



# Obstructive Sleep Apnea Endophenotypes

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Sleep Sci 2025;18(1):e109–e113.

## Abstract

Obstructive sleep apnea (OSA) is a common disorder with major neurocognitive and cardiometabolic consequences. It is now recognized as a heterogeneous disease with multiple different underlying mechanisms (endotypes) as well as variable clinical expression of disease (phenotypes). The importance of this variability is emphasized since one variable in isolation typically explains only a fraction of the variance in OSA occurrence. This review provides an update of what is known regarding OSA heterogeneity. The importance of OSA endotypes is discussed in the context of how mechanism might affect disease management and/or design of subsequent randomized trials. Further research is recommended to provide further validation of OSA endophenotypes and how this information may influence clinical management in the future.

## Keywords

- sleep
- lung
- hypoxemia
- arousal

Obstructive sleep apnea (OSA) is known to affect almost a billion people worldwide based on recent estimates.<sup>1</sup> Even using a strict definition of an apnea-hypopnea index (AHI) > 15 events/hr, the estimates suggest that roughly half a billion people worldwide are afflicted. The HypnoLaus study from Switzerland showed that, in a community sample, 23% of women and 50% of men had an AHI > 15 events per hour.<sup>2</sup> Although one may question the importance of disease identified in the community not coming to clinical fruition, the AHI predicted diabetes mellitus, hypertension, and depression. Thus, these patients cannot be ignored given the important observed associations.

Although OSA is now accepted to be highly prevalent, the disease is clearly heterogeneous.<sup>3</sup> There are multiple underlying mechanisms of OSA (endotypes) as well as variable clinical expression of the disease (phenotypes).<sup>4</sup> A new concept is emerging that the mechanism underlying OSA may be a determinant of clinical expression of disease.

Obstructive sleep apnea pathogenesis is thought to involve a complex interplay of anatomical predisposition, pharyngeal dilator muscle control, ventilatory control instability (elevated loop gain), and low arousal threshold.<sup>5–9</sup> People with OSA are anatomically predisposed to pharyngeal collapse based on biomechanical properties compared to

matched controls.<sup>10–13</sup> The pharyngeal anatomy can be assessed using drug-induced sleep endoscopy, although its utility in this context has been controversial. Through compensatory mechanisms present during wakefulness, the upper airway muscles have increased activity allowing the maintenance of pharyngeal patency.<sup>14</sup> However, with the onset of sleep, there is a fall in dilator muscle activity yielding collapse in those who are anatomically predisposed. Elevated loop gain refers to instability in the ventilatory control system whereby oscillations in the output from the central pattern generator (CPG) can occur, such that activation of the upper airway muscles is low during periods of low output from the CPG.<sup>15–20</sup> A low arousal threshold refers to a propensity to wake up that can predispose to repetitive apnea.<sup>21,22</sup> Respiratory stimuli can accumulate during sleep, allowing activation of the pharyngeal dilator muscles; however, premature arousal leads to repetitive apnea if there is inadequate duration or magnitude of stimuli to activate the pharyngeal dilator muscles.<sup>23,24</sup> The upper airway dilator muscles are necessary and sufficient to stabilize breathing based on evidence of high activity occurring during spontaneous periods of stable breathing.<sup>25,26</sup> Some individuals have multiple underlying mechanisms adding to the complexity of OSA pathogenesis.<sup>27,28</sup>

received  
November 29, 2023  
accepted after revision  
February 5, 2024

DOI <https://doi.org/10.1055/s-0044-1788287>.  
ISSN 1984-0659.

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Thieme Revinter Publicações Ltda., Rua do Matoso 170, Rio de Janeiro, RJ, CEP 20270-135, Brazil

Obstructive sleep apnea endotypes are clearly important for a number of reasons. First, OSA endotype may guide therapy. For example, the subset of patients with anatomical compromise at the level of the velopharynx may be the subgroup who benefits from uvulopalatopharyngoplasty (UPPP).<sup>29,30</sup> Similarly, genioglossus advancement and hypoglossal nerve stimulation may be particularly helpful for patients with retroglossal anatomical compromise. Patients with instability in ventilatory control may benefit from agents such as oxygen or acetazolamide, which can lower loop gain and stability breathing.<sup>31,32</sup> Mandibular advancement devices appear to be particularly effective for OSA patients with moderate pharyngeal collapsibility and weaker pharyngeal dilator muscle compensation as well as lower loop gain and higher arousal threshold. Secondly, the risk factors for OSA may be explained by endotypes. For example, patients with neuromuscular disease or various myopathies are at risk of OSA, likely due to impairment in pharyngeal dilator muscle function. Third, the endotypes of OSA may predict clinical phenotypes. For example, OSA in older adults is thought to be related to pharyngeal mechanics while OSA in younger adults may be more a function of elevated loop gain.<sup>33–36</sup> Given that data strongly suggest that OSA in older adults has fewer consequences than OSA in matched younger individuals, a concept is emerging that the consequences underlying OSA in older adults may explain the minimal observed complications in these individuals.<sup>37,38</sup> Fourth, OSA endotypes may explain treatment responses. Individuals with elevated loop gain are at high risk of treatment emergent central apnea upon initiation of continuous positive airway pressure (CPAP).<sup>39</sup> Patients undergoing UPPP are at high risk of surgical failure if they have elevated loop gain given that surgical intervention has minimal direct impact on breathing control per se.<sup>40,41</sup> Obstructive sleep apnea endotypes could potentially be used to stratify surgical risk as underlying mechanisms may explain why some patients have robust surgical response whereas other patients have minimal response to surgery. Thus, OSA endotypes are important for various clinically important reasons (see ►Fig. 1).

With regards to OSA phenotypes, considerable heterogeneity has been reported. Ye et al.<sup>42</sup> reported various OSA clusters in which some OSA patients were asymptomatic, some had fragmented sleep, while others had excessive daytime sleepiness. Of note, the group with severe sleepiness appears to be at cardiovascular risk, whereas the other groups may be at lower risk for these complications.<sup>43,44</sup> The approach of conducting randomized trials of OSA to prevent cardiovascular disease has largely failed to show major benefits to apnea therapy, perhaps because fewer than half of OSA patients are at major cardiovascular risk.<sup>45–47</sup> Thus, the failure of the one-size-fits-all approach may be a result of underlying heterogeneity in OSA endophenotypes.

After considering the heterogeneity of OSA, multiple potential explanations exist for the equivocal results from clinical trials in showing hard outcome benefit:

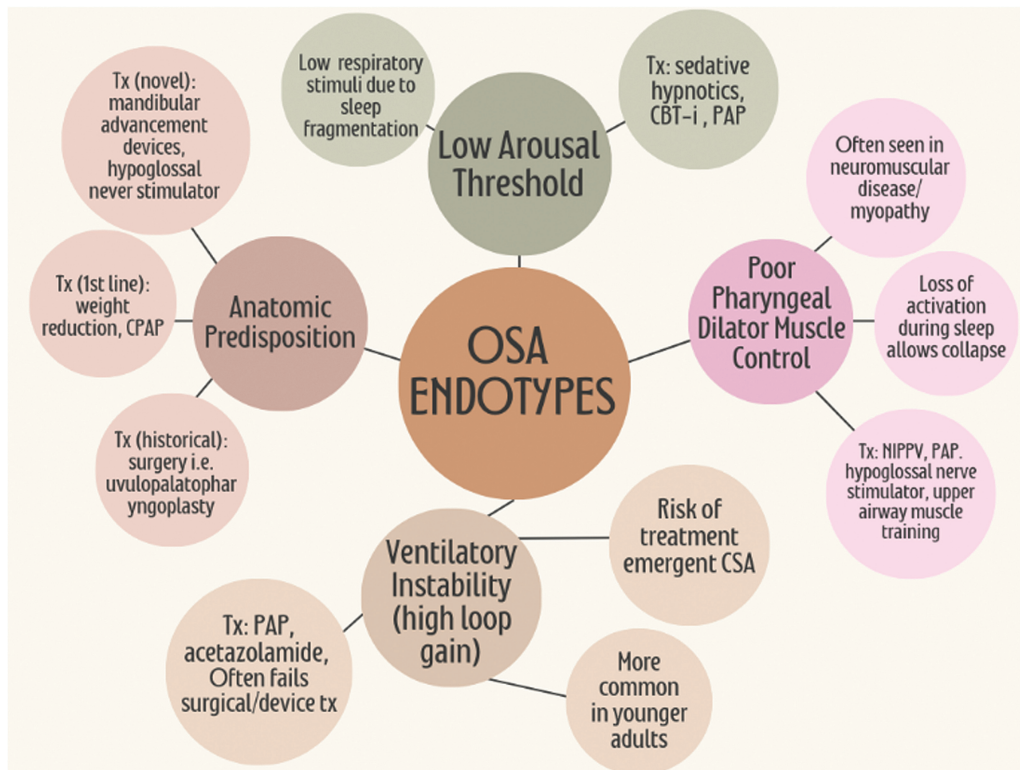
- 1) Given that only a subset of OSA patients may be at cardiovascular risk, the failure of CPAP trials to show cardiovascular benefit may reflect a need to identify a

*priori* high-risk patients or those most likely to benefit from intervention. Various approaches have been suggested, such as enrolling the most symptomatic patients, those with the greatest hypoxic burden or various biomarkers including microRNAs (miR-210), which may help to characterize high risk patients.<sup>48–52</sup>

- 2) Recent studies have shown that patients who adhere to PAP therapy show hard outcome benefits in individual patient meta-analyses.<sup>52</sup> These findings suggest that improved adherence may be required to demonstrate the cardiovascular benefits to CPAP. In addition, the large sample size available for this meta-analysis suggests the possibility that statistical power may have been an issue in some of the randomized trials. On the other hand, analyses based on adherence are subject to the healthy user effect, whereby PAP therapy may be a marker of a highly motivated patient with good health literacy rather than a direct effect of PAP per se.<sup>53</sup>
- 3) Some recent studies have shown potential deleterious effects of high levels of CPAP, including the release of angiopoietin 2, which is a marker seen in lung injury.<sup>54,55</sup> Whether CPAP is leading to low level lung injury over time is unproven, but the possibility that CPAP has risks as well as benefits may be one explanation for why longer-term studies have shown mixed results.

Future priorities for research in this context are multiple, but a few examples are offered here:

- a) Increased validation regarding the various techniques to estimate endotypic traits will be required.<sup>56</sup> The gold standard physiological techniques to define arousal threshold and loop gain as well as upper airway muscle function are quite cumbersome and, thus, unlikely to be scalable or accessible to most clinicians.<sup>57–59</sup> A number of sources of variance are present with techniques to characterize OSA pathogenesis, including biological and methodological variability.<sup>59,60</sup> Given that OSA varies night to night and with body position as well as with sleep stage, one would not predict the underlying mechanisms to be static. However, further data regarding the reproducibility and validity of various signal processing techniques would help to address skepticism regarding these methods.<sup>60,61</sup>
- b) Further work regarding the biomarkers of OSA may help to identify robust surrogate outcome measures for future clinical trials. The ideal biomarker would be: easily obtainable and have good sensitivity and specificity for disease; predictive of disease complications; responsive to therapy, and be involved in an important causal pathway.<sup>62,63</sup> Although no ideal biomarker exists, several candidates have been reported, which may require further study.<sup>64</sup> In theory, a trial could be designed to show improvements in a surrogate outcome measure if there was confidence that such changes would predict improvements in hard outcomes.



**Fig. 1** A figure illustrating the various mechanisms underlying obstructive sleep apnea (OSA) as well as key clinical pearls regarding potential manipulation of each of these traits. There are complex interactions between the various traits that are not fully depicted in this figure.

**Abbreviations:** CBTi, cognitive behavioral therapy for insomnia; CSA, central sleep apnea; NIPPV, non-invasive positive pressure ventilation; OSA, obstructive sleep apnea; PAP, positive airway pressure.

c) The recent insights into OSA endophenotypic heterogeneity have led to novel approaches for interventional studies.<sup>65</sup> In theory, therapeutic interventions could be determined based on underlying mechanisms (e.g., oxygen or acetazolamide for patients with unstable ventilatory control or sedative/hypnotics for patients with low arousal threshold).<sup>66</sup> Given the robust benefits of CPAP for some patients, sophisticated trials could be designed, such as rescue strategies for CPAP failures. Comparative effectiveness studies could also be designed to allow identification of optimal therapy, which may differ for patients based on their personal preferences or underlying physiology.<sup>67,68</sup>

In summary, considerable progress has been made in understanding OSA heterogeneity. Such findings may already be clinically directive and could help to guide future research studies. Only by further efforts with basic, clinical, and translational research are new therapeutic approaches and strategies likely to emerge.

#### Funding Source

The authors declare that they have received funding from the U.S. Department of Health and Human Services, the National Institutes of Health, and the National Heart, Lung, and Blood Institute.

#### Conflict of Interests

The authors have no conflict of interests to declare.

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