. The need for big data approaches

In the future, clinical practice will likely rely increasingly on automatically derived SDB characteristics and datamarkers instead of relying on simplistic metrics (Fig. 1). Automatic analysis methods and machine learning have already been used to automatize sleep staging [20,45–47,49,50,144,145] and respiratory event scoring [21,146,147] with high accuracy. Similar solutions will likely become more widely adopted and implemented in clinical practice while also enabling the efficient

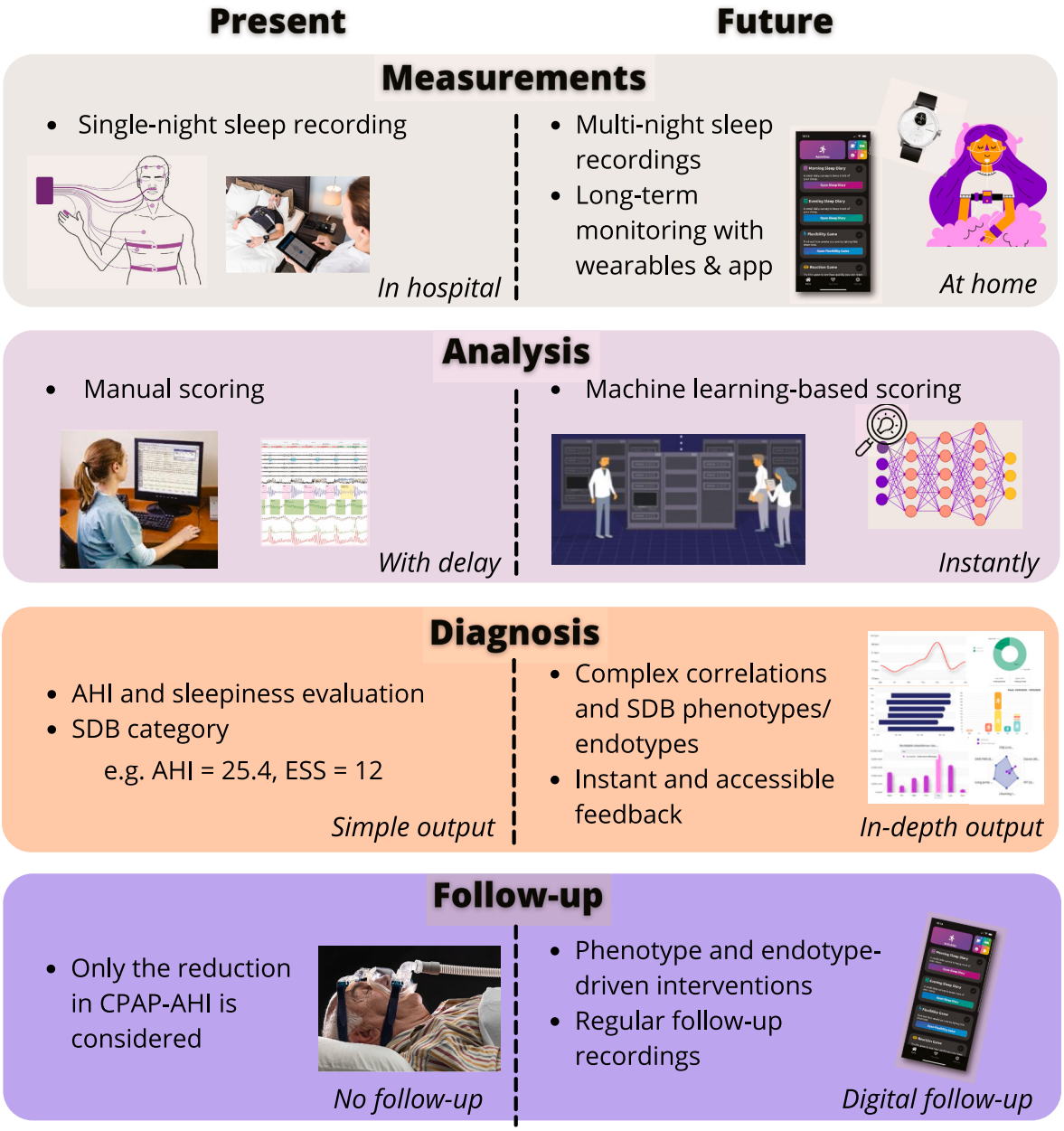

Fig. 1. The diagnostic process of sleep-disordered breathing (SDB). Currently (left side), the diagnostic progress for SDB relies on a complex, in-lab recording conducted only over a single night. This recording is manually scored by a healthcare professional and can take up to hours. However, this information is then compressed into simplistic metrics (e.g. apnea-hypopnea index, AHI) to guide the diagnosis alongside subjective measures (e.g. Epworth sleepiness scale, ESS). Afterwards, no consistent follow-up is conducted and only patients treated with continuous positive airway pressure (CPAP) receive a rough estimate of the reduction of AHI. We propose that in the future (right side), the diagnosis will rely more on multi-night recordings with the possibility of at-home recordings alongside long-term follow-up studies of sleep patterns and SDB characteristics. These are then comprehensively, but automatically, analyzed to provide detailed information on the complex disease characteristics, correlations, and phenotypes. Finally, the progression and treatment of SDB are consistently followed by at-home recordings that are automatically analyzed and the information is accessible to both the patient and healthcare provider.

generation of reliable, comparable, and consistent scoring for large research datasets. However, while the methods can make scoring more robust and reproducible, a large proportion of the benefits that come with machine learning and other data analytical methods are lost. Ultimately, these methods could, for example, resolve temporal patterns in EEG that do not reflect any of the known sleep patterns but correlate well with symptomology. Similarly, the AHI should not be used as a sole baseline and outcome metric when devising novel data analytical and machine learning-based methods and novel biomarkers and metrics. Moving forward will require a paradigm shift in research; the data analysis methods should be used to reveal patterns and datamarkers in the PSG data that are directly associated with clinical outcomes of interest. Meanwhile, these results should promote and guide further prospective clinical trials to validate the new clinical pathways and outcomes. Targeted clinical trials are needed where researchers and clinicians embrace novel and innovative approaches without limiting the studies only to methods that have been used for decades.

One major demand in sleep research is large-scale multicenter datasets. In addition, the application of complementary methods in novel ways, and multidisciplinary efforts are needed. Currently, sleep clinics are the primary source of research data and a major part of studies rely solely on single-centre study populations. Most importantly, the datasets usually lack a healthy reference group without any complaints of poor sleep quality or daytime sleepiness. Moreover, the data does not always contain sufficient variance in terms of ethnicity, age, body mass index, and gender, and the datasets usually lack some demographical or clinical aspects as well as information on comorbidities and medications. Additionally, there is a need to embrace the possibilities wearables and nearables provide as complementary data sources for long-term continuous monitoring. While wearables cannot yet reach the diagnostic accuracy of an in-laboratory PSG, they could still enable noticing patient-specific trends and variability in SDB severity, especially when combined with traditional overnight studies. However, most commercial wearables are designed and optimized for the general, healthy population and may initially produce unreliable outputs for SDB populations and may be sensitive to the effects of various medications. There is a need to implement these in clinical studies to validate and optimize their usage for different clinical populations to enhance their adaption. However, separate considerations are needed for pediatric populations, as the symptomology, clinical manifestations, and diagnostic criteria differ in children.

Besides multicenter datasets, the field needs prospective clinical trials and follow-up studies implementing the new methodologies and not only limiting to traditional clinical practice. Even though researchers have been able to distinguish several new biomarkers, PSG parameters, endotypes, and phenotypes, the underlying traits behind the progression of SDB remain partially unknown. As SDB often develops slowly over time unknown to the affected, discerning how long the individual has suffered from it is practically impossible from a single-night PSG recording. Multiple-night studies, as well as follow-up studies, could help enable a better understanding of the underlying physiological cascades of residual excessive daytime sleepiness, development of neurocognitive deficits, and cardiometabolic consequences. In addition, long-term treatment monitoring could reveal insights for optimized treatment pathways and move away from the mentality that CPAP is the treatment choice for all and the single most important monitored effect is a reduction in the AHI. As the current diagnostic devices are not best suited for long-term monitoring, there is a clear need to also develop simplified recording setups.

Alongside comprehensive clinical trials and follow-up studies gathering objective data, there is a pressing need to incorporate more relevant and detailed outcome metrics of patients, including patient-reported outcome measures (PROMs). PROMs can provide invaluable insights into the perspective of the patient, capturing the impact of SDB on their quality of life, daily functioning, and overall well-being [148,149]. Incorporating PROMs could facilitate a more comprehensive approach to patient care while also helping in identifying subtler, yet significant, effects of the disease and its treatment that may not be captured by traditional clinical measures alone. This approach could facilitate a better understanding of the disease trajectory, treatment responsiveness, and long-term outcomes, ultimately leading to more personalized and effective treatment strategies. By combining objective clinical measures with subjective patient experiences, we can develop a more nuanced understanding of SDB, its impact on patients' lives, and the effectiveness of different treatment approaches to both drive clinical care and research forward.

4.2. Translation of research to clinical practice

Ultimately, SDB research will lead to a more efficient diagnosis, help in informed decision-making, and assist in personalized and individualized SDB severity assessment and treatment. Before implementation, these will require stringent studies, clinical trials, and large collaborative multi-centre efforts. Overall, all the obtained results must be linked back to measurable and interpretable characteristics to provide a diagnostic benefit [86]. Explainability, reliability, and generalizability are essential to translate novel diagnostic methods to clinical practice and will help in the regulatory processes as well as clinical validation and acceptance.

Currently, the in-laboratory PSG is considered the most comprehensive and reliable diagnostic method for SDB [18,150]. However, alternatives to in-laboratory PSG already exist and all devices have their intended usages with advantages and limitations [22]. For example, a home sleep apnea test is often used for individuals with a high pre-test probability for OSA but omits information on sleep architecture. In addition, actigraphy and other wearables and nearables can be used for long-term monitoring of wake-sleep patterns but are less capable of assessing detailed sleep structure and currently suffer from low reliability in determining the total sleep time [151,152]. However, there has been a surge in technological development in recent years in creating more precise, simpler wearable and nearable solutions for the recording setup [153–160]. The home-based measurements allow the patient to sleep in a familiar environment and are a more cost-effective option [161]. While sleep may be more natural in a home environment, the measurements are done without supervision by a healthcare professional and can suffer from a higher failure rate [161,162]. However, advancements in telemedicine and remote monitoring may be viable options to mitigate the failure risk. While this will likely not scale up to multi-night studies, these methods can guide the individual and ensure that the first recorded night is as high-quality as reasonably possible. All in all, both home and in-laboratory measurements have their flaws and benefits; these should be considered carefully when interpreting studies. One important future direction would, thus, be the optimization and harmonization of the measurement setup. Investigating the streamlined recording setup would be beneficial for both clinical purposes as well as research aspects.

Finally, while PSG is an extensive measurement setup and the rise of wearables and nearables, machine learning, and precision medicine can move the field forward, it should be acknowledged that explanatory factors for disease progression and symptomatology may remain outside the conventional or wearable-based sleep recordings. For example, magnetic resonance imaging may give insight into pathophysiological factors, novel blood biomarkers may explain the restorativeness of sleep and physiological effects of the disease, and participatory medicine supported by digital follow-up may engage patients [163–167]. Consequently, we should emphasize cross-speciality interactions in clinical work and multidisciplinarity in sleep research. Novel scientific discoveries from biomedicine, radiology, computer science, and animal studies can help us to resolve the highly fascinating and complex puzzle that is called SDB.

5. Conclusions

There has been a surge of recent advances in diagnosing and assessing the severity of SDB and the related health sequelae mostly due to innovations that have been enabled by technological and computational advancements. However, clinical practice is still getting acquainted with these new methodologies and AHI has remained the status quo. To advance the diagnosis and management of SDB, large-scale multidisciplinary research efforts alongside clinical validation and implementation of the outcomes of prospective clinical trials, and eventually, clinical practice are needed.

In the future, the simplistic parameters should be complemented by metrics better explaining the phenomenon of interest accurately, whether it is SDB severity, physiological effects, treatment outcomes, or risk of developing comorbidities. While the interpretation of metrics may initially require adaptation, this will be a step toward more individualized diagnostics and provide benefits to both the patient and the sleep experts with the ultimate goal being improved health and quality of life. The diagnoses and treatment decisions should not rely on simple metrics but instead, be driven by and based on individual pathologies and optimized treatment pathways; this will require informed data-analysis-assisted decision-making. It remains to be seen what the final pathways will be that drive the clinical practice forward. However, as researchers and clinicians, we should remember that this is not a race to the finish line with only a single winner: rather we should focus on tirelessly working together in a multidisciplinary way toward the future of sleep medicine.

Practice points

1. Sleep research and diagnostic practices mostly rely on outdated metrics and laborious methods reducing the diagnostic capacity and preventing timely diagnosis and treatment.
2. Collaboration among multiple medical specialties, disciplines, and professions is crucial for a comprehensive evaluation of sleep-disordered breathing. This interdisciplinary approach is equally important in sleep research to foster a holistic understanding of sleep disorders.
3. In the future, the simplistic parameters should be complemented by metrics better explaining the phenomenon of interest accurately, whether it is sleep-disordered breathing severity, physiological effects, treatment outcomes, or the risk of developing comorbidities.

Research agenda

1. Research should not be driven by conventional diagnostic practices; rather, it should renew the current status quo in clinics towards improved, patient-centered care.
2. A major demand in sleep research is large-scale multi-centre datasets including cohorts of non-symptomatic, healthy volunteers and openly available data together with multi-night studies and follow-up series.
3. The application of different realms of big data, data analytical, machine learning, and other data-driven approaches could provide breakthroughs in the coming years to fully utilize the potential of all the collected medical and overnight data.

Glossary of terms

AHI	apnea-hypopnea index
CAP	cyclic alternating pattern
CO_2	carbon dioxide
(C)PAP	(continuous) positive airway pressure
CRC	cardiorespiratory coupling
ECG	electrocardiogram
EEG	electroencephalography
ESS	Epworth sleepiness scale
HRV	heart rate variability
N1	light sleep stage 1
N2	light sleep stage 2
N3	deep sleep
NREM	non-rapid eye movement sleep
OSA	obstructive sleep apnea
ORP	Odds Ratio Product
PPG	photoplethysmography
PSG	polysomnography
REM	rapid eye movement sleep
SDB	sleep-disordered breathing
SpO_2	blood oxygen saturation
UA	upper airway

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