

REVIEW ARTICLE

Obstructive Sleep Apnea: Mechanisms, Clinical Phenotypes, and Precision Management

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Abstract

Objective: To review current evidence regarding the epidemiology, pathophysiology, molecular mechanisms, clinical phenotypes, systemic consequences, diagnostic approaches, and therapeutic strategies of obstructive sleep apnea (OSA), with emphasis on precision medicine.

Methods: A narrative review of the contemporary literature was conducted focusing on epidemiological data, pathophysiological mechanisms, molecular pathways, phenotypic and endotypic classification, diagnostic methodologies, and emerging therapeutic approaches.

Results: OSA is a highly prevalent and underdiagnosed disorder affecting approximately 936 million adults worldwide. The disease results from the interaction of anatomical susceptibility, impaired upper airway neuromuscular control, ventilatory instability, altered arousal threshold, and reduced lung volumes. Intermittent hypoxia contributes to oxidative stress, systemic inflammation, sympathetic activation, and endothelial dysfunction, leading to cardiovascular, metabolic, and neurocognitive complications. Recent phenotypic and endotypic approaches have improved understanding of disease heterogeneity and support individualized treatment strategies.

Conclusion: OSA is a complex multisystem disorder extending beyond sleep-related breathing abnormalities. Precision medicine approaches integrating clinical phenotypes and physiological endotypes may improve diagnostic assessment, treatment selection, adherence, and long-term outcomes.

Keywords: Obstructive Sleep Apnea, Sleep Apnea Syndromes, Precision Medicine, Continuous Positive Airway Pressure, Hypoxia, Phenotype.

Obstructive sleep apnea (OSA) is a highly prevalent yet underdiagnosed sleep-related breathing disorder characterized by recurrent episodes of upper airway collapse during sleep (1,2,3). These episodes lead to intermittent hypoxemia, hypercapnia, sleep fragmentation, and significant intrathoracic pressure swings, ultimately contributing to widespread systemic effects (4,5, 6). It is estimated that approximately 936 million adults worldwide are

affected, making OSA a major global public health concern (1). Despite its prevalence, OSA remains substantially underdiagnosed, with up to 70–80% of moderate-to-severe cases remaining unrecognized (7, 4, 8).

Traditionally, disease severity has been quantified using the apnea–hypopnea index (AHI); however, this metric inadequately reflects the true physiological burden of the disease and demonstrates limited predictive value for clinical outcomes (9,10).

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Increasing recognition of the heterogeneity of OSA has led to the emergence of phenotyping and endotyping approaches, which aim to characterize patients based on clinical presentation and underlying pathophysiological mechanisms (10,11, 12,13).

Key pathophysiological traits include anatomical susceptibility, impaired upper airway neuromuscular control, ventilatory control instability (loop gain), variability in arousal threshold, and reduced lung volumes (4,14,15,12). Intermittent hypoxia triggers oxidative stress, systemic inflammation, sympathetic activation, and endothelial dysfunction, linking OSA to cardiovascular and metabolic diseases (3,16,6,17).

This review synthesizes current evidence on the epidemiology, risk factors, pathophysiology, molecular mechanisms, clinical phenotypes, systemic consequences, diagnostic approaches, and therapeutic strategies of OSA, with particular emphasis on the evolving role of precision medicine in tailoring individualized management strategies (11,13).

1. Introduction

Obstructive sleep apnea (OSA) is one of the most common chronic respiratory disorders, characterized by repetitive episodes of partial or complete upper airway obstruction during sleep despite ongoing respiratory effort (1,12,3). These events result in cyclical oxygen desaturation, hypercapnia, and recurrent arousals from sleep, leading to sleep fragmentation and impaired sleep architecture (1,4,12).

Although OSA has long been recognized as a cause of excessive daytime sleepiness, it is now widely understood to be a complex multisystem disorder with profound cardiovascular, metabolic, and neurocognitive consequences (5,16,3). Chronic exposure to intermittent hypoxia and sleep disruption induces a cascade of physiological responses, including sympathetic nervous system activation, systemic inflammation, oxidative stress, and metabolic dysregulation (5,15, 17).

Despite its clinical significance, OSA remains markedly underdiagnosed (7,18,8). Many individuals do not report classic symptoms such as excessive daytime sleepiness, and alternative presentations—including insomnia, fatigue, or mood disturbances—may obscure recognition. Additionally, limited access to diagnostic testing, particularly polysomnography, contributes to delayed diagnosis (19).

Importantly, OSA is not a uniform disease entity. Patients vary significantly in terms of symptomatology,

anatomical features, physiological traits, and response to therapy. This variability has led to the development of phenotyping and endotyping frameworks, which aim to classify patients based on observable clinical characteristics and underlying pathophysiological mechanisms, respectively (20,11 12,13). These approaches form the basis of precision medicine, enabling tailored therapeutic strategies that optimize clinical outcomes (11, 13).

2. Epidemiology and Global Burden

OSA represents a major global health burden. Large-scale epidemiological studies estimate that approximately 936 million adults aged 30–69 years have some degree of OSA, with nearly 425 million experiencing moderate-to-severe disease (1). Mild OSA may affect up to 30% of the adult population, while clinically significant disease occurs in approximately 10–17% of men and 3–9% of women (17–19, 8).

The prevalence of OSA increases with age, reflecting age-related changes in upper airway anatomy and neuromuscular control (8, 3). Sex differences are also prominent, with men exhibiting higher prevalence rates than women. However, the risk in women increases significantly after menopause, suggesting a protective role of female sex hormones such as estrogen and progesterone (8, 3).

Ethnic differences further influence OSA risk. Individuals of East Asian descent may develop OSA at lower body mass indices due to craniofacial anatomical characteristics, including maxillary and mandibular structure (13, 17). In contrast, obesity is a more dominant risk factor in Western populations (14, 8).

The societal and economic burden of OSA is substantial. Untreated OSA is associated with increased healthcare utilization, decreased workplace productivity, and a higher incidence of motor vehicle and occupational accidents (5, 3). Cardiovascular disease remains the leading cause of morbidity and mortality among individuals with OSA, underscoring the importance of early detection and effective management (5,21–22).

3. Risk Factors and Predisposing Conditions

OSA results from a complex interplay between modifiable and non-modifiable risk factors (1, 3).

3.1 Modifiable Risk Factors

Obesity is the most significant risk factor for OSA (14, 8,3). Excess adipose tissue around the neck

and upper airway leads to narrowing of the airway lumen and increased collapsibility. Additionally, obesity reduces lung volumes, particularly functional residual capacity, which further predisposes to airway obstruction (14).

Alcohol consumption and sedative use exacerbate OSA by decreasing upper airway muscle tone and impairing arousal responses (1, 3). Smoking contributes through chronic inflammation, mucosal edema, and structural changes in the upper airway (1). Physical inactivity indirectly increases OSA risk by promoting weight gain and metabolic dysfunction (3, 17).

3.2 Non-Modifiable Risk Factors

Advancing age is associated with reduced neuromuscular responsiveness and structural alterations in the airway (8, 3). Male sex is linked to differences in fat distribution and airway anatomy that increase susceptibility to collapse (8).

Genetic predisposition plays a role in determining craniofacial morphology, ventilatory control stability, and fat distribution patterns (14, 3). Craniofacial abnormalities such as retrognathia, micrognathia, and maxillary constriction reduce airway size and increase the likelihood of obstruction (14).

Endocrine disorders, including hypothyroidism and acromegaly, contribute to OSA through soft tissue enlargement and altered airway mechanics (1,3).

4. Pathophysiology

OSA is a multifactorial disorder resulting from the interaction of several physiological traits (4,15,12).

Anatomical susceptibility is a primary determinant, with reduced upper airway caliber predisposing individuals to collapse during sleep (4,14,12). This narrowing may result from obesity, craniofacial abnormalities, or soft tissue hypertrophy (14).

Upper airway muscle dysfunction also plays a critical role. During wakefulness, pharyngeal dilator muscles maintain airway patency; however, during sleep, reduced neuromuscular activation allows airway collapse, particularly during rapid eye movement (REM) sleep (4,2).

Ventilatory control instability, often described as high loop gain, reflects an exaggerated response of the respiratory control system to changes in blood gases (15,12). This instability leads to oscillatory breathing patterns and recurrent apnea–hypopnea events.

Arousal threshold variability influences the frequency of sleep interruptions. Individuals with a low arousal

threshold awaken easily in response to airway obstruction, resulting in fragmented sleep without effective restoration of airflow (15,12).

Lung volume effects further modulate airway stability. Reduced lung volumes decrease caudal traction on the upper airway, increasing its collapsibility and contributing to obstruction (4,14).

5. Molecular and Cellular Mechanisms

Intermittent hypoxia is central to the pathogenesis of OSA-related complications (6,3). It activates hypoxia-inducible factors (HIFs), which regulate gene expression and promote the production of reactive oxygen species (ROS), leading to oxidative stress (6).

Oxidative stress activates inflammatory pathways, including nuclear factor kappa B (NF-κB), resulting in increased production of pro-inflammatory cytokines such as interleukin-6 and tumor necrosis factor-alpha (6). These mediators contribute to endothelial dysfunction and vascular injury (5,6).

Sympathetic nervous system activation, partly mediated by carotid body stimulation, leads to sustained elevations in blood pressure and heart rate (5,16). Additionally, oxidative stress interferes with insulin signaling pathways, promoting insulin resistance and metabolic dysfunction (6,17).

These molecular processes collectively link OSA to a range of cardiometabolic diseases, including hypertension, atherosclerosis, and type 2 diabetes (5,16,6,17).

6. Clinical Phenotypes and Endotypes

OSA exhibits substantial clinical heterogeneity, which can be described using phenotypes and endotypes (20,11,12-13).

Clinical phenotypes include the “sleepy” phenotype, characterized by excessive daytime sleepiness, and the insomnia phenotype, marked by difficulty initiating or maintaining sleep (20,11). The cardiometabolic phenotype includes individuals with significant cardiovascular and metabolic comorbidities, while some patients remain asymptomatic despite physiological abnormalities (20).

Endotypes refer to the underlying mechanisms driving OSA. These include anatomical collapsibility, high loop gain, low arousal threshold, and upper airway muscle dysfunction (11,15,12). Identification of these traits allows for targeted therapeutic interventions (11,13).

For example, patients with high loop gain may benefit from therapies that stabilize ventilatory control, such

as supplemental oxygen or acetazolamide (12,14). Those with anatomical obstruction may respond better to oral appliances or surgical interventions (12,25). Individuals with low arousal thresholds may benefit from carefully selected pharmacological agents that increase sleep stability (11,15).

7. Cardiovascular, Metabolic, and Neurocognitive Consequences

OSA is strongly associated with cardiovascular disease, including hypertension, coronary artery disease, heart failure, atrial fibrillation, and stroke (5,16,21-22). The relationship with hypertension is particularly well established, with OSA recognized as a major contributor to resistant hypertension (5,16).

Metabolic consequences include insulin resistance, impaired glucose tolerance, and dyslipidemia (17). The coexistence of obesity and OSA creates a bidirectional relationship that amplifies metabolic dysfunction (17).

Neurocognitive impairment is also common, affecting attention, memory, and executive function (3). Structural brain changes, particularly in the hippocampus and prefrontal cortex, have been documented. These impairments contribute to decreased quality of life and increased risk of accidents (5,3).

8. Diagnostic Approaches and Limitations

Polysomnography remains the gold standard for diagnosing OSA, providing comprehensive data on sleep architecture, respiratory events, and oxygen saturation (19). However, reliance on the apnea-hypopnea index has important limitations, as it does not fully capture disease severity or predict clinical outcomes (9-10).

Emerging metrics, including hypoxic burden, oxygen desaturation index, and measures of sleep fragmentation, offer a more comprehensive assessment of disease impact (9-10). Home sleep testing and wearable devices are increasingly used to improve accessibility and facilitate longitudinal monitoring (19).

Advances in artificial intelligence and machine learning are enhancing the analysis of sleep data, enabling automated detection of OSA and personalized risk stratification (10,13).

9. Therapeutic Strategies and Precision Medicine

Continuous positive airway pressure (CPAP) remains the first-line therapy for OSA (23,24). It effectively

prevents airway collapse, improves symptoms, and reduces cardiovascular risk (23-24). However, adherence remains a significant challenge, with long-term compliance rates of approximately 50–60% (23).

Lifestyle interventions, including weight loss, dietary modification, and regular exercise, are essential components of management, particularly in obese individuals (3,25). Even modest weight reduction can lead to clinically meaningful improvements in OSA severity (25).

Oral appliances, particularly mandibular advancement devices, are effective in selected patients with mild-to-moderate disease (26). Surgical interventions may be indicated in cases of anatomical obstruction (11,26).

Hypoglossal nerve stimulation is an emerging therapy that improves upper airway muscle tone during sleep and has shown promising results in carefully selected patients (27).

Precision medicine approaches integrate phenotypic and endotypic information to tailor treatment strategies, improving effectiveness and patient adherence (11,13).

10. Future Directions

Future research in OSA is focused on identifying biological subtypes through multi-omics approaches, including genomics, proteomics, and metabolomics (13). Biomarkers capable of predicting disease progression and treatment response are under development.

Artificial intelligence is expected to play a transformative role in diagnosis and management, enabling automated analysis, personalized treatment selection, and adherence monitoring (10,13). Telemedicine and wearable technologies will further enhance accessibility and long term care (19,13).

Mechanism-based therapies targeting specific pathophysiological traits are likely to replace traditional symptom-based approaches, representing a paradigm shift in OSA management (11,13).

11. Conclusion

Obstructive sleep apnea is a complex, multifactorial, and highly heterogeneous disorder that extends far beyond a simple sleep-related breathing abnormality. Its pathophysiology involves a dynamic interplay between anatomical vulnerability, impaired neuromuscular control, ventilatory instability, and altered arousal mechanisms, all of which contribute to recurrent upper airway collapse and

its downstream physiological consequences. The resulting cascade—characterized by intermittent hypoxia, sleep fragmentation, and intrathoracic pressure fluctuations—drives systemic processes including sympathetic overactivation, oxidative stress, inflammation, and endothelial dysfunction

The clinical implications of OSA are substantial and far-reaching. Strong associations with cardiovascular diseases, particularly hypertension, atrial fibrillation, heart failure, and stroke, underscore its role as a major contributor to global morbidity and mortality .. In parallel, metabolic dysfunction, including insulin resistance and type 2 diabetes, highlights the bidirectional relationship between OSA and metabolic disease . Neurocognitive impairment, reduced quality of life, and increased accident risk further amplify the individual and societal burden of this condition.

Despite these consequences, OSA remains significantly underdiagnosed and undertreated . Traditional diagnostic approaches, centered on the apnea–hypopnea index, fail to capture the multidimensional nature of the disease and do not adequately predict clinical outcomes . This limitation has driven a paradigm shift toward more comprehensive assessment strategies that incorporate hypoxic burden, sleep fragmentation, and physiological traits.

A key advancement in the field has been the recognition of OSA as a heterogeneous disorder requiring individualized evaluation. The integration of clinical phenotyping and physiological endotyping has provided a framework for understanding patient variability and tailoring treatment accordingly . This approach challenges the traditional “one-size-fits-all” model of therapy and supports a transition toward precision medicine.

While continuous positive airway pressure remains the cornerstone of treatment, its effectiveness is often limited by suboptimal adherence. Alternative and adjunctive therapies—including lifestyle interventions, oral appliances, surgical approaches, hypoglossal nerve stimulation, and emerging pharmacological treatments—offer opportunities for more personalized care. Matching these interventions to specific patient phenotypes and endotypes is critical for optimizing therapeutic outcome.

Looking forward, advances in digital health technologies, wearable monitoring systems, and artificial intelligence are poised to transform the diagnosis and management of OSA . These tools have the potential to enable early detection, continuous monitoring, and data-driven treatment decisions. In

parallel, the integration of multi-omics approaches may uncover novel biomarkers and mechanistic pathways, further refining risk stratification and therapeutic targeting.

Ultimately, the future of OSA management lies in the transition from symptom-based to mechanism-based care. A deeper understanding of the underlying biological and physiological drivers of the disease will allow clinicians to move beyond generalized treatment strategies and toward truly individualized interventions . Such an approach holds the promise of improving patient outcomes, enhancing treatment adherence, and reducing the substantial global burden associated with OSA .

In conclusion, obstructive sleep apnea represents a critical and evolving challenge in modern medicine. Addressing this challenge requires not only improved awareness and diagnostic strategies but also the continued integration of scientific innovation into clinical practice. Through the adoption of precision medicine principles, the management of OSA can be fundamentally transformed, leading to more effective, patient-centered care and improved long-term health outcomes.

12. References

1. Jordan AS, McSharry DG, Malhotra A. Adult obstructive sleep apnoea. *Lancet* 2014;383(9918):736-747. doi:10.1016/S0140-6736(13)60734-5.
2. Malhotra A, White DP. Obstructive sleep apnoea. *Lancet* 2002;360(9328):237-245. doi:10.1016/S0140-6736(02)09464-3.
3. Lévy P, Kohler M, McNicholas WT, Barbé F, McEvoy RD, Somers VK, et al. Obstructive sleep apnoea syndrome. *Nat Rev Dis Primers* 2015;1:15015. doi:10.1038/nrdp.2015.15.
4. Eckert DJ, Malhotra A. Pathophysiology of adult obstructive sleep apnea. *Proc Am Thorac Soc* 2008;5(2):144-153. doi:10.1513/pats.200707-114MG.
5. Somers VK, White DP, Amin R, Abraham WT, Costa F, Culebras A, et al. Sleep apnea and cardiovascular disease. *Circulation* 2008;118(10):1080-1111. doi:10.1161/CIRCULATIONAHA.107.189420.
6. Lavie L. Oxidative stress in obstructive sleep apnea and intermittent hypoxia. *Sleep Med Rev* 2015;20:27-45. doi:10.1016/j.smrv.2014.05.002.
7. Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea: A population health perspective. *Am J Respir Crit Care Med* 2002;165(9):1217-1239. doi:10.1164/rccm.200203-331SO.

8. Punjabi NM. The epidemiology of adult obstructive sleep apnea. *Proc Am Thorac Soc* 2008;5(2):136-143. doi:10.1513/pats.200709-155MG.
9. Azarbarzin A, Sands SA, Stone KL, et al. Hypoxic burden predicts cardiovascular mortality. *Am J Respir Crit Care Med* 2019;199(7):903-912. doi:10.1164/rccm.201806-1195OC.
10. Malhotra A, Ayappa I, Ayas N, et al. Metrics of sleep apnea severity beyond AHI. *Sleep* 2021;44(7):zsab030. doi:10.1093/sleep/zsab030.
11. Eckert DJ. Phenotypic approaches to obstructive sleep apnoea – New pathways for targeted therapy. *Sleep Med Rev* 2018;37:45-59. doi:10.1016/j.smrv.2017.01.004.
12. Eckert DJ, White DP, Jordan AS, Malhotra A, Wellman A. Phenotypic causes of OSA. *Am J Respir Crit Care Med* 2013;188(8):996-1004. doi:10.1164/rccm.201303-0448OC.
13. Pack AI. Precision medicine in OSA. *Sleep Med Clin* 2019;14(3):363-372. doi:10.1016/j.jsmc.2019.04.002.
14. Schwab RJ, Kim C, Siegel LC, et al. Examining the interaction between obesity and upper airway anatomy in obstructive sleep apnea. *J Appl Physiol* 2015;118(5):533- 540. doi:10.1152/jappphysiol.00698.2014.
15. Wellman A, Eckert DJ, Jordan AS, et al. A method for measuring and modeling the physiological traits causing obstructive sleep apnea. *J Appl Physiol* 2011;110(6):1627- 1637. doi:10.1152/jappphysiol.00582.2010.
16. Javaheri S, Barbe F, Campos-Rodriguez F, Dempsey JA, Khayat R, et al. Sleep apnea: Types, mechanisms, and clinical cardiovascular consequences. *J Am Coll Cardiol* 2017;69(7):841-858. doi:10.1016/j.jacc.2016.11.069.
17. Tasali E, Ip MSM. Obstructive sleep apnea and metabolic syndrome. *Proc Am Thorac Soc* 2008;5(2):207-217. doi:10.1513/pats.200708-139MG.
18. Peppard PE, Young T, Barnet JH, Palta M, Hagen EW, Hla KM. Increased prevalence of sleep-disordered breathing in adults. *Am J Epidemiol* 2013;177(9):1006-1014. doi:10.1093/aje/kws342.
19. Heinzer R, Vat S, Marques-Vidal P, Marti-Soler H, Andries D, Tobback N, et al. Prevalence of sleep-disordered breathing in the general population: The HypnoLaus study. *Lancet Respir Med* 2015;3(4):310-318. doi:10.1016/S2213-2600(15)00043-0
20. Edwards BA, Eckert DJ, McSharry DG, Sands SA, Desai A, et al. Clinical phenotypes of obstructive sleep apnea: Identification and implications. *Sleep* 2014;37(2):319-327. doi:10.5665/sleep.3418.
21. Marin JM, Carrizo SJ, Vicente E, Agusti AGN. Long-term cardiovascular outcomes in men with obstructive sleep apnea-hypopnea with or without CPAP treatment. *Lancet* 2005;365(9464):1046-1053. doi:10.1016/S0140-6736(05)71141-7.
22. Arzt M, Young T, Finn L, Skatrud JB, Bradley TD. Association of sleep-disordered breathing and stroke. *Am J Respir Crit Care Med* 2005;172(11):1447-1451. doi:10.1164/rccm.200505-702OC.
23. McEvoy RD, Antic NA, Heeley E, et al. CPAP for prevention of cardiovascular events in obstructive sleep apnea. *N Engl J Med* 2016;375(10):919-931. doi:10.1056/NEJMoa1606599.
24. Sullivan CE, Issa FG, Berthon-Jones M, Eves L. Reversal of OSA by CPAP. *Lancet* 1981;1(8225):862-865. doi:10.1016/S0140-6736(81)92140-1.
25. Greenburg DL, Lettieri CJ, Eliasson AH. Weight loss and OSA. *Chest* 2009;136(3):683- 690. doi:10.1378/chest.09-0047.
26. Ramar K, Dort LC, Katz SG, et al. Oral appliance therapy guideline. *J Clin Sleep Med* 2015;11(7):773-827. doi:10.5664/jcsm.4858.
27. Strollo PJ, Soose RJ, Maurer JT, et al. Upper-airway stimulation for OSA. *N Engl J Med* 2014;370(2):139-149. doi:10.1056/NEJMoa1308659.