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Sleep apnoea and its consequences: from animal models to precision medicine☆

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ABSTRACT

A European Respiratory Society research seminar entitled "Sleep Apnoea and Its Consequences: From Animal Models to Precision Medicine" was held in January 2024 in Lisbon, Portugal. It provided an in-depth analysis of the current landscape and future directions in OSA research, integrating recent findings from metabolomics, animal models, clinical predictors of cardiometabolic consequences of OSA, artificial intelligence (AI), and advances in diagnostic algorithms. This article presents a narrative review of the seminar's key discussions and conclusions.

The limitations of current randomized controlled trials (RCTs) in assessing OSA treatment, such as low adherence and patient selection bias (e.g., absence of sleepiness or severe hypoxemia), were critically discussed. The expert panel recommended the use of real-world data, including patients commonly seen in clinical practice, and the use of digital tools for real-time monitoring of adherence and side effects. The concept of platform "disease-focused" trials was discussed as a more efficient and adaptable research design that could allow clinical trials to be more representative of the general OSA population and to compare CPAP with emerging treatments

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such as new drugs, devices and lifestyle interventions to gain a broader understanding of effective management strategies.

The seminar concluded that a multifaceted approach to OSA research that leverages the strengths of animal models, advanced AI, metabolomics, and improved diagnostic algorithms is needed to gain deeper insights into the mechanisms of OSA and its treatment response. This new approach, coupled with new "platform" clinical trial designs, could contribute to improved outcomes in patients with OSA.

1. Introduction

Obstructive sleep apnoea (OSA) is a chronic and common condition that affects 10 %–49 % of men and 5 %–23 % women depending on age and body mass index [1–4]. It is a disease with significant clinical and socio-economic impact, closely linked to impaired quality of life and excessive daytime sleepiness [5]. Additionally, it has been associated with cardiometabolic pathology and cognitive impairment [6].

Despite being a widely studied condition, many important questions remain unresolved. OSA is conventionally diagnosed by the apnoea-hypopnoea index (AHI), a limited metric that does not reflect the complexity of the disease [7]. Recently, significant evidence has emerged regarding the usefulness of new biometrics for diagnosis, risk stratification, and prediction of response to continuous positive airway pressure (CPAP) therapy [8]. Beyond the need to improve the characterization of this pathology, it is also essential to identify additional biomarkers that enhance disease classification and deepen our understanding of its pathophysiological mechanisms [9]. Artificial intelligence could also help integrate these new sources of information to improve diagnosis and guide treatment decisions in clinical practice.

One of the main topics widely studied in recent years is the evaluation of the beneficial effect of treating OSA with CPAP. Although the benefit is clear in symptomatic patients, randomized controlled trials in secondary cardiovascular prevention were neutral [10–12]. These results led to the questioning of the benefit of CPAP treatment but a recent individual data meta-analysis of these RCTs and non-RCT controlled studies have suggested the relevance of maintaining adequate adherence to CPAP therapy to achieve a cardiovascular preventive benefit [13–16], even though a “healthy adherer effect” cannot be excluded in the non-RCT studies [17].

Additionally, exploring gender differences and the different endophenotypes of the disease is crucial for the understanding of the heterogeneous response to the consequences of this pathology and its response to treatment as recently proposed in an American Thoracic society (ATS) statement. [9,18–20]. Detailed analyses have also suggested the possible existence of patient profiles in which there could be cardioprotection and a potential therapeutical effect from exposure to moderate hypoxia [21]. All these findings suggest the need to properly define the patients’ profile and to personalize their management.

Finally, all these recent advances indicate the need to identify collaborative actions and international strategies for real-world data analysis, the generation of databases, and intervention studies to improve the understanding of this pathology and its clinical management. It is a priority to promote task force actions that will help to improve the understanding of the pathophysiological consequences of OSA, the characterization of the different phenotypes of the disease, and the effect of treatment on the various associated pathological outcomes. All of those will contribute to the development of precision medicine tools for the personalized management of this chronic, common disease with significant socioeconomic consequences.

To advance this crucial field, the European Respiratory Society (ERS) hosted a research seminar titled "Sleep Apnoea and Its Consequences: From Animal Models to Precision Medicine" in Lisbon, Portugal, in January 2024. This event gathered international experts and research groups specialized in sleep breathing disorders to foster knowledge exchange, identify specific research questions, and facilitate future collaborative projects. This narrative review summarizes the seminar's key insights, conclusions, and proposals.

2. Predictors of OSA-related consequences

2.1. Contribution of animal models

Observational studies, randomized controlled trials and analyses of real-world data provide major progress in the phenotyping of OSA patients and evaluation of treatments [19]. However, important questions relative to the mechanisms involved in OSA-related consequences are not fully resolved and cannot be addressed in humans. In that context, animal models are crucial. They allow the conduction of invasive studies that are not ethically feasible in humans, enable the control of risk factors (i.e. age, genetics, environment and health status) and provide new insights to identify cellular and molecular changes. Animal models also provide a unique way to perform longitudinal studies over extended periods and to assess the efficacy of pharmacological treatments [20].

Ideally, animal models should be homologous, meaning that they would recapitulate, as closely as possible, what happens in human diseases. Accordingly, the first models developed in the 1990s aimed to induce recurrent airway occlusions during the animals’ sleep time, resulting, as in humans, in cyclic desaturations and resaturations, called intermittent hypoxia (IH), an increase in intra-thoracic pressures and ultimately sleep fragmentation [21–23]. However, although very close to human OSA pathophysiology, such models proved to be very complex and difficult to set up, as they require complex surgery and the use of large animals (i.e. dog and pig) with ethical and economic constraints. Thus, rodent models were favoured and allowed to provide new insight into both the initiation and consequences of apneas [24].

Among them, “simplistic” models have been developed and most of the research groups worldwide currently use the well-described model of IH in rodents, where the animals alternately breathe nitrogen-enriched air to simulate hypoxia and air for the reoxygenation phase (i.e., inspired oxygen fraction (FiO2) oscillating from 21 to 5–6 %). Even if IH does not allow to investigate the causes of the disease, this model offers undeniable advantages. Indeed, such a model makes it possible to isolate the hypoxic component of the human disease, to strictly control hypoxic conditions (e.g., duration, intensity and pattern) and to manage various modifying factors (e.g., obesity, age, sex, comorbidities). Abundant literature over the last 20 years highlights the detrimental role of severe IH on vessels [25], myocardium [26], as well as on the genesis of metabolic perturbations [27,28], at both organ and systemic levels. In addition, these IH protocols allowed identifying several interconnected intermediate mechanisms (i.e. sympathetic activation, inflammation, oxidative stress, HIF-1 activation, endoplasmic reticulum stress …), which now need to be validated as potential biomarkers or therapeutic targets in clinical cohorts [29,30]. Conversely, a major limitation of these rodent models is that they do not reproduce other key features of OSA, such as negative intrathoracic pressure swings and sleep fragmentation. This limits their ability to fully capture the multifactorial physiological stress induced by real-life apneas.

Although very important to improve knowledge on mechanistic insights, studies using animal models of IH are conducted in rodents that are generally resistant to pathologies, and most of the studies use the same severe IH paradigm (i.e. FiO2 oscillating from 21 to 5–6 %, 60 to 120 cycles per hour) [26]. Therefore, while this specific IH paradigm could be relevant to model hypoxia experienced by certain OSA patients,

it does not reproduce the heterogeneous response of the OSA population in terms of consequences and response to treatment. As clinical data have suggested that some OSA patients may exhibit cardioprotection [18,31] and considering the emerging importance of hypoxic burden severity as a predictor of cardiovascular outcomes in OSA patients, future preclinical studies are needed to decipher whether the effect of IH could be dose-dependent [32]. Ideally, new studies should be designed to compare different severities (from mild to severe), durations and patterns of IH, as well as their respective consequences on cardiovascular outcomes and related mechanisms. Furthermore, it seems mandatory to address several important questions in future experimental studies: What kind of patient's phenotype do we want to reproduce in animal models? Will it be possible to determine specific IH paradigms in term of frequencies and magnitude that reproduce specific clusters of OSA patients? Would specific mechanisms be activated in response to these different IH paradigms?

Animal models constitute valuable tools to study OSA-related consequences in a controlled and ethically acceptable manner. They allow investigations of multiple hypoxic conditions and underlying mechanisms, which should help characterize different patients' phenotypes and their response to treatment. Nevertheless, future efforts should aim to develop more integrative models that include not only intermittent hypoxia, but also intrathoracic pressure changes and sleep disruption, in order to more faithfully replicate the full spectrum of OSA pathophysiology. Efforts to better integrate findings from animal studies with clinical observations are now needed to allow the development of new diagnostic tools and personalized therapeutic strategies for managing OSA-related complications.

2.2. Contribution of polysomnography-based algorithms

The apnoea-hypopnoea index (AHI), currently used to define OSA severity, does not take into account the complexity of respiratory events and may not be sufficient to assess OSA-associated cardiovascular risk [7,22] or to select patients likely to respond to CPAP treatment [10–12]. Moreover, extracting only one number from complex sleep investigations is a waste of information. In recent years, several new markers of cardiovascular risk in OSA have been proposed based on the analysis of sleep recordings (Fig. 1).

The Hypoxic Burden (HB) is based on the pulse oximetry signal and refers to the quantification of the amount and severity of oxygen desaturation during sleep [23]. Although the severity of hypoxemia can be assessed using different metrics such as the oxygen desaturation index (ODI), time spent with an oxygen saturation (SaO_2) below 90 % or the mean/lowest SaO_2, Azarbarzin et al. demonstrated that HB, calculated as the area above the oxygen desaturation curve, may be superior in predicting incident heart failure and cardiovascular death independently of other known risk factors, including AHI, in two large cohorts. [24,25]. This prospective association was confirmed in the "Pays de la Loire Sleep cohort" (PLSC) and a high HB was further associated with a significant response to CPAP treatment in the reduction of the risk of recurrent CV events as secondary prevention in the ISAACC cohort [26–28].

Sleep apnoea-specific pulse rate response or "delta heart rate» (dHR) is the difference between the maximum pulse rate after airway reopening and the minimum pulse rate during respiratory events [29]. This marker represents the autonomic response to a stress and was shown to have a "U" shaped relationship with cardiovascular morbidity and mortality among patients with OSA in the sleep heart health study [29]. Moreover, among OSA patients with a previous coronary event in the RICCADSA study, CPAP was able to reduce the risk of recurrent CV event only in those with a high dHR [30]. A recent analysis also showed that higher dHR can be calculated based on a simple oximeter (dHRoxi) and that higher dHR and dHRoxi are both independently associated with a better response to CPAP in terms of cardiovascular risk reduction [31].

The Pulse Wave Amplitude Drop Index (PWADi) is based on the

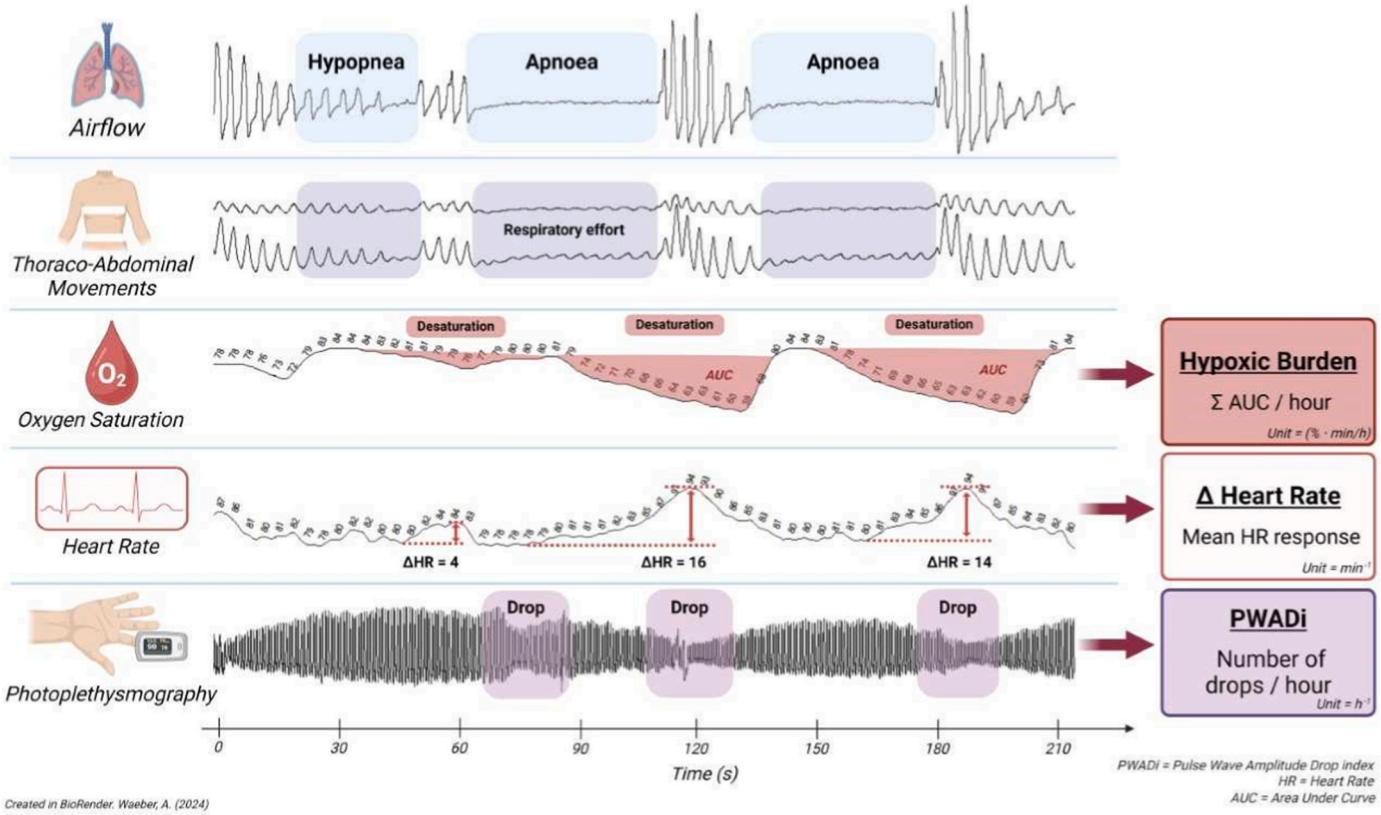

Fig. 1. New markers of OSA severity: Hypoxic burden, Delta Heart Rate, and pulse wave amplitude drop index (PWADi).

photoplethysmography (PPG) signal of the pulse oximeter (Fig. 1) and reflects sympathetic activations and vasoreactivity [32–35]. It is calculated as the number of pulse amplitude drops per hour on the PPG signal. A recent analysis of three cohorts (HypnoLaus, PLSC and ISAACC) showed that a decreased PWADi was associated with an increased risk of incident major adverse cardiovascular event [36], which was further confirmed in an Australian cohort [37]. We hypothesize that this reflects a progressive blunting of the autonomic nervous system due to chronic baroreceptor overstimulation and/or reduced vascular reactivity resulting from prolonged exposure to OSA, ultimately contributing to increased cardiovascular risk.

Combining these novel markers with the AHI, ideally derived from multi-night recordings [38,39], could more accurately capture the impact of respiratory events on cardiovascular risk and support the development of a precision medicine approach to CPAP treatment by identifying patients most likely to benefit in terms of cardiovascular risk reduction [40]. However, there is an urgent need to standardize how these markers are measured and to establish stratified or physiologically scaled reference values for biomarkers such as HB, ΔHR, and PWADi, as their absolute values and physiological interpretation vary substantially across age, sex, and body composition. Incorporating such stratification will improve interpretability and reduce confounding, thereby advancing a truly precision-based framework for OSA.

2.3. Contribution of OMICS

The lack of personalized management of OSA often leads to limited treatment efficiency [41]. Multi-omics, or multilevel 'omics', analysis refers to the integration of normalized data from different biomolecular levels to establish the data relationship between molecules at different levels [42]. The implementation of multi-omic methodologies in sleep medicine is gaining momentum aiming to improve patient risk stratification and guide more personalized therapy decisions.

Multiple evidence is emerging on the role of multi-omics in the understanding of the pathophysiology of sleep disorders, the application of diagnostic OMICS markers, and targeting of interventions aimed at mitigating or resolving the adverse consequences of sleep disorders. Sleep insufficiency was demonstrated to cause marked molecular changes at transcriptomics, proteomics, and metabolomics level [43]. Aberrant metabolites, inflammation and the alterations in the gut microbiome have been reported in insomnia patients [44]. Using a large multiethnic dataset including sleep parameters, an association was reported between P2XR4 expression to average oxyhemoglobin saturation during sleep and butyrylcarnitine (C4) levels [45]. Epigenomics analysis demonstrated a link between epigenomic variation in Peripheral Blood Mononuclear Cells (PBMCs) and systemic epigenetic age acceleration with OSA severity and response to CPAP treatment [46]. Single-cell transcriptomics analysis demonstrated OSA-induced heterogeneity in cellular composition and enabled the identification of previously undescribed cell types in PBMCs that varied with the severity of the disease, as well as the building of molecular signatures distinguishing OSA patients from controls with over 95 % accuracy [47]. Multi-omic analysis of blood circulating exosomes revealed changes at lipidomic, proteomic, and microRNA (miRNAs) cargo in OSA patients that were responsive to adherent CPAP therapy [48]. In addition, several studies using animal models provided mechanistic insights on the multi-level molecular changes in sleep deprivation [49,50], the impact of sleep disturbance in atrial fibrillation inducibility [51], the effect of gestational OSA in the epigenome and obesogenic phenotype of the offspring [52–54], and the senolytic-facilitated reversal of end-organ dysfunction in OSA [55].

Multi-omics analysis provides an opportunity to precisely study and characterize sleep disorders by associating phenotypic data with a large amount of distinctive molecular measures in a systematic manner [56]. Further studies on the application and clinical utility of OMICS biomarkers and OMICS-based therapies in sleep disorders are therefore encouraged and should pave the way for major advances in for the implementation of Precision Sleep Medicine.

2.4. Contribution of artificial intelligence

Several studies worldwide have proposed various biomarkers to improve sleep diagnosis, aiming to predict cardiovascular (CV) disease risk or assess treatment effects like CPAP on CV health. Most studies demonstrate these connections using statistical methods such as univariate and multivariate Cox proportional-hazards models. However, combining several biomarkers using these statistical approaches requires stratification of the population, which reduces the statistical power. Artificial intelligence (AI) methods can overcome this disadvantage and merge all clinical and sleep-related data to produce a global risk estimator, automatically selecting the most pertinent data [57]. A subset of AI, supervised learning, relies on training and evaluation phases for model development. This underlines the essential role of meticulous attention to training data and validation methods in ensuring the reliability and relevance of AI-derived results in clinical decision-making [58].

A few studies have proposed a CV risk estimator based on AI for OSA patients. For example, Segura et al. [59] combined clinical and polysomnographic features to achieve an area under the curve (AUC) of 0.76, while Zhang et al. [60] achieved a sensitivity of 87.9 % and a specificity of 57.0 %. Another study suggests employing deep neural networks to estimate CV risk from electrocardiogram signals [61]. However, the use of electrocardiogram signals and polysomnographic features in all recordings restricts the use of this estimator to polysomnography. One additional study shows promising results with an AUC of 0.84 [62], but like the research conducted by Mazzotti et al. [63] it requires an additional examination, which is both time-consuming and costly. All studies using the Sleep Heart Health Study cohort [35–39] evaluated the same predefined incident cardiovascular outcomes: hospitalized acute myocardial infarction, coronary surgical intervention (angioplasty, stent placement, or bypass grafting), angina pectoris, coronary heart disease death, any coronary heart disease (composite endpoint), and stroke. Recently, two AI-based models have been proposed to predict the CV risk using only an overnight oximetry. The first model, based on machine learning and decision trees, is easy to interpret. It automatically calculates thresholds of interest for sleep biomarkers. With an AUC of 0.78, it predicts CV risk by combining five clinical variables and four sleep biomarkers [64]. The second model, utilizing deep learning achieved the highest AUC of 0.82 with the autonomic manifestations signal [65]. Deep learning models use more complex algorithms, enabling the direct analysis of raw signals, thus avoiding the biomarker extraction step. Both models, developed using data from the IRSR-PLSC cohort, assessed the prediction of cerebrovascular disease, coronary heart disease, heart failure, and mortality. Together, these findings suggest that sleep data are particularly relevant for use in women and individuals under 60 to predict the CV risk.

AI offers numerous advantages in healthcare, including its ability to find and combine information to provide risk estimators and demonstrate remarkable performance, particularly with advanced deep learning techniques. However, it is important to use AI carefully, considering clinician knowledge, training population, ethical considerations and usability.

3. Depicting heterogenous clinical manifestation of OSA

3.1. Metabolic, cognitive and cerebrovascular consequences

OSA adversely affects multiple organs and is strongly associated with obesity, as well as several cardiovascular, cerebrovascular and metabolic diseases, including diabetes and chronic liver disease [66]. The cardiometabolic complications of OSA are primarily driven by intermittent hypoxia (IH), characterized by repetitive occurrence of oxygen

desaturation and re-oxygenation sequences during sleep. This intermediary mechanism contributes to dysmetabolism through effects on adipose tissue and ectopic fat depots, such as nonalcoholic fatty liver disease (NAFLD). [67–71]. NAFLD, which ranges from simple steatosis to more severe liver conditions, is exacerbated by IH through increased liver lipogenesis and oxidative stress, as well as early liver inflammation [68–70,72,73]. Management of NAFLD in OSA patients typically involves lifestyle changes and CPAP therapy, though CPAP's effectiveness in reversing NAFLD remains uncertain [74,75].

OSA has a bidirectional relationship with diabetes, with high OSA prevalence in both type 1 and type 2 diabetes [76–78]. IH and sleep fragmentation in OSA contribute to insulin resistance and beta-cell dysfunction, increasing diabetes risk. [76]. Untreated OSA is linked to poorer glycemic control and exacerbates diabetic complications [78,79].

While the impact of CPAP on diabetes control is debated, recent studies suggest a potential benefit in reducing HbA1c levels and improving blood pressure in OSA patients with type 2 diabetes. Adherence to CPAP is also associated with reduced healthcare utilization [80–82].

OSA is also associated with an increased risk of mild cognitive impairment (MCI) and Alzheimer's disease (AD) [83,84]. The severity of hypoxic burden in OSA correlates with biomarkers and imaging patterns of neurodegeneration in AD. [85,86]. Although CPAP may improve cognition in OSA patients with AD, this evidence is so far limited, and the feasibility of randomized controlled trials is questionable. Real-world data are needed to determine if OSA is a modifiable risk factor for cognitive decline [87].

In stroke survivors, OSA is highly prevalent and significantly impacts recovery, increasing the risk of stroke recurrence and overall mortality [88–90]. and there is a bidirectional relationship between OSA and stroke. [91]. While initial refusal of PAP therapy is common, adherence may reduce stroke recurrence and improve survival. [92]. However, stroke prevention strategies in these patients should integrate comprehensive care, addressing multiple risk factors beyond OSA alone [88].

3.2. Endotyping and phenotyping OSA for a precision medicine approach

The idea of disease endotypes first gained popularity in asthma research and has been used to describe specific pathophysiologic/biological mechanisms leading to disease [93]. More recently, this idea has spread to the field of OSA. Four main OSA endotypes [94,95] have been described including an anatomical endotype typified by a high critical closing pressure of the upper airway (Pcrit), and non-anatomical endotypes. These include decreased pharyngeal dilator muscle responsiveness, low central nervous system arousal threshold, and high loop gain/unstable respiratory control. While it has been hypothesized that treatment could be guided by endotype [96], there is evidence demonstrating considerable endotypic overlap within individuals [97]. Consequently, targeting a single endotype may not enable effective treatment of obstructive respiratory events, which would require combination therapy in some cases. Additional considerations regarding the utility of OSA endotypes are firstly, the ability to clinically evaluate for these distinct subtypes using non-invasive approaches [98], and secondly, their intraindividual variability within and across nights [99,100]. Nonetheless, there are emerging data to suggest that endotype-driven approaches can predict response to treatment; namely Schmickl et al. [101] found that the presence of high loop gain can predict greater reductions in blood pressure with CPAP therapy. Further, given the high rate of CPAP discontinuation [102,103] these methods can be used to achieve at least partial disease control through novel targeted therapeutics [104,105].

This raises the question of what is meant by “disease control”? While treatment by endotype may reduce the AHI, it is still unclear which patients with an elevated AHI even require OSA therapy. Though recent global estimates of OSA using AHI criteria alone suggest a disease prevalence of almost a billion people worldwide [1], it is unreasonable to believe that all of these individuals will require treatment to reduce their AHI. Subtyping patients by clinical, physiologic, biologic disease consequences and sex/menopausal status rather than mechanisms which lead to disease development (i.e., endotype), will better identify the goals of treatment. These disease consequences can be described as distinct observable traits also known as disease phenotypes. OSA phenotypes have taken on several forms including subtyping by symptoms [5], physiologic response to respiratory events [24,25,29,106–108], and associated biology such as inflammatory status subgroups [109,110]. Therefore, describing and characterizing patients by phenotype may lead to a better understanding of treatment indications and objectives. For example, patients with OSA and sleepiness experience symptomatic improvement with CPAP [111], while patients with OSA and either a high hypoxic burden [26], high PWAD index [36], or elevated pulse rate response [30] may experience cardiovascular benefit. Gender differences in response to CPAP in terms of reductions in cardiovascular risk have also been observed [18,20]. Further, novel machine learning approaches can uncover phenotypes based in unique combinations of multiple baseline predictor variables from various domains to identify patients that experience benefit, no effect, or even harm from therapy [112,113]. While endotypes may tell us how to treat patients with OSA, phenotypes will tell us who to treat. By combining these approaches, we will finally achieve an era of precision medicine in OSA.

3.3. Why are the randomized controlled studies (RCT) neutral?

CPAP treatment has proven beneficial in alleviating OSA symptoms, particularly daytime sleepiness, and has demonstrated a positive impact on reducing blood pressure, especially in patients with resistant hypertension and those adherents to CPAP therapy [114]. While randomized trials and meta-analyses confirm that CPAP use is associated with significant blood pressure reductions in primary cardiovascular prevention, this favourable effect remains unverified in secondary prevention of cardiovascular events. Three large-scale randomized clinical trials (RCTs) with extensive participant cohorts have investigated the potential of CPAP in preventing cardiovascular events in individuals with OSA [10–12]. It has been argued that the neutral results of RCTs of CPAP for secondary cardiovascular prevention OSA could be flawed due to design biases. The RCTs used broad inclusion criteria, deployed simplified home-based sleep studies, and initiation and follow-up of patients allocated to CPAP were consistent with specialist sleep clinic processes. While RCTs can never include all “real-world” patients, their primary purpose is to provide a reliable answer to a clinically meaningful question, based on sensible estimates of the treatment effect and in an efficient manner over a realistic time frame. From the different reasons that could explain the neutral results of these RCTs, patients’ profile (non-sleepy patients), potential ceiling deleterious effect of OSA in specific profiles of patients with high comorbid burden, composite cardiovascular outcome (major adverse cardiac and cerebrovascular events; MACCEs), together with a low CPAP compliance could, at least partly, explain these unexpected results. In fact, a recent individual patient data meta-analysis concluded that adherence to CPAP was associated with a reduction in the risk of cardiovascular event recurrence, suggesting that CPAP adherence is a key factor in secondary cardiovascular prevention in patients with OSA [13]. Finally, available evidence contributes to discussing the reasons justifying the lack of a positive effect of CPAP treatment and encourage the improvement of future trial designs by appropriately selecting the patient profile, stratifying the severity of the disease, the outcome measure, and, above all, enhancing treatment adherence (Fig. 2).

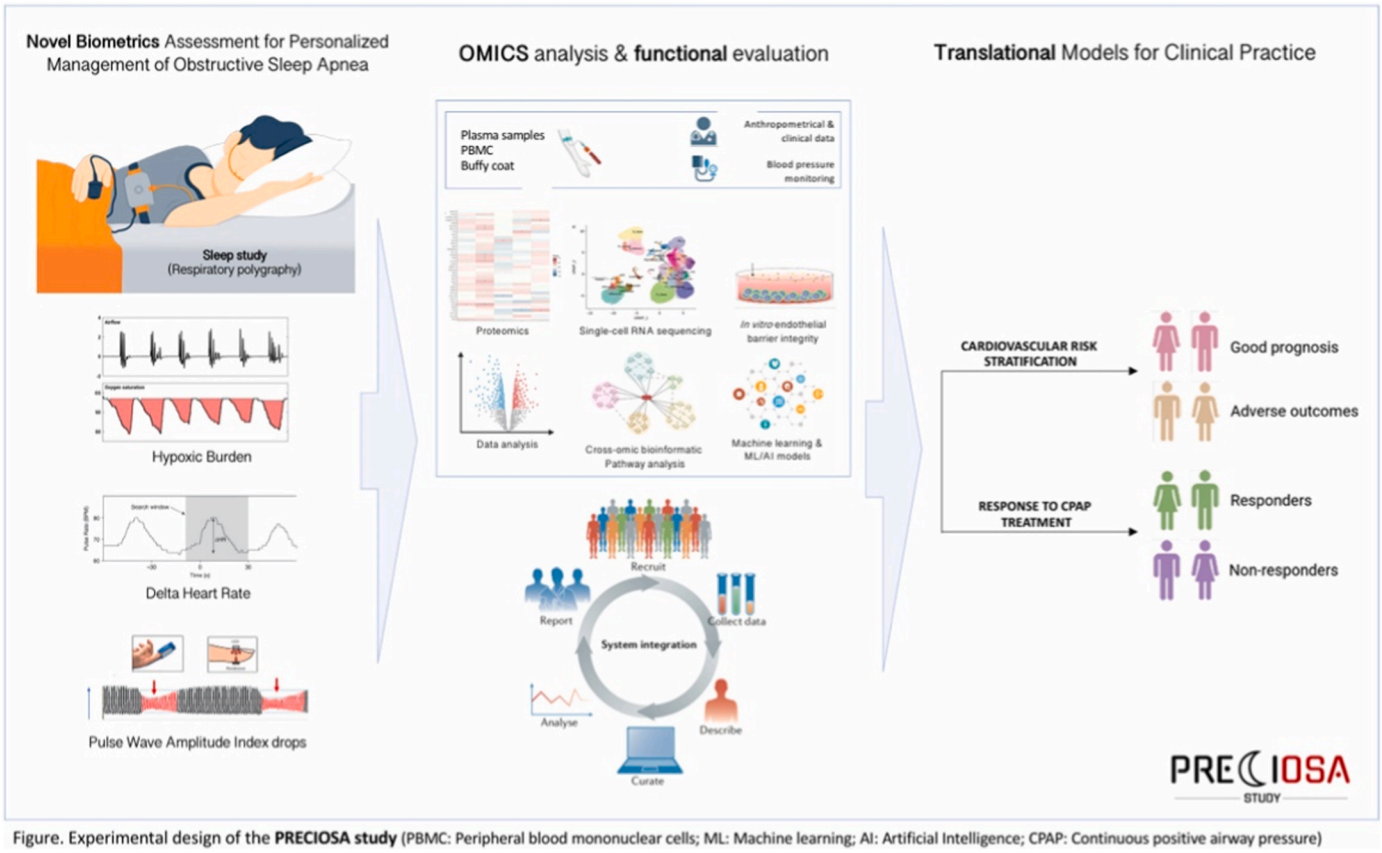

Fig. 2. Experimental design of the PRECIOSA study (PBMC: Peripheral blood mononuclear cells; ML: Machine learning; AI: Artificial Intelligence; CPAP: Continuous positive airway pressure.

4. How to move forward? Upcoming research scenario

4.1. New design of the studies

Building on the limitations identified in previous randomized controlled trials, future studies targeting cardiovascular outcome in obstructive sleep apnea (OSA) require a fundamental redesign in terms of patient's selection, trial conduct, monitoring, and combination of therapeutic strategies.

Patients' selection: upcoming trials should prioritize the inclusion of patient subgroups most likely to benefit from treatment, based on novel PSG-derived markers of cardiovascular risk (hypoxic burden, ΔHR, and PWAD) and clinically relevant symptoms [26,29,30,36,40]. Enrolling these populations will require careful consideration of ethical aspects related to sleepiness-related risks and safety, as well as clear communication of equipoise to clinicians and patients. Several design strategies may help mitigate sleepiness-related risks, including excluding extreme Epworth Sleepiness Scale (ESS) values or individuals with a history of near-miss accidents. The use of wake-promoting agents that have no significant adverse cardiovascular impact in the control arm [115–117].

Trial conduct: Wearable devices and digital health technologies have the potential to substantially improve trial feasibility, patient engagement, and cost-efficiency. The implementation of partially or fully "siteless" trial models can reduce participant burden through virtual visits, remote data capture, and continuous monitoring of clinically meaningful digital endpoints. Importantly, early detection of poor treatment adherence through connected devices may enable timely behavioral interventions, peer support strategies, and adaptive adherence-enhancing approaches during the study [118-120].

Advances in diagnostic technologies provide new opportunities to optimize patient identification and reduce misclassification of OSA severity. End-to-end digital solutions incorporating multi-night home sleep recordings and artificial intelligence–assisted analysis may facilitate more accurate phenotyping at scale and accelerate recruitment in large outcome-driven trials [121].

Beyond improvements in CPAP-focused trial design, there is a pressing need to move beyond siloed therapeutic evaluation in OSA. Future studies should directly compare CPAP with emerging non-CPAP alternatives [13,122], including pharmacological therapies, medical devices, neurostimulation techniques, and lifestyle interventions, either alone or in combination [123,124]. In this context, platform trial designs represent a particularly attractive and efficient approach [120]. Platform trials are multi-arm, multi-stage studies conducted under a single master protocol, allowing multiple interventions to be evaluated against a shared control group and enabling the seamless addition or discontinuation of treatment arms over time [125,126]. Such adaptive and perpetual designs may be especially well suited to the sleep field, where resources are limited and innovation is rapidly evolving, while simultaneously fostering collaboration between academic investigators and industrial partners (Fig. 3).

In summary, rather than representing an endpoint, the neutral results of earlier cardiovascular outcome trials in OSA provide a unique opportunity to reimagine the future of clinical research in this field. Embracing innovative trial designs, digital monitoring tools, adaptive methodologies, and broader therapeutic comparisons will be essential to generate clinically meaningful evidence and to align OSA research with contemporary precision medicine frameworks. [120].

4.2. Big data analysis

While in the past most research data had to be collected ad hoc, now large amounts of healthcare data are being generated continuously.

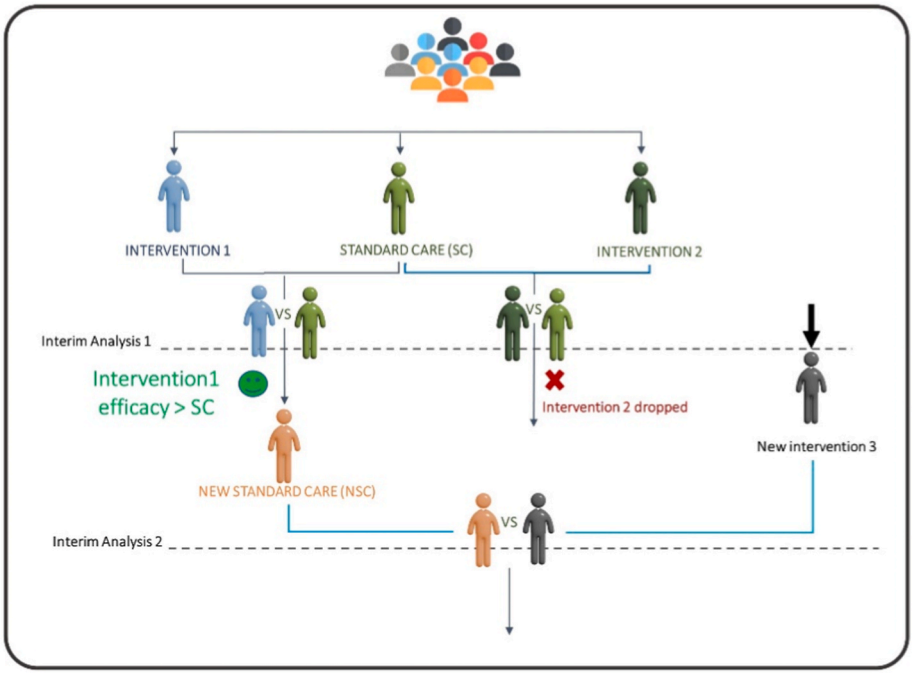

Fig. 3. Platform trials.

These real-world data (RWD) can be gathered from diverse sources like electronic health records, medical claims, registries, and digital health technologies. Studies involving RWD have a different set of strengths and limitations than randomized controlled trials (RCTs), which makes both complementary [127]. In the field of OSA, RWD studies are particularly well-suited for the study of the effects of CPAP treatment. First, RWD studies bypass some RCT constraints like the inability to randomize sleepy patients, resulting in study populations diverging significantly from real-world patients [128], and limiting generalizability. Second, CPAP devices produce massive data, enabling the utilization of Big Data to improve understanding of sleep-disordered breathing, personalize treatments, and optimize healthcare policies [129].

Various RWD studies have examined the link between CPAP use and overall mortality and cardiovascular outcomes. A Spanish population-based study including all CPAP-treated OSA patients in Catalonia and matched non-OSA controls found that CPAP-treated individuals had lower mortality risk (HR, 0.67; 95 % CI, 0.61–0.74) [130]. Similarly, French administrative data showed CPAP continuation being associated with reduced all-cause death risk (HR, 0.61; 95 % CI, 0.57–0.65) [102] and, among patients resuming CPAP after a discontinuation, not quitting treatment a second time was also associated with lower mortality risk (HR, 0.62, 95 % CI 0.48–0.79) [131]. Data from the Pays de la Loire Sleep Cohort linked to health administrative data showed that CPAP discontinuation was associated with a 30 % increased risk of MACEs (HR, 1.30; 95 %CI, 1.12–1.47) [132]; and, CPAP adherence of 6–7 h/night and ⩾7 h/night showed lower MACE risk compared to non-adherence (HR, 0.75; 95 % CI, 0.62–0.92; HR, 0.78; 95 % CI, 0.65–0.93; respectively) [18]. Finally, US data showed that CPAP treatment initiation was prospectively associated with lower all-cause mortality (HR, 0.53; 95 %CI, 0.52–0.54) and MACE incidence (HR, 0.90; 95 %CI, 0.89–0.91) [133]. Overall, these studies, with varied strengths and limitations, consistently showed HR for all-cause mortality ranging from 0.53 to 0.62 and HR for MACE from 0.75 to 0.90.

RWD studies face three core challenges. Firstly, accessing data involves navigating ownership, protection, and ethical concerns, alongside integrating diverse data sources with varying formats. Secondly, ensuring data quality and standardization involves managing completeness, accuracy, and addressing unobserved confounders. Lastly, effective data analysis strategies are essential to minimize bias and interpret complex datasets generated by sensors and devices. Efforts to address these challenges will mitigate the drawbacks of RWD studies, bridging the gap with RCTs while preserving their superior generalizability and external validity. This will render RWD studies indispensable complements to RCTs.

4.3. *Mendelian Randomization*

Mendelian Randomization (MR) leverages genetic variants, typically identified through Genome-Wide Association Studies (GWAS), to infer causal relationships between exposures and outcomes [134] These genetic variants, which are randomly assigned at conception, act as proxies for exposure to risk factors, effectively replicating the design of a randomized controlled trial. This approach overcomes many limitations inherent in both observational and randomized trials. MR studies have provided significant insights into the causal effects of OSA on cardiovascular health. For instance, Li et al. demonstrated that genetically predicted OSA increases the risk of heart failure, hypertension, and atrial fibrillation [135] The adverse effect of OSA on heart failure persisted even after adjusting for confounders such as BMI, smoking, and education, and could be partially mediated by Apolipoprotein B. Similarly, MR has been used to assess independent risk factors for OSA like triglyceride levels [136] inflammatory cytokines and plasma metabolites [137] or gut microbiota [138] These findings not only enhance our understanding of the pathophysiology of OSA but also provide insights into targeted interventions to mitigate its adverse health effects. Therefore, databases like that of the UK Biobank are invaluable for MR studies due to their extensive and well-curated genetic and health data from large populations.

4.4. *European projects*

While innovative European research in OSA has been ongoing for over 5 decades [139], a major step forward was the award of a 15-million euro grant in 2021 by the European Union's Horizon 2020 Research and Innovation Program to a multicentre European consortium

involving 39 partners (Grant Agreement no. 965417). The project, entitled Sleep Revolution (SR), includes clinical and basic researchers, engineers, statisticians, software experts, and industry. SR has the ambitious objectives to transform current diagnostic methods for OSA and to shift advanced sleep diagnostics from the hospital into patients' homes [140]. Current capacity constraints in the context of the high global prevalence of OSA require innovative solutions to facilitate high volume application in the evaluation of affected patients [141], especially as the diagnosis evolves beyond the traditional metric of AHI [7]. The process in SR involves technological solutions developed in collaboration with industry that allow polysomnography (PSG) studies in the home using self-applied techniques by the patient [142]. The development and implementation of novel machine learning algorithms suitable for automatic analysis of sleep-related signals are designed to improve and simplify the diagnostic pathway in OSA [143,144]. An important objective of SR is to promote participatory health care and to develop different personalized treatment options for OSA patients. Patient participation in their management is facilitated by the development of a state-of-the-art digital management platform (DMP) that stores all clinically relevant information and sleep study results, which are accessible by the individual patient through a smartphone app. The app enables the collection of a subjective morning and evening sleep diary in addition to other relevant activities during the day [145]. The development of a comprehensive sleep questionnaire by SR aims to improve on the poor relationship between current subjective measures such as excessive daytime sleepiness and objective measures of sleep disordered breathing [146].

As part of SR, a multicentre randomised controlled trial (RCT) is underway by the European Sleep Apnoea Database (ESADA) network [147], which includes 24 academic sleep centres around Europe with over 45,000 patients in the database. The RCT represents a verification trial of many innovations that are developed within the SR project. These include the application of specific sleep diagnostic technologies such as self-applied PSG and wearables, automated data download and cloud-based automated sleep analysis techniques, in addition to the DMP to evaluate the different dimensions of patient reported outcome measures (PROM) and the sleep questionnaire [148]. A total of 1035 patients were randomised to local standard care, or to the Sleep Revolution managed care model. Resource utilization, PROM improvement, and CPAP compliance are the major study outcomes to be compared between the two pathways in the RCT. The study is now completed and data analysis is in progress.

5. Discussion

The Lisbon ERS Seminar 2024 “Sleep apnoea and its consequences: from animal models to precision medicine” provided an in-depth analysis of the current landscape and future directions in OSA research, integrating findings from clinical predictors, animal models, artificial intelligence, advancements in diagnostic algorithms and propositions for clinical trials.

With the prevalence of OSA estimated at nearly one billion, it would not be possible, and certainly not clinically indicated, to treat all patients with OSA. Therefore, it is crucial to better characterize not only OSA endotypes that may tell us how to treat patients with OSA but also phenotypes will tell us who to treat. It is also critical to better understand the predictors of OSA-related consequences and to identify high-risk patients based on more specific markers than the AHI in order to effectively tailor treatment approaches. Among these markers, those related to OSA-related hypoxemia (hypoxic burden) and autonomic or vascular dysfunction (delta heart rate/PWAD) appear to be the most promising (Fig. 1). However, prospective studies are needed to determine how they should be incorporated into clinical decision algorithms for OSA treatment (example in Fig. 2). Multi-omics analysis can also provide an opportunity to precisely study and characterize OSA by associating phenotypic data with a large amount of distinctive molecular measures (transcriptomics, proteomics, and metabolomics). This improvement in diagnostic precision will contribute to improved management and treatment of OSA.

Our field should also better investigate the pathophysiological pathways linking OSA and various comorbidities and their role in exacerbating the severity of OSA. This is essential for developing comprehensive treatment strategies targeting not only nocturnal breathing but also associated comorbidities such as obesity. In this regard, animal models can play a significant role in advancing our understanding of OSA by providing invaluable insights into the cardiovascular and metabolic consequences of intermittent hypoxia and delve deeply into the pathophysiological mechanisms of OSA.

The integration of artificial intelligence in OSA research is also promising due to its ability to analyze vast datasets from polysomnography (PSG) for the identification of patterns and the prediction of cardiovascular risks associated with OSA. Artificial intelligence could significantly enhance clinical decision-making by integrating multiple biomarkers and clinical variables leading to more precise risk stratification and the development of a personalized treatment approach tailored to the individual unique profiles.

During this seminar, prospective actions were proposed to advance OSA research, particularly in understanding the benefits of OSA treatment. Considering the neutral results of previous RCTs focusing on the effect of CPAP as secondary prevention of cardiovascular events, a key recommendation is to redesign clinical trials to overcome RCT limitations such as low adherence and patient selection bias (absence of sleepiness and/or severe hypoxemia). The use of real-world data, including patients commonly seen in clinical practice with a high hypoxic burden, and the use of digital tools for real-time monitoring of adherence and side effects would ensure that clinical trials are more representative of the general OSA population and that the data collected is accurate and comprehensive.

The panel of experts also advocates for integrating non-CPAP alternatives in clinical trials. By comparing CPAP with emerging treatments like new drugs, devices, and lifestyle interventions, researchers can gain a broader understanding of effective management strategies. The concept of platform trials was proposed as a more efficient and adaptable research design. This type of trials allows multiple interventions to be tested against a common control group, providing a more flexible and cost-effective way to evaluate different treatments (Fig. 3).

In conclusion, a multifaceted approach to OSA research that capitalizes on the strengths of animal models, advanced AI, and improved diagnostic algorithms is needed to gain deeper insights into the mechanisms of OSA and its treatment response. This new approach will contribute to the advancement of personalized medicine and lead to improved outcomes for patients with OSA.

CRediT authorship contribution statement

Raphael Heinzer: Writing – review & editing, Writing – original draft, Resources, Project administration, Conceptualization. **Jean-Louis Pepin:** Writing – review & editing, Writing – original draft, Conceptualization. **Silke Ryan:** Writing – review & editing, Writing – original draft, Conceptualization. **Claire Arnaud:** Writing – review & editing, Writing – original draft, Conceptualization. **Margaux Blanchard:** Writing – review & editing, Writing – original draft, Conceptualization. **Rene Cortese:** Writing – review & editing, Writing – original draft, Conceptualization. **Carolina Lombardi:** Writing – review & editing, Writing – original draft, Conceptualization. **Oren Cohen:** Writing – review & editing, Writing – original draft, Conceptualization. **Adrien Waeber:** Writing – review & editing, Writing – original draft. **Martino Pengo:** Writing – review & editing, Writing – original draft, Conceptualization. **Yuksel Peker:** Writing – review & editing, Writing – original draft, Conceptualization. **Jordi de Batlle:** Writing – review & editing, Writing – original draft, Conceptualization. **Walter T. McNicholas:** Writing – review & editing, Writing – original draft, Conceptualization.

Winfried Randerath: Writing – review & editing, Writing – original draft, Conceptualization. **Frederic Gagnadoux:** Writing – review & editing, Writing – original draft, Conceptualization. **Ali Azarbarzin:** Writing – review & editing, Writing – original draft, Conceptualization. **Manuel Sanchez-de-la-Torre:** Writing – review & editing, Writing – original draft, Methodology, Funding acquisition, Conceptualization.

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Declaration of competing interest

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