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MULTIDISCIPLINARY NETWORK OSA CODE (OBSTRUCTIVE APNEA SYNDROME): DIGITAL OPERATIVE MODEL IN PUBLIC HEALTH FOR AN EARLY DIAGNOSIS AND THERAPY MONITORING

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ABSTRACT

Obstructive sleep apnea (OSA) is linked to an increased risk of cognitive impairment and progression to mild cognitive impairment (MCI) and Alzheimer's Disease (AD), yet it remains unclear whether standard clinical and polysomnographic data collected at diagnosis can reliably predict short-term cognitive decline. This study investigated the utility of baseline demographic, anthropometric, mood-related, and polysomnographic variables in forecasting incident cognitive deterioration over a two-year follow-up in a cohort of adults with OSA. The study included 154 patients diagnosed with OSA at Sleep Disorders Center – IRCCS San Raffaele Hospital. Cognitive outcomes were assessed using the PEBL neuropsychological battery with decline defined as meaningful performance reduction across one or multiple domains.

Two complementary modeling approaches were employed: Firth penalized logistic regression—to address small-sample bias and separation—and a Random Forest machine learning classifier—to capture potential non-linear relationships and interactions. Type 2 diabetes emerged as a statistically significant predictor of cognitive decline in the Firth model (OR $\approx$ 5.2, p = 0.026), independent of OSA severity and mood symptoms. Polysomnographic markers of nocturnal hypoxemia (e.g., minimum SaO_2, % time SaO_2 < 90%) showed expected directional associations but did not reach significance ($p \approx 0.09$). Despite comprehensive predictor sets, both models demonstrated limited discriminative ability (Random Forest AUC = 0.51), indicating poor individual-level predictive performance.

These findings suggest that while certain baseline factors—particularly type 2 diabetes—are significantly associated with short-term cognitive impairment in OSA, routinely collected clinical and polysomnographic data alone are inadequate for reliable early prediction. This thesis underscores a critical gap between group-level risk associations and individual-level forecasting in OSA-related cognitive outcomes, and argues for the integration of more sensitive biomarkers (e.g., neuroimaging, blood-based markers of neural injury) in future predictive frameworks. Methodologically, it demonstrates the value—and limitations—of combining penalized regression with machine learning in modest-sized clinical cohorts, offering a template for transparent, reproducible modeling in sleep and cognitive research.

ABSTRACT

La sindrome delle apnee ostruttive del sonno (OSA) è associata a un aumento del rischio di declino cognitivo e di progressione verso forme di deterioramento come il mild cognitive impairment (MCI) e la malattia di Alzheimer (AD). Tuttavia, resta da chiarire se i dati clinici e polisonnografici raccolti al momento della diagnosi siano in grado di prevedere con affidabilità un peggioramento cognitivo nel breve termine. Questo studio ha esaminato il valore predittivo di variabili demografiche, antropometriche, dell'umore e polisonnografiche rilevate al basale in una coorte di 154 adulti con diagnosi di OSA presso il Centro di Medicina del Sonno dell'IRCCS Ospedale San Raffaele.

Le performance cognitive sono state valutate tramite la batteria PEBL. Il declino cognitivo è stato definito come una riduzione significativa e multidimensionale della performance. Per l'analisi predittiva sono stati adottati due approcci complementari: la regressione logistica penalizzata di Firth, utile per gestire campioni moderati e problemi di separazione, e un classificatore Random Forest, adatto a identificare relazioni non lineari e interazioni tra variabili.

Il diabete di tipo 2 è emerso come il predittore più robusto di declino cognitivo, con un rischio circa cinque volte superiore rispetto ai pazienti non diabetici, indipendentemente dalla gravità dell'OSA o dai sintomi depressivi. Alcuni indici di ipossiemia notturna hanno mostrato associazioni nella direzione attesa, ma senza raggiungere la significatività statistica. Complessivamente, entrambi i modelli hanno evidenziato una bassa capacità discriminativa, indicando che i dati clinici e polisonnografici di routine non sono sufficienti a prevedere con precisione il rischio individuale di deterioramento cognitivo.

I risultati sottolineano la necessità di integrare biomarcatori più sensibili—come misure neuroimaging o marcatori ematici di danno neuronale—per migliorare i modelli predittivi. Dal punto di vista metodologico, lo studio mette in luce il potenziale e i limiti dell'uso combinato di regressione penalizzata e machine learning in coorti cliniche di dimensioni contenute, offrendo indicazioni per future ricerche nel campo del sonno e della cognizione.

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ACRONYMS AND ABBREVIATIONS

AASM	American Academy of Sleep Medicine
AD	Alzheimer's Disease
AGE	Advanced Glycation End-product
AHI	Apnea-Hypopnea Index
ANP	Atrial Natriuretic Peptide
ApoE4	Apolipoprotein E E4 Allele
AUC	Area Under the Curve
BBB	Blood–Brain Barrier
BiPAP	Bilevel Positive Airway Pressure
BDI	Beck Depression Inventory
BL	Baseline
BMI	Body Mass Index
CBT	Cognitive Behavioural Therapy
CI	Confidence Interval
CPAP	Continuous Positive Airway Pressure
CSA	Central Sleep Apnea
CSF	Cerebrospinal Fluid
C-SVD	Cerebral Small Vessel Disease
DAN	Dorsal Attention Network
DMN	Default Mode Network
DST	Digit-span Task
DSTB	Digit-span Task Backward
DSTF	Digit-span Task Forward
DTI	Diffusion Tensor Imaging
ECG	Electrocardiogram
EDS	Excessive Daytime Sleepiness
EEG	Electroencephalogram
EMG	Electromyogram
EOG	Electrooculogram
EDS	Excessive Daytime Sleepiness
ESS	Epworth Sleepiness Scale
FA	Fractional Anisotropy
FDG-PET	Fluorodeoxyglucose Positron Emission Tomography
FOSQ	Functional Outcomes of Sleep Questionnaire
FRC	Functional Residual Capacity
FTO	Fat Mass and Obesity-Associated
FU	Follow-up
GG	Genioglossus
GH	Growth Hormone
GM	Gray Matter
GWAS	Genome-Wide Association Studies
HNS	Hypoglossal Nerve Stimulation
ICSD-3-TR	International Classification of Sleep Disorders, Third Edition Text Revised
IH	Intermittent Hypoxia

LH	Luteinizing Hormone
MAD	Mandibular Advancement Device
MC4R	Melanocortin-4 Receptor
MCI	Mild Cognitive Impairment
MCT	Mackworth Clock Test
MD	Mean Diffusivity
MET	Motivational Enhancement Therapy
MMA	Maxillomandibular Advancement
MoCA	Montreal Cognitive Assessment
MRI	Magnetic Resonance Imaging
MSLT	Multiple Sleep Latency Test
MVA	Motor Vehicle Accident
MWT	Maintenance Of Wakefulness Test
NAWM	Normal-Appearing White Matter
NfL	Neurofilament Light
NHS	National Health Service
NREM	Non–Rapid Eye Movement
nTS	Nucleus Tractus Solitarius
ODI	Oxygen Desaturation Index
OR	Odd Ratio
OSA	Obstructive Sleep Apnea
$PaCO_2$	Arterial Carbon Dioxide Tension
PaO_2	Arterial Oxygen Tension
PAP	Positive Airway Pressure
Pcrit	Critical Pressure
PEBL	Psychology Experiment Building Language
POMC	Pro-Opiomelanocortin
PSG	Polysomnography
PSQI	Pittsburgh Sleep Quality Index
PVT	Psychomotor Vigilance Task
QoL	Quality Of Life
RD	Radial Diffusivity
REM	Rapid Eye Movement
SaO2	Oxygen Saturation
SAQLI	Sleep Apnea Quality of Life Index
SBD	Sleep Related Breathing Disorders
SBM	Surface-Based Morphometry
SCWT	Stroop Colour and Word Test
SD	Standard Deviation
SF-36	Short Form-36 Health Survey
SIDS	Sudden Infant Death Syndrome
SN	Salience Network
SPECT	Single Photon Emission Computed Tomography
SWA	Slow-Wave Activity
SWS	Slow Wave Sleep
T2DM	Type 2 Diabetes Mellitus

TMT	Trial Making Test
UARS	Upper Airway Resistance Syndrome
UPP	Uvulopalatoplasty
VAN	Ventral Attention Network
VBM	Voxel-Based Morphometry
$\dot{V}E$	Minute Ventilation
WM	White Matter

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CHAPTER 1 - RESPIRATORY PHYSIOLOGY

1.1 NEURAL CONTROL AND PHYSIOLOGICAL REGULATION OF BREATHING

Respiratory control is governed by highly coordinated feedforward and feedback mechanisms that maintain arterial blood gas homeostasis through the integrated action of three functional components: (1) brainstem neurons that generate the respiratory rhythm (central controllers), (2) respiratory muscles that serve as effectors to produce airflow, and (3) sensory pathways that convey input from peripheral and central chemoreceptors and mechanoreceptors to brainstem centers, enabling dynamic adjustments to physiological demands. The respiratory system fulfills two essential physiological roles: delivering oxygen to metabolically active tissues and eliminating carbon dioxide, a byproduct of cellular metabolism. This gas exchange occurs continuously in the pulmonary circulation, where deoxygenated blood from the right heart is oxygenated in the lungs before being distributed systemically via the left heart; concurrently, carbon dioxide diffuses from venous blood across the alveolocapillary membrane into the airways for exhalation. The precise regulation of this process relies on the coordinated interplay of neural respiratory control, thoracopulmonary mechanics, circulatory dynamics, and blood gas transport. Although compensatory inputs during wakefulness can often maintain stable ventilation despite underlying deficits in core respiratory control, these protective influences are withdrawn during sleep, unmasking or exacerbating breathing abnormalities when the system's integrity is compromised (Eckert & Butler, 2017). Given that even brief interruptions in respiration can be fatal, the robustness of this regulatory network is critical for survival.

1.2 CENTRAL NEURAL CIRCUITS UNDERLYING RESPIRATORY RHYTHMOGENESIS

The precise neuroanatomical substrates underlying respiratory rhythm generation within the brainstem remain incompletely defined. The central respiratory control network comprises both inspiratory and expiratory neurons, with rhythmogenesis and

control occurring primarily within the pons and medulla. Within the medulla, the dorsal and ventral respiratory groups are of particular significance (Eckert & Butler, 2017).

The dorsal respiratory group contains the nucleus tractus solitarius (nTS), a key site for cardiorespiratory sensory integration. Afferent input from the phrenic and vagus nerves, as well as from peripheral chemoreceptors via the glossopharyngeal nerve, converges on the nTS. This nucleus projects to multiple regions critical for respiratory control, including the retrotrapezoid nucleus. The ventrolateral portion of the nTS is thought to play a major role in inspiratory activity, with additional projections to other centers within the ventral respiratory group. Whether the nTS provides direct output to respiratory motoneurons, however, remains uncertain (Eckert & Butler, 2017).

The pre-Bötzinger complex, located within the ventral respiratory group, is widely regarded as the principal candidate for the central respiratory pacemaker. Evidence for this role comes from studies demonstrating persistence of rhythmic respiratory activity in minimal medullary slice preparations containing these neurons. The pre-Bötzinger complex also projects extensively to other respiratory centers within the brainstem, further supporting its central role in rhythm generation. Adjacent to this structure, the Bötzinger complex contributes to expiratory control by inhibiting respiratory motor neurons, thereby shaping overall motor output. The rostral ventral respiratory group additionally contains inspiratory premotoneurons, including those within the nucleus ambiguus, which provide motor innervation to the larynx and pharynx via the vagus nerve. The nucleus retroambiguus has also been implicated in respiratory rhythm generation (Smith et al., 1991; Subramanian et al., 2018).

Although neurons involved in rhythm generation are primarily localized to the medulla, pontine structures also exert a significant influence on central respiratory control. The pontine respiratory group (formerly termed the pneumotaxic center) includes the nucleus parabrachialis medialis, which contains expiratory neurons, as well as the parabrachialis lateralis and Kölliker-Fuse nuclei of the upper pons, which contain inspiratory neurons. Activation of the pontine respiratory group can attenuate inspiratory activity within the dorsal respiratory group, thereby reducing inspiratory duration. This inspiratory-to-expiratory phase transition serves to increase breathing frequency (Orem & Kubin, 2000; Dutschmann & Dick, 2012; Eckert & Butler, 2017).

1.3 NEURAL AND CHEMICAL REGULATION OF VENTILATION

Chemical regulation represents the primary mechanism controlling ventilation in healthy individuals during quiet breathing, both in wakefulness and in sleep. While all cells can alter their activity in response to major changes in the chemical environment, specific populations of cells demonstrate high sensitivity to even minor fluctuations. These chemically sensitive regions influence respiratory control either directly or through projections to central respiratory control centers. Collectively, these specialized cells—referred to as chemoreceptors—are essential to the regulation of ventilation (Eckert & Butler, 2017).

1.3.1 Peripheral and Central Chemoreceptors

Chemoreceptors are located both peripherally and centrally. The principal peripheral chemoreceptors are the carotid bodies, situated at the bifurcation of the common carotid arteries. These structures have long been recognized as sensitive to changes in arterial oxygen tension (PaO_2), arterial carbon dioxide tension ($PaCO_2$), and hydrogen ion concentration. Detection of such stimuli can produce rapid ventilatory adjustments, often within one to two breaths. More recent evidence indicates that carotid bodies also respond to a broader array of stimuli, including potassium, norepinephrine, temperature, glucose, insulin, and immune-related cytokines. Repeated hypoxic exposure induces plasticity within the carotid bodies, changes that may contribute to pathological states such as heightened ventilatory instability during sleep. In addition to the carotid bodies, the nearby aortic bodies also participate in chemosensation, particularly in response to alterations in oxygen and other circulating factors (Guyenet et al., 2010; Fung, 2014).

While peripheral chemoreceptors are essential for rapid, moment-to-moment modulation of ventilation, central chemoreceptors provide the dominant input to respiratory control during quiet wakefulness. These receptors are located on the ventral medullary surface, in close proximity to the ventral respiratory group, within a region termed the retrotrapezoid nucleus. This nucleus has extensive projections to major respiratory control centers, including the nTS of the dorsal respiratory group, and plays a pivotal role in central chemoreception. Central chemoreceptors detect changes in $PaCO_2$ indirectly through shifts in extracellular pH. Because CO_2 readily diffuses across the blood–brain barrier, it alters cerebrospinal fluid hydrogen ion concentration, thereby driving

chemoreceptor activity. Compared to the rapid responses of peripheral chemoreceptors, central chemoreceptors display slower kinetics, often requiring up to one minute to respond fully to changes in $PaCO_2$. These response delays are critically important for the development of cyclic breathing instability during sleep (Moreira et al., 2021).

Although peripheral and central chemoreceptors are anatomically distinct and exhibit different response characteristics, recent studies highlight their complex interdependence. Activity within central chemoreceptors is strongly modulated by peripheral chemoreceptor activity, and vice versa, underscoring their integrated role in the regulation of ventilation (Smith et al., 2010).

1.4 ADDITIONAL NEURAL AND SENSORY INPUTS REGULATING BREATHING

In addition to chemoreceptor input, a variety of other afferent signals and sensory mechanisms contribute to the regulation of respiratory rate and tidal volume. Mechanoreceptors located within limb muscles and joints respond to movement and can increase minute ventilation ($\dot{V}E$). Similarly, stimulation of cutaneous receptors sensitive to touch, temperature, and pain augments respiratory drive. An independent excitatory influence on breathing, known as the wakefulness drive to breathe, may also be recruited. Conversely, excessive lung inflation activates pulmonary stretch receptors, which inhibit $\dot{V}E$ through the Hering–Breuer reflex (Xie, 2012).

Additional modulatory inputs arise from higher neural centers. For example, the limbic system can influence breathing in response to emotional stimuli, while voluntary cortical control allows for conscious modulation of respiratory activity. The precise mechanisms by which voluntary override occurs remain incompletely defined. It is uncertain whether such control acts indirectly through modulation of central respiratory pattern generation, directly via excitation of phrenic motoneurons, or through a combination of both pathways (Haouzi et al., 2006, Schottelkotte & Crone, 2022).

Despite these uncertainties, the physiological capacity for modulation of breathing is considerable. During sleep, when metabolic demand is reduced, very low ventilation levels ($< 5\ L \cdot min^{-1}$) can be maintained without compromise. In contrast, during periods of intense exercise, $\dot{V}E$ can exceed $200\ L \cdot min^{-1}$, highlighting the broad dynamic range of the respiratory control system (Krimsky & Leiter, 2005; Eckert & Butler, 2017).

1.5 STRUCTURAL AND FUNCTIONAL ANATOMY OF THE RESPIRATORY SYSTEM

The upper airway, comprising the nasal cavities, pharynx, and larynx, functions primarily to humidify, warm, and channel inspired air toward the trachea and lungs. In addition to this respiratory role, the musculature of the upper airway participates in phonation and swallowing. It has been proposed that the evolutionary development of speech—requiring enhanced pharyngeal mobility—resulted in the reduction of structural rigidity within the upper airway, rendering it more prone to collapse in humans compared to most other mammals. Although ventilation can occur through either the nasal or oral route, nasal breathing constitutes the physiologically preferred pathway (Heinzer & Sériès, 2017).

The lower airway consists of the trachea and lungs, including bronchi and alveoli. Gas exchange occurs at the alveolar level, where capillaries in close contact with alveolar surfaces facilitate diffusion between inhaled air and the bloodstream. The thoracic cage provides structural support through articulation of the ribs with the thoracic vertebrae posteriorly and their flexible cartilaginous junctions with the sternum anteriorly. The lungs themselves are enveloped by the visceral pleura, while the inner thoracic cavity is lined with parietal pleura. The narrow pleural space separating these layers contains a small volume of lubricating fluid that enables smooth gliding movements during respiration. Because of its close anatomical relationship to the pleura, esophageal pressure fluctuates in parallel with pleural pressure and is frequently employed as an indirect measure of respiratory effort (Heinzer & Sériès, 2017).

1.5.1 Anatomy and Function of the Respiratory Muscles

The diaphragm constitutes the principal muscle of respiration. This dome-shaped structure forms the anatomical boundary between the thoracic and abdominal cavities and receives its motor innervation from the phrenic nerves. During inspiration, neural signals originating in the central respiratory centers trigger diaphragmatic contraction. The resultant shortening of muscle fibers flattens the diaphragm, reducing its dome configuration and thereby increasing intrathoracic volume. The intercostal muscles contribute to this process by elevating the ribs and expanding the anteroposterior diameter of the thoracic cage. Under normal conditions, accessory muscles of respiration—such as

the scalene and sternocleidomastoid muscles—remain inactive, but they may be recruited during heightened ventilatory demand or in the context of thoracopulmonary pathology (Heinzer & Sériès, 2017).

1.5.2 Mechanics of the Breathing Cycle and Ventilatory Dynamics

Airflow within the respiratory system follows pressure gradients, moving from regions of higher pressure toward those of lower pressure until equilibrium is achieved. Pleural pressure, generated by the mechanical forces of inspiration and expiration, is directly related to the intensity of respiratory effort and serves as the principal driving pressure. During inspiration, contraction of the diaphragm and intercostal muscles lowers intrathoracic pressure below atmospheric levels, creating a negative transpulmonary pressure gradient that drives air from the atmosphere through the upper airways and tracheobronchial tree into the alveoli. Expiration at rest is a passive process that occurs as the inspiratory muscles relax. In contrast, active expiration—whether voluntary or during increased ventilatory demand such as exercise—involves contraction of the abdominal and external intercostal muscles. This action raises pleural pressure toward less negative values, simultaneously elevating alveolar pressure and producing a positive pressure gradient from the alveoli to the external environment, thereby facilitating exhalation. As air exits, lung and thoracic volumes decrease, and elastic recoil pressure diminishes until a new equilibrium is reached at the functional residual capacity (FRC). Respiratory rate, defined as the number of breaths per minute, averages approximately 12 in healthy adults at rest, with a physiological range of 10–18 breaths per minute (Heinzer & Sériès, 2017).

1.6 SLEEP-RELATED CHANGES IN FUNCTIONAL RESIDUAL CAPACITY AND BREATHING DYNAMICS

In most healthy individuals, FRC (the lung volume in the natural resting end-expiratory position), exhibits a modest but significant reduction during sleep. Measurements using helium dilution indicate that FRC decreases by approximately 200 mL during stage 2 non–rapid eye movement (NREM) sleep and by 300 mL during slow-wave sleep and rapid eye movement (REM) sleep, relative to the awake baseline of roughly 2.4 L in an average adult male. When assessed via plethysmography, a reduction of 440–500 mL in lung volume has been observed during NREM sleep (stages 2–4), with

a comparable decrease during REM sleep. Several mechanisms have been proposed to explain the sleep-related decline in FRC, including rostral displacement of the diaphragm secondary to diaphragmatic hypotonia, alterations in respiratory timing originating from central respiratory centers, reductions in lung and thoracic compliance, and central blood pooling (Luo et al., 2017; Zwitserloot et al., 2020).

Tidal volume has been reported to decrease by approximately 6–15% during NREM sleep (stages N2 and N3), with a further reduction of about 25% during REM sleep compared to wakefulness. Minute ventilation is significantly lower in all NREM stages relative to the awake state and declines further during REM sleep, particularly during phasic REM, reaching approximately 84% of awake levels. This reduction is generally attributed to a faster, shallower breathing pattern with decreased tidal volume, especially during REM sleep. However, this interpretation is contested, as some studies report no significant change in tidal volume across sleep stages, suggesting that decreased minute ventilation (8% in NREM and 4% in REM) results primarily from a reduced respiratory rate (Ballard et al., 1996; Choudhary & Choudhary, 2009; Heinzer & Sériès, 2017).

Despite these variations, most studies consistently report an increased contribution of the rib cage to tidal volume during NREM sleep, accompanied by an approximate 34% elevation in intercostal muscle activity. This apparent paradox—enhanced thoracic muscle electromyogram (EMG) activity alongside reduced minute ventilation—may be explained by a decrease in the efficiency of muscle contraction during NREM sleep, limiting the generation of negative thoracic pressure. During REM sleep, the relative contributions of the rib cage and abdomen to ventilation remain largely comparable to wakefulness. Age and sex do not appear to significantly influence these sleep-related alterations in lung volume (Choudhary & Choudhary, 2009; Xie, 2012).

1.7 SLEEP-RELATED CHANGES IN BREATHING PATTERNS AND BLOOD GAS REGULATION

During NREM sleep, the reduction in minute ventilation results in a decrease in PaO_2 of approximately 3–9 mm Hg and an increase in $PaCO_2$ of 2–4 mm Hg. In stable NREM sleep, breathing is generally regular; however, periodic fluctuations in ventilation often occur at sleep onset, corresponding to unstable NREM sleep. In some cases, brief cessations of breathing may occur, either with continued respiratory effort (obstructive sleep apnea) or without effort (central sleep apnea), even in healthy individuals. These

transient episodes of periodic breathing are thought to arise from instability in the ventilatory feedback loop, commonly described in terms of loop gain. A low arousal threshold during this stage may further destabilize the sleep-wake cycle and contribute to irregular breathing. Because the CO_2 set point is elevated during sleep, arousal events provoke abrupt increases in ventilation, which reduce CO_2 levels. If CO_2 falls below the apnea threshold—the level at which central respiratory drive is inhibited—an apneic interval may follow, with respiration resuming only once CO_2 returns to the sleep-specific set point. The magnitude of these ventilatory fluctuations is influenced by multiple factors, including chemoreceptor sensitivity (controller gain), circulation time between lungs and chemoreceptors, and the respiratory system's efficiency in modifying CO_2 levels (plant gain) (Dempsey et al., 2004; Deacon-Diaz & Malhotra, 2018; Sands et al., 2018).

In REM sleep, ventilation becomes markedly irregular in both amplitude and frequency, largely reflecting the intensity of phasic activity as indicated by bursts of rapid eye movements and muscle twitches. Phasic REM activity appears to exert an inhibitory effect on ventilation. Overall, alveolar ventilation decreases by approximately 20% relative to wakefulness, primarily due to reductions in tidal volume (Millman et al., 1988; Choudhary & Choudhary, 2009; Xie, 2012).

1.7.1 Sleep-Related Changes in Upper Airway Mechanics

Among the mechanical determinants of ventilation, the upper airway plays a distinctive role due to its pronounced sensitivity to sleep-related changes. Structurally, the airway can be divided into intrathoracic and extrathoracic segments, encompassing the upper trachea, larynx, and various pharyngeal regions, including the nasopharynx, velopharynx, oropharynx, and hypopharynx. Functionally, the upper airway consists of pharyngeal and laryngeal components and must remain patent throughout the respiratory cycle. Unlike the intrathoracic, tracheal, and laryngeal structures, which are reinforced by cartilage and resist collapse during tidal breathing in healthy individuals, pharyngeal airways lack rigid support and are susceptible to closure when the balance of forces promoting airway dilation versus collapse is disrupted (Edwards & White, 2011; Heinzer & Sériès, 2017).

Mechanically, the upper airway can be conceptualized as a Starling resistor, with the pharyngeal segment representing the collapsible portion situated between two

noncollapsible structures (the nasopharynx and larynx). Airflow through this segment is determined by the transmural pressure gradient, defined as the net difference between forces favoring collapse and those promoting patency. Collapsing forces arise from the negative inspiratory transmural pressure gradient and the pressure exerted by surrounding soft tissues, whereas airway-stabilizing muscles (upper airway dilators) and tracheal traction provide the primary dilating forces. Consequently, both the magnitude and timing of neuromuscular activation of upper airway dilators, along with the mechanical properties of airway tissues, are critical determinants of airway stability (Strohl et al., 2012; Sunwoo & Malhotra, 2024).

According to the Starling resistance model, inspiratory flow increases proportionally with rising driving pressure until it reaches a maximal value, beyond which further increases in inspiratory effort do not augment flow, a phenomenon termed flow limitation. The initial slope of the flow-pressure relationship is influenced by upstream and downstream resistances surrounding the collapsible segment. The pressure at which flow plateaus depends on the mechanical properties of the airway, with the critical pressure (Pcrit) representing the point at which dilating forces are insufficient to counteract collapsing forces, resulting in airway closure. Modifications in upstream pressure alter maximal inspiratory flow, allowing determination of both Pcrit and upstream resistance. A linear, positive correlation exists between these variables, where the slope corresponds to the reciprocal of upstream resistance and the pressure at zero flow reflects Pcrit. An increased tendency for upper airway collapse shifts the flow-pressure curve to the right, increasing Pcrit without altering slope, whereas a reduction in upstream resistance steepens the slope without changing Pcrit (Schwartz & Smith, 2013; Wellman et al., 2014).

1.8 SLEEP-RELATED MODULATION OF UPPER AIRWAY MUSCLE FUNCTION

The reduction of wakefulness-related stimuli contributes to the sleep-associated decline in upper airway muscle activity. Both tonic and phasic activities of these muscles are significantly modified during sleep, with distinct patterns observed among individual muscles. The tensor palatini exhibits predominantly tonic activity, whereas the genioglossus, palatoglossus, and levator palatini display primarily phasic activity. Although activity levels are generally higher during wakefulness, only the tensor palatini demonstrates a consistent reduction at sleep onset. This decline correlates with the sleep-

induced increase in upper airway resistance, whereas genioglossus activity often rises as a compensatory response (Fogel et al., 2005; Edwards & White, 2011; Cori et al., 2018). Tensor palatini and genioglossus muscles also differ markedly in their responses to negative airway pressure during both wakefulness and sleep, and no correlation exists between tensor palatini activity and driving pressure. Despite being controlled by separate efferent pathways—the trigeminal motor nucleus for tensor palatini and the hypoglossal motor nucleus for genioglossus—both muscle activities depend on central neuromodulatory input. The preferential reduction in tonic upper airway muscle activity during sleep likely reflects a decrease in central excitatory drive to the respective motor nuclei, arising from both loss of corticomotor stimulation associated with wakefulness and diminished neuromodulator activity (Edwards & White, 2011; Cori et al., 2018).

Sleep may further compromise airway stability by disrupting the preactivation pattern of upper airway muscles. Loss of such preactivation is associated with increased airway resistance and potential closure, whereas reappearance of alpha activity on the electroencephalogram restores normal preactivation patterns, reducing airway resistance and facilitating ventilatory resumption. The neuromuscular activation of upper airway and respiratory muscles is closely coordinated; tidal inspiration enhances diaphragm bulbospinal activity by increasing amplitude and reducing response latency, an effect amplified during sleep. This is attributed to the loss of wakefulness-related tonic depolarization of phrenic motor neurons, which unmasks the influence of bulbospinal drive on diaphragm corticomotor excitability. However, the interaction between sleep and the facilitative effect of inspiration on upper airway muscle excitability remains unclear (Fogel et al., 2005; Schäfer, 2006; Choudhary & Choudhary, 2009).

Evidence suggests that instability in ventilation during sleep may promote upper airway collapse. Obstructive breathing events primarily occur during stages N1 and N2 of NREM sleep and during REM sleep, when ventilation is physiologically unstable, and are rare during slow-wave sleep, when breathing is most regular. In patients with obstructive sleep apnea, periodic breathing persists even after tracheostomy, indicating that ventilatory instability contributes to airway collapse. In healthy sleepers, experimentally induced periodic breathing can produce partial upper airway obstruction. Conversely, ventilatory stimulation with CO_2 reduces the incidence of obstructed breaths in affected patients. Furthermore, in individuals with moderately increased airway collapsibility, the

frequency of obstructive sleep-disordered breathing correlates with the degree of ventilatory instability (Heinzer & Sériès, 2017; Lee, 2022).

1.9 SLEEP-INDUCED CHANGES IN UPPER AIRWAY PATENCY AND COLLAPSE

Sleep represents a challenge, rather than a period of rest, for the ventilatory system. The loss of wakefulness contributes to several changes: decreased upper airway caliber, increased airway resistance, heightened pharyngeal compliance, and greater collapsibility. Collectively, these alterations result in reduced tidal volume and hypoventilation (Rowley & Badr, 2017).

1.9.1 Sleep-Related Alterations in Upper Airway Diameter and Resistance

Sleep is consistently associated with narrowing of the upper airway and a corresponding increase in airway resistance. Nasopharyngoscopic studies in healthy individuals have demonstrated that, during NREM sleep, the cross-sectional areas of both the retropalatal and retroglossal regions decrease to approximately 70% of their wakeful dimensions, with further retroglossal narrowing occurring in REM sleep. This reduction in caliber parallels the decline in upper airway dilator muscle activity during NREM sleep, along with an additional reduction in genioglossus activity during REM. Notably, retroglossal narrowing is more pronounced than retropalatal narrowing in REM sleep. Evidence supporting elevated upper airway resistance during sleep is strong, even in individuals without pathology. In fact, resistance begins to rise at sleep onset and progressively increases, reaching its peak during slow-wave sleep. Most studies indicate no additional increase in resistance during REM compared with NREM in healthy humans. In summary, sleep is characterized by upper airway narrowing, manifesting as increased resistance and reduced pharyngeal caliber. However, airway resistance alone does not fully capture the dynamic behavior of the pharynx during sleep. Many individuals exhibit inspiratory flow limitation, in which the pressure–flow relationship shows progressive dissociation: inspiratory pressure continues to decrease without a corresponding rise in airflow. Consequently, the most physiologically meaningful index of upper airway resistance is the slope of the linear portion of the pressure–flow curve, which likely reflects airway caliber at its narrowest point at the onset of inspiration (Jordan & White, 2008; Marques et al., 2018).

1.10 SLEEP-STATE MODULATION OF RESPIRATORY CONTROL

Major alterations in the regulation of breathing occur during the transition from wakefulness to sleep. The most notable change is that most of the inputs capable of influencing breathing are either absent or substantially downregulated (see Figure 16-3). Consequently, chemical control becomes the predominant driver of respiration during sleep, with carbon dioxide playing a particularly critical role in sustaining ventilatory activity. Several pathological conditions can impair this chemical regulation, predisposing susceptible individuals to sleep-disordered breathing (Eckert & Butler, 2017).

1.10.1 Impact of Brief Arousals on Ventilation

Brief cortical arousals from sleep, typically lasting less than 15 seconds, occur approximately 10 to 20 times per hour in healthy individuals, with frequency increasing with age. These arousals may arise spontaneously or in association with sleep disorders such as sleep apnea or periodic limb movement disorder. Historically, arousal was thought to play a critical role in reopening the upper airway during obstructive breathing events (Eckert & Younes, 2014). In certain contexts, arousal can indeed be advantageous, enabling rapid correction of blood gas disturbances and reducing the work of breathing during flow-limited respiration (Osman et al., 2018; Smardz et al., 2024). Nevertheless, although the immediate physiologic effects of arousal may support respiratory homeostasis, the abrupt transition from sleep to wakefulness and the subsequent reentry into sleep can destabilize ventilatory control (Amatoury et al., 2016; Malhotra & Jordan, 2016). The degree to which arousals promote instability and contribute to central or obstructive respiratory events depends primarily on two factors: (1) the individual's arousal threshold, and (2) the ventilatory response triggered by the arousal (Eckert & Butler, 2017).

1.10.1.1 Role of Arousal Threshold in Sleep-Related Breathing Instability

Whether an arousal occurs spontaneously, in association with a periodic limb movement, or secondary to a respiratory disturbance, individuals with a low arousal threshold are particularly susceptible to sleep-state breathing instability. A predisposition to sleep-onset ventilatory instability, when combined with a low arousal threshold, can lead to recurrent respiratory disturbances as the individual oscillates between wakefulness

and sleep (Hoshino et al., 2022). Approximately one third of patients with obstructive sleep apnea arouse in response to modest respiratory stimuli, such as negative airway pressure less than 15 cm H2O (Edwards et al., 2014; Subramani et al., 2017). This relatively low threshold likely contributes to the persistence of sleep-disordered breathing (Sands et al., 2018; Hoshino et al., 2022). Increasing the arousal threshold in these patients has been shown to stabilize ventilation (Malhotra & Jordan, 2016). Although the precise mechanisms remain unclear, both the arousal threshold and upper airway muscle activity increase with deeper stages of sleep, during which the severity of sleep-disordered breathing decreases (Hicks et al., 2017; Li et al., 2019). It remains uncertain, however, whether deeper sleep stages are inherently more stable with respect to respiratory control, or whether improved ventilatory stability facilitates sleep consolidation (Eckert & Butler, 2017).

1.10.1.2 Respiratory Effects of Sleep Arousal

Just as rapid changes in respiratory control occur at sleep onset, arousal from sleep produces an equally abrupt alteration in the homeostatic regulation of breathing. During stable sleep, lower levels of minute ventilation and higher arterial CO_2 levels (approximately 3–8 mm Hg above wakefulness values) are well tolerated. Upon arousal, however, the wakefulness pattern of chemical control is reinstated, rendering the previously tolerated CO_2 levels excessive. Concurrently, activation of upper airway motoneurons rapidly reverses sleep-related increases in airway resistance (Eckert et al., 2007; Guyenet, 2014). The wakefulness drive to breathe is also reintroduced, leading to a marked increase in ventilation. The magnitude of this ventilatory response to arousal depends on the integrated influence of the aforementioned factors and may be further amplified by an independent wakefulness reflex (Horner et al., 2001; Jordan et al., 2015; Amatoury et al., 2016). Notably, this ventilatory arousal response exhibits substantial inter-individual variability (Jordan et al., 2015). Upon resumption of sleep, the heightened ventilatory drive induced by arousal can lower $PaCO_2$ below a critical level, referred to as the apnea threshold (Jordan et al., 2015).

1.11 APNEA THRESHOLD AND SLEEP-RELATED RESPIRATORY CESSATION

During wakefulness, multiple compensatory mechanisms act to prevent breathing cessation even in the presence of substantial reductions in $PaCO_2$. In contrast, these protective mechanisms are diminished during sleep. Specifically, if $PaCO_2$ falls below a critical threshold during sleep, breathing ceases. This critical level, referred to as the apnea threshold, typically lies between 2 and 6 mm Hg below the stable sleep $PaCO_2$ level. Notably, the apnea threshold approximates the wakefulness $PaCO_2$ value (Dempsey et al., 2010; Benner et al., 2025). The difference between the wakefulness $PaCO_2$ level and the apnea threshold is commonly termed the CO_2 reserve. The degree of $PaCO_2$ reduction required to trigger apnea is critically influenced by peripheral chemoreceptor activity (Benner et al., 2025).

1.11.1 Loop Gain: Sensitivity of Ventilatory Control During Sleep

Multiple inputs shape the control of breathing. One framework for conceptualizing and quantifying the overall sensitivity of the ventilatory control system is loop gain. Loop gain is defined as the ratio of the ventilatory response to a given ventilatory disturbance (Burgess, 2012; Gederi et al., 2014; Deacon-Diaz & Malhotra, 2018). It comprises three principal components: (1) plant gain, reflecting the efficiency with which ventilation eliminates CO_2, determined by the properties of the lungs, blood, and body tissues; (2) mixing and circulation delays, representing the time required for changes in alveolar CO_2 to equilibrate with blood in the heart and systemic circulation before reaching the chemoreceptors; and (3) controller gain, which describes chemoreceptor sensitivity. Because CO_2 is the dominant regulator of ventilatory control during sleep, assessing loop gain in this state provides important insight into ventilatory control sensitivity and facilitates comparisons across individuals and patient groups. Accordingly, several techniques have been developed to quantify steady-state loop gain during sleep (Wellman et al., 2013; Orr, 2018; Nassi et al., 2025). Abnormalities in individual components of loop gain (e.g., plant or controller gain) can promote breathing instability. Circulation delay, in particular, is a critical determinant; without it, cyclic breathing would not occur. However, while prolonging circulation delay increases the duration and cycle length of

instability, it is not sufficient on its own to induce unstable breathing (Eckert & Butler, 2017).

CHAPTER 2 - SLEEP RELATED BREATHING DISORDERS: OBSTRUCTIVE SLEEP APNEA SYNDROME

Sleep-related breathing disorders (SBDs) constitute a broad spectrum of conditions characterized by abnormalities in respiration during sleep. This group includes obstructive sleep apnea (OSA), central sleep apnea (CSA), periodic breathing (such as Cheyne–Stokes respiration), and sleep-related hypoventilation. Historically, recurrent central—or nonobstructive—apneic events, characterized by the absence of both airflow and respiratory effort, were primarily identified in association with the pathophysiology of congestive heart failure and central nervous system disorders, including stroke. In contrast, OSA—defined by the cessation of airflow despite continued respiratory effort—has now been recognized as the most prevalent form of sleep-disordered breathing. Each type of apnea demonstrates distinct pathophysiologic mechanisms and clinical manifestations (Mehra et al., 2017).

The clinical recognition of obstructive sleep apnea (OSA) emerged in the 1960s, when several research groups in Europe reported observations of disordered sleep among patients presenting with excessive daytime sleepiness (Burwell et al., 1956; Gastaut et al., 1966). Suspecting upper airway obstruction as the underlying cause of these disturbances, some investigators pursued a radical intervention—tracheostomy—which successfully normalized breathing during sleep and led to the resolution of both daytime hypersomnolence and associated cardiopulmonary abnormalities (Lugaresi et al., 1971; Guilleminault et al., 1973; Guilleminault et al., 1981).

During the 1970s, a growing number of OSA case series were reported, and the term polysomnography became established to describe the comprehensive monitoring of sleep stages, body movements, and cardiopulmonary function. In 1978, Motta and colleagues reported the successful use of tracheostomy for OSA in a large patient cohort (Motta et al., 1978). The 1980s marked a shift toward understanding the neurophysiologic regulation of respiration and the anatomic vulnerabilities of the upper airway, emphasizing how their interaction produces recurrent obstructive and nonobstructive apneas and hypopneas (Remmers et al., 1978).

At that time, OSA was still regarded as a rare and peculiar condition, typically considered only after other causes of polycythemia, pulmonary hypertension, or severe daytime

somnolence had been excluded. The first modern treatments for OSA appeared in 1981 with the introduction of positive airway pressure (PAP) therapy (Sullivan et al., 1981) and uvulopalatopharyngoplasty (UPPP) surgery (Fujita et al., 1981), targeting abnormalities in the size and compliance of the nasopharynx and oropharynx.

In 1993, the first large-scale epidemiologic study established an estimated OSA syndrome prevalence of 2%–4% among adults, placing OSA among common chronic medical conditions such as asthma and diabetes mellitus (Young et al., 1993). Since then, structured clinical management pathways have been developed alongside advances in PAP delivery systems and the emergence of oral appliance therapy as a validated alternative treatment. Detailed investigations of both treated and untreated OSA have allowed the establishment of standardized severity thresholds: mild (apnea–hypopnea index [AHI] 5–15 events/hour), moderate (AHI 15–30), and severe (AHI >30).

Historically, central sleep apnea (CSA) and Hunter–Cheyne–Stokes respiration (CSR) were among the first sleep-related breathing disorders (SBDs) described, predating the recognition of OSA. Although less prevalent than OSA, their symptomatology and physiologic perturbations are often more striking. In 1818, Dublin physician John Cheyne described a 60-year-old patient exhibiting cyclic breathing oscillations during the terminal phase of illness; autopsy revealed cardiomegaly with fatty infiltration of the myocardium (Fletcher & Moor, 2017). In 1854, another Dublin physician, William Stokes, attributed the abnormal breathing to a “weakened state of the heart.” (Mulcahy, 1955).

Treatment of CSA associated with Hunter–Cheyne–Stokes respiration initially focused on stabilizing underlying conditions—most commonly heart failure—and, to a limited extent, pharmacologic intervention. With modern advancements, more sophisticated PAP modalities and other targeted approaches are now available for management (Mehra et al., 2017).

2.1 OBSTRUCTIVE SLEEP APNEA: EPIDEMIOLOGY, PATHOPHYSIOLOGY, AND CLINICAL IMPACT

Obstructive Sleep Apnea (OSA) is a sleep-related breathing disorder with significant physical and social implications, leading to a deterioration in quality of life (QoL). This syndrome is the most common among sleep disorders, with a prevalence ranging from 12% to 20.5% in the Italian population—specifically between 2% and 4% in men and

between 1% and 2% in women. This indicates that the syndrome is significantly more frequent in men, with a male-to-female ratio of approximately 2:1 in the general population, a ratio that tends to decrease after menopause. In women, female sex hormones—particularly estrogens and progesterone—appear to exert a protective effect on upper airway patency and on the regulation of muscular tone during sleep. With the cessation of ovarian activity, this protective effect is lost, leading to an increased risk of developing OSA in the postmenopausal period (Benjafield et al., 2019). Indeed, prevalence increases with age in both men and women, reaching 65% among individuals over 60 years of age (Senaratna et al., 2017).

OSA is characterized by recurrent and periodic obstructions of the upper airways, particularly partial or complete collapses of the pharyngeal soft tissues during sleep, which cause episodes of hypopnea (partial reduction in airflow) and apnea (cessation of respiratory airflow for ten seconds or more), resulting in intermittent hypoxia (oxygen deficiency at the tissue level) and hypercapnia (excessive accumulation of carbon dioxide in the blood) (Pham et al., 2022). Upper airway anatomy is a key factor in the pathogenesis of OSA; indeed, many patients affected by this disorder present with adipose tissue deposits in the pharyngeal and parapharyngeal muscles, macroglossia, and mandibular retrognathia (Sisson, 2023). However, structural anatomical defects are not the only factors contributing to the onset of OSA. Often, the disease develops when neuromuscular responses fail to adequately compensate for airway obstruction. These characteristics are frequently observed in conditions of obesity; indeed, the prevalence of OSA increases to 50–60% among obese patients and those with metabolic syndrome (Pham et al., 2022).

A systematic review by Borsoi and colleagues highlights important information regarding the adverse effects associated with OSA. Intermittent respiratory collapse and fragmented sleep lead to several complications that compromise the patient's physical health, making OSA a risk factor for several conditions, including arterial hypertension, diabetes, cardiovascular and cerebrovascular diseases, and cognitive impairment. Furthermore, OSA has been found to be associated with a reduced QoL, diminished work performance, and an increased risk of traffic accidents (Borsoi et al., 2022).

Symptoms of OSA range from snoring and daytime sleepiness to sudden sleep attacks, which may increase the likelihood of traffic accidents, cardiovascular damage, and cognitive deficits (Maspero et al., 2015).

Despite the high prevalence and serious consequences of this condition, OSA is often underdiagnosed—both because patients do not recognize the symptoms as indicators of a possible disorder and because many symptoms are ignored or underestimated. This leads to the condition being frequently overlooked and, consequently, undertreated (Young et al., 2009)

2.2 CLINICAL MANIFESTATIONS AND DAYTIME CONSEQUENCES OF OBSTRUCTIVE SLEEP APNEA

OSA is a heterogeneous disorder with a multifactorial aetiology. OSA is characterized by variable clinical manifestations, which are essential for recognizing and diagnosing the syndrome and for determining an effective treatment approach (Maspero et al., 2015). The clinical features in patients with OSA vary in number and combination, but symptoms can generally be categorized into two main types:

- Nocturnal symptoms: snoring, gasping, choking sensations, fragmented sleep, difficulty maintaining sleep, nocturia, enuresis, and night sweats.
- Diurnal symptoms: excessive daytime sleepiness, asthenia, morning headache, impaired memory and concentration, mood disturbances or irritability, and reduced libido (Rundo, 2019).

One of the most commonly reported nocturnal symptoms by both OSA patients and their bed partners is snoring. This condition results from the vibration of the soft palate and the posterior pillars of the fauces. When associated with the periodic or recurrent upper airway obstructions typical of OSA, snoring is accompanied by intermittent cessations of breathing. These pauses typically last from 10 to 60 seconds and lead to a reduction in blood oxygen levels. Snoring usually begins shortly after falling asleep, increases in intensity during deeper stages of sleep, and becomes more irregular during REM sleep. Snoring intensity may increase in the presence of obesity or following alcohol consumption.

Patients with OSA often experience jerks or spasms at sleep onset, followed by involuntary and sudden movements, typically occurring during episodes of respiratory

recovery. Additionally, patients may perceive a sensation of choking during sleep, caused by the cyclical interruption of breathing.

Nocturia—defined as the need to urinate during the night—and enuresis—defined as involuntary urinary incontinence during sleep—are also common symptoms in patients with OSA. These symptoms may be linked to intermittent hypoxia, as oxygen deprivation can lead to increased oxidative stress and the oxidation of proteins and lipids, resulting in bladder hyperactivity. Furthermore, elevated levels of atrial natriuretic peptide (ANP) have been observed in OSA patients. ANP promotes increased nocturnal urine production in an attempt to restore normal blood pressure levels, which tend to rise during apneic events.

These clinical manifestations are interrelated, with nocturnal symptoms significantly affecting daytime functioning. Most OSA patients report asthenia upon waking, regardless of the total sleep duration. Indeed, both fatigue and excessive daytime sleepiness (EDS) are frequently reported in this population. Daytime sleepiness is most evident during periods of monotony or inactivity, but in severe cases, it can occur during active tasks such as speaking, eating, or driving. This condition tends to worsen as the syndrome progresses, potentially leading to sudden sleep attacks that increase the risk of traffic accidents (ICSD-3-TR) (AASM, 2023). Indeed, studies—including one by Udholm and colleagues (2022)—have shown that, compared to the general population, OSA patients are at a higher risk of motor vehicle accidents due to excessive daytime sleepiness, inattention, reduced vigilance, and sudden sleep episodes. However, the same study noted that OSA patients show a lower risk of accidents involving other modes of transportation, such as cycling. A possible explanation for this is the attenuation of symptoms during physical activity (Udholm et al., 2022).

EDS is one of the most prevalent and clinically significant manifestations of OSA, frequently resulting in unintended or inappropriate sleep episodes. EDS markedly impairs daytime performance, cognitive function, and overall quality of life (QoL). The clinical expression of EDS is highly variable—it may manifest subtly as drowsiness during sedentary or monotonous activities, or more severely as sudden sleep attacks during tasks requiring sustained attention, such as driving. The primary mechanism underlying EDS in OSA is sleep fragmentation secondary to recurrent respiratory events, which disrupt sleep architecture and impair attention and vigilance. However, not all individuals with

OSA exhibit EDS, underscoring the heterogeneous nature of symptom expression within this disorder (Garbarino et al., 2018). Furthermore, the correlation between EDS severity and the apnea–hypopnea index (AHI) is only modest, indicating that AHI alone is an inadequate predictor of subjective sleepiness (Malhotra et al., 2021).

Multiple additional factors are believed to contribute to the development of EDS in OSA. These include nocturnal intermittent hypoxia, autonomic nervous system dysfunction, and comorbid conditions such as obesity, cardiovascular disease, type 2 diabetes, and depression (Malhotra et al., 2021). Importantly, the absence of self-reported EDS does not exclude the diagnosis of OSA, as many individuals may fail to recognize or report sleepiness, instead describing their symptoms as generalized fatigue (Emsellem et al., 2025). In clinical practice, EDS is most commonly evaluated using subjective assessment tools, such as the Epworth Sleepiness Scale (ESS) (Scharf, 2022; Emsellem et al., 2025). The presence of EDS has been associated with an increased risk of cognitive dysfunction, decreased daily performance, workplace errors, occupational injuries, and motor vehicle accidents (MVAs). Notably, some patients demonstrate limited awareness of their functional impairments, including driving performance deficits, despite objective evidence of excessive sleepiness (Li et al., 2017).

It is important to recognize that the term “excessive daytime sleepiness (EDS)” can be somewhat misleading, as increased sleep propensity may similarly impair performance in night-shift workers, where sleepiness manifests during nocturnal hours but carries comparable functional and safety risks. Beyond EDS, obstructive sleep apnea (OSA) is consistently associated with reduced quality of life (QoL), as demonstrated by findings from both generic and disease-specific QoL assessment tools. The Functional Outcomes of Sleep Questionnaire (FOSQ) is a validated and sensitive instrument designed to quantify the functional impairments related to sleep disorders and is widely utilized to assess both the disease burden and therapeutic response in patients with OSA (Chaiyaporntanarat et al., 2024). Objective indicators of sleepiness, including shortened sleep latency on the Multiple Sleep Latency Test (MSLT) and reduced wakefulness ability on the Maintenance of Wakefulness Test (MWT), are frequently observed in individuals with moderate to severe OSA, further substantiating the physiological basis of EDS in this population (Taillard et al., 2024).

The lack of restorative sleep impacts daytime functioning not only through EDS but also through other significant symptoms, such as morning headache. This is likely caused by intracranial vasodilation resulting from hypercapnia (excessive accumulation of carbon dioxide).

Among the OSA-related symptoms affecting QoL, reduced libido is particularly noteworthy. A study by Mun and colleagues (2018) shows that 23% of patients with OSA report decreased libido, attributable to conditions such as nocturia, depression, and anxiety. Furthermore, these patients often exhibit reduced levels of testosterone, luteinizing hormone (LH), and growth hormone (GH) (Mun et al., 2018).

Other factors that significantly affect the QoL of OSA patients include cognitive difficulties and mood disturbances. Cognitive impairment may involve deficits in attention, concentration, and memory. Intermittent hypoxia plays a critical role in initiating and exacerbating these cognitive deficits, as well as depressive symptoms, which tend to develop as a consequence of neuroinflammation (Kerner & Roose, 2016).

Cognitive dysfunction is a well-recognized consequence of obstructive sleep apnea (OSA) and is believed to result from the combined effects of cortical arousals, sleep fragmentation, excessive daytime somnolence, and nocturnal intermittent hypoxia (IH). These pathophysiological disturbances disrupt neural homeostasis and impair higher-order cognitive functions, particularly sustained attention (vigilance)—a critical domain for maintaining consistent performance during prolonged or monotonous activities such as driving (Liguori et al., 2021).

Beyond attentional deficits, individuals with OSA frequently demonstrate impairments in information processing, reaction time, distractibility, and overall cognitive efficiency (Liguori et al., 2021). These neurocognitive disturbances substantially contribute to the increased risk of motor vehicle accidents (MVAs) observed in this population, with studies reporting a two- to sevenfold elevation in accident risk among affected individuals (Borsoi et al., 2022). Such incidents—ranging from near misses to actual collisions—are often attributed to microsleeps, lapses in attention, and fatigue-related performance decrements, all of which compromise the ability to respond rapidly and appropriately to environmental demands (Borsoi et al., 2022).

Executive function—a domain encompassing problem-solving, cognitive flexibility, decision-making, and the initiation and regulation of goal-directed behavior—is

frequently impaired in individuals with OSA. The neural mechanisms underlying these cognitive impairments likely involve both functional disruptions, driven by excessive sleepiness and attentional instability, and structural brain changes resulting from oxidative stress and neuronal injury in regions such as the prefrontal cortex and hippocampus, which are particularly vulnerable to intermittent hypoxia (IH) (Ogbu et al., 2024). Notably, improvements in memory, attention, and executive function following continuous positive airway pressure (CPAP) therapy have been correlated with increased gray matter volume in these brain areas, suggesting a degree of neuroplastic recovery with effective treatment (Ogbu et al., 2024).

Elevated rates of mood disorders have been consistently documented among individuals with obstructive sleep apnea (OSA). For example, a Veterans Administration study reported that 21.8% of patients with OSA met diagnostic criteria for major depressive disorder, while 16.7% were diagnosed with an anxiety disorder (Babson et al., 2013). Moreover, individuals newly diagnosed with OSA exhibit twice the risk of developing depression within one year compared with those without OSA (Chen et al., 2013; Kerner & Roose, 2016). Conversely, studies in patients with major depressive disorder have demonstrated a higher prevalence of previously unrecognized OSA, suggesting a bidirectional relationship between the two conditions. This association is further supported by interventional evidence showing that continuous positive airway pressure (CPAP) therapy produces sustained improvements in depressive symptoms (Vanek et al., 2020).

Gastroesophageal reflux is another symptom commonly reported by patients with OSA. This condition is caused by respiratory effort during apneic episodes and oscillations in intrathoracic pressure, and it is particularly prevalent among obese patients (Lim et al., 2018).

2.3 CRITERIA

In the International Classification of Sleep Disorders, Third Edition, Text Revision (ICSD-3-TR), obstructive sleep apnea (OSA) is rigorously defined by a combination of clinical symptoms and objective respiratory metrics. According to ICSD-3-TR, a diagnosis of adult OSA requires the presence of at least one symptom—such as excessive daytime sleepiness, fatigue, non-restorative sleep, or other complaints that impair sleep-related quality of life—coupled with documented breathing disturbances during sleep

(AASM, 2023). The objective measure is the Apena-Hypopnea Index (AHI), which encompasses apneas and hypopneas. ICSD-3-TR further stipulates threshold values: an AHI of ≥ 5 events/hour is diagnostic when associated with symptoms, whereas an AHI ≥ 15 events/hour may suffice even in asymptomatic individuals (AASM, 2023). Importantly, the revision clarifies that comorbid conditions must be carefully considered: the sleep disturbance should not be wholly attributable to another sleep disorder, medical illness, mental disorder, or substance use (AASM, 2023). This dual requirement of clinical manifestations and polysomnographic (or equivalent) evidence ensures that the diagnosis of OSA under ICSD-3-TR is both symptom-sensitive and physiologically grounded, aligning with its nosological purpose within the sleep-related breathing disorders category.

In the ICSD-3-TR, the diagnostic criteria for adult obstructive sleep apnea retain the core structure of the ICSD-3, but important refinements have been made to enhance clinical specificity and clarity. One of the most notable changes concerns the symptom criterion: while ICSD-3 allowed diagnosis of OSA in asymptomatic individuals with comorbidities such as hypertension, type 2 diabetes, or cardiovascular disease, ICSD-3-TR removes this as a standalone qualifying criterion (i.e., criterion A.4 in ICSD-3 is deleted in ICSD-3-TR) (AASM, 2023). Instead, ICSD-3-TR emphasizes "other symptoms leading to impaired sleep-related quality of life," broadening the clinical presentation beyond somnolence or non-restorative sleep but requiring a more patient-centered impairment (AASM, 2023). This change reflects the text revision's intent to align diagnostic thresholds more closely with functional impact rather than simply coexisting medical diagnoses (AASM, 2023). The TR does not substantially lower or raise the numerical AHI thresholds (i.e., the "≥ 5 with symptoms / ≥ 15 even if asymptomatic" schema remains), but by refining the symptom criteria, the emphasis shifts to a more holistic appraisal of how sleep breathing abnormalities affect a person's quality of life. Additionally, the ICSD-3-TR improves conceptual clarity by removing potentially redundant or less predictive criteria (e.g., the comorbidity-based criterion mentioned above), and by clarifying that the sleep disturbance should not be solely due to another disorder or substance use, promoting careful differential diagnosis (AASM, 2023). In sum, the evolution from ICSD-3 to ICSD-3-TR preserves the physiological basis of OSA

diagnosis while sharpening the clinical judgment elements, reinforcing a balance between objective respiratory metrics and meaningful patient-centered symptoms.

2.4 RISK FACTORS FOR OBSTRUCTIVE SLEEP APNEA

The clinical symptomatology of OSA is modulated by a multitude of factors, attributable to anatomical, physiological, pathological, and genetic components. In recent years, scientific literature has increasingly focused on analyzing the contribution of genetic predisposition to the disease's etiopathogenesis. In this context, the study conducted by Strausz et al. (2021) aims to identify specific genetic loci associated with an increased risk of developing OSA, as well as to assess the potential sharing of a common genetic basis with certain comorbidities frequently observed in affected individuals. The findings highlight a significant role of genetics in the manifestation of the syndrome, suggesting the existence of molecular determinants that interact with environmental and behavioral factors, thereby modulating individual susceptibility (Strausz et al., 2021).

Notably, the high genetic correlation observed between body mass index (BMI) and OSA confirms obesity as one of the primary etiological drivers of the disease. This association may reflect a specific OSA phenotype influenced by a combination of genes regulating adiposity, craniofacial morphology, chemosensory responsiveness, and ventilatory control. The clinical relevance of this link is supported by evidence demonstrating that targeted interventions for weight reduction can lead to a significant improvement in the apnea-hypopnea index (AHI) and, consequently, in the overall severity of the syndrome (Strausz et al., 2021).

Obesity is a major and well-established risk factor for obstructive sleep apnea (OSA), conferring a two- to tenfold increase in risk, with the strongest associations observed during middle adulthood (Ogbu et al., 2024). Multiple anatomical and physiological mechanisms contribute to this relationship. Adipose tissue deposition in the parapharyngeal and peripharyngeal regions leads to mechanical narrowing of the upper airway, increasing its susceptibility to collapse during sleep, particularly when neuromuscular tone in the upper airway dilator muscles declines. In parallel, excess visceral adiposity within the thoracic and abdominal cavities imposes a mechanical load on the respiratory system, impairing diaphragmatic excursion and reducing lung volumes, most notably functional residual capacity (FRC). The consequent reduction in lung

volume decreases caudal traction on the trachea and adjacent airway structures, thereby enhancing upper airway collapsibility and predisposing to obstructive events (Redline, 2017).

Reduced lung volumes not only diminish oxygen reserves but also increase the likelihood of oxygen desaturation during breathing disruptions and may lead to a higher frequency of airflow reductions being classified as hypopneas. This effect not only elevates the calculated apnea–hypopnea index (AHI) but also amplifies the physiological burden of each respiratory event. Furthermore, decreased lung volumes can destabilize ventilatory control by altering loop gain—a critical parameter governing the stability of the respiratory control system—thereby fostering oscillatory breathing patterns and enhancing vulnerability to recurrent apneas and hypopneas. In addition, adipose tissue contributes to the pathophysiology of OSA through its endocrine and paracrine activity; notably, leptin, a hormone secreted by adipocytes, plays a role in modulating ventilatory drive and may influence central respiratory control mechanisms (Redline, 2017).

Alongside genetic factors, several acquired risk factors also play a decisive role. Advanced age is a predisposing factor, as it is associated with a progressive reduction in pharyngeal muscle tone and increased laxity of soft tissues, both of which promote the collapse of the upper airways during sleep (Gottlieb & Punjabi, 2020). Similarly, male sex constitutes an independent risk factor, with a significantly higher prevalence of the disorder compared to females—particularly before menopause, after which this difference tends to diminish, likely due to the decline in estrogen and progesterone levels (Heinzer et al., 2015).

Additional risk factors are related to individual anatomical characteristics, such as retrognathia, mandibular hypoplasia, macroglossia, adenotonsillar hypertrophy, or nasal septal deviation. All of these conditions may impair upper airway patency and facilitate the occurrence of nocturnal obstructive events.

Craniofacial morphology, encompassing both skeletal and soft tissue structures, is a major determinant of upper airway configuration and represents a significant anatomical risk factor for obstructive sleep apnea (OSA). Structural variations predisposing to OSA include soft tissue abnormalities, such as an elongated soft palate, macroglossia (enlarged tongue), and hypertrophy of the adenoids and tonsils. Magnetic resonance imaging (MRI) studies have demonstrated that individuals with OSA exhibit increased tongue and lateral

pharyngeal wall volumes relative to matched controls, resulting in airway narrowing (Chi et al., 2011; Sinha et al., 2024). Cephalometric analyses further identify characteristic skeletal features in OSA, including a shortened anterior–posterior cranial base, increased lower facial height, mandibular retrognathia or micrognathia, and inferior positioning of the hyoid bone (Bajrovic et al., 2021; Xia et al., 2025).

A brachycephalic (short and broad) head shape, identifiable through anthropometric assessment, is frequently associated with reduced upper airway dimensions. This craniofacial configuration has been linked to a modest but statistically significant increase in OSA risk among individuals of European ancestry and may also identify families predisposed to both obstructive sleep apnea (OSA) and sudden infant death syndrome (SIDS) (Capistrano et al., 2015). In contrast, brachycephaly is less prevalent among African American populations and does not appear to confer an elevated OSA risk. Its role in Asian populations remains under investigation but may similarly contribute to increased susceptibility.

Findings from the Cleveland Family Study further emphasize ethnic variation in the structural determinants of OSA. Among European Americans, both hard tissue features (e.g., head shape, intermaxillary length) and soft tissue characteristics (e.g., soft palate length, tongue volume) were predictive of apnea-hypopnea index (AHI) severity. Conversely, in African Americans, only soft tissue factors significantly correlated with AHI, while hard tissue anatomy showed minimal association (Dudley & Patel, 2016).

Collectively, these observations underscore the importance of craniofacial structure in OSA pathogenesis and suggest that the relative contributions of skeletal versus soft tissue components—and potentially the genetic and developmental factors influencing them—may vary across ethnic groups edline, 2017).

Finally, behavioral factors such as alcohol consumption, use of sedative medications, and cigarette smoking contribute to the worsening of OSA symptoms. In particular, alcohol and sedatives reduce pharyngeal muscle tone and impair respiratory chemoreceptor sensitivity, while smoking induces chronic inflammation and mucosal edema in the upper airways (Epstein et al., 2009).

In conclusion, the etiology of OSA is best understood as the result of a complex interaction between genetic predisposition and environmental, behavioral, and structural factors. A thorough understanding of these mechanisms is essential for enabling early

diagnosis, personalizing therapeutic interventions, and developing effective preventive strategies.

2.5 ASSESSMENT OF OSA

2.5.1 Objective assessment

The diagnostic criteria for OSA are based on clinical signs and symptoms identified through a comprehensive sleep evaluation, including a sleep-oriented medical history, physical examination, and findings from polysomnography—particularly overnight cardiorespiratory monitoring (Kapur et al., 2017; AASM, 2023).

After identifying typical symptoms of the syndrome—particularly habitual and prolonged snoring (occurring every night for six months or more)—the following are assessed: breathing pauses during sleep as reported by a bed partner (indicative of suspected apneas), episodes of awakening with a sensation of choking, and EDS. Daytime sleepiness is evaluated both subjectively, using tools such as the ESS, and objectively, through objective testing such as the MSLT or the MWT.

Polysomnography (PSG) is the most accurate and reference standard method—not only for diagnosis but also for guiding treatment decisions, with the goal of reducing morbidity and mortality associated with the condition. PSG is considered the gold standard for diagnosing sleep-related breathing disorders (Lee & Sundar, 2021). It is a non-invasive test involving the simultaneous recording of multiple physiological parameters during sleep. In rare cases, it may also be performed during daytime hours. Using electrodes and sensors, PSG monitors the following: brain activity (Electroencephalogram - EEG), eye movements (Electrooculogram - EOG), muscle activity (EMG), respiratory airflow, blood oxygen saturation via pulse oximetry, thoracoabdominal respiratory effort, and cardiac activity through electrocardiogram (ECG) recording (AASM, 2023).

Through polysomnography and the detection of changes in airflow, the following types of respiratory events can be distinguished in the presence of sleep-disordered breathing:

- Apneas: near-complete cessations of airflow lasting at least ten seconds.
- Hypopneas: partial reductions in airflow, also lasting a minimum of ten seconds.
- RERAs (Respiratory Effort-Related Arousals): events characterized by increased respiratory effort leading to arousal from sleep, without full cessation of airflow.

These abnormal breathing events can occur during any sleep stage but are most frequently observed during light non-REM sleep (N1 and N2 stages) and REM sleep, while being

less common during deep slow-wave sleep (N3). In particular, more frequent or severe apneas and hypopneas, along with greater oxygen desaturation, tend to occur during REM sleep or when the patient is in the supine position (lying on the back). When normal breathing resumes, oxygen saturation typically returns to baseline levels. However, if apneic or hypopneic episodes are particularly frequent, prolonged, or occur in patients with pre-existing pulmonary conditions, blood oxygen levels may remain low for extended periods (AASM, 2023).

PSG allows for the identification of three types of apneas, which differ in their characteristics and underlying mechanisms of respiratory arrest during sleep:

- Obstructive apneas: the most common form of sleep apnea. These are characterized by complete or partial cessation of breathing due to collapse of the upper airway. Despite the obstruction, respiratory effort by the body continues. This mechanism is known as paradoxical breathing, referring to inward movement of the abdomen during inspiration.
- Central apneas: these are not caused by a physical obstruction of the upper airway, but rather by a temporary interruption in the neural signal from the central nervous system responsible for regulating respiration.
- Mixed apneas: a combination of central and obstructive apneas. Initially, there is a failure in the neural respiratory drive (central component), but as breathing resumes, airflow is obstructed due to collapse of the upper airway (obstructive component).

The utility of PSG lies in the wide range of physiological data collected during sleep. However, due to the extensive volume of data, there is a risk of misleading or misinterpreted findings. Additionally, PSG has certain limitations, particularly related to poor sleep quality during the clinical recording. For this reason, it is generally required that the patient sleeps for at least two hours during the monitoring period for the recordings to be considered valid and clinically useful. Other common complications include the influence of certain medications taken prior to the test, which may interfere with results, and discomfort from the electrodes, which can cause skin irritation at the attachment sites (AASM, 2023).

In addition to PSG, objective methods for assessing excessive daytime sleepiness are essential in the diagnosis of OSA. Among these, the MSLT and the MWT are particularly important.

The MSLT objectively measures a patient's propensity to fall asleep in the absence of external arousing stimuli. Its primary purpose is to assess the individual's physiological tendency to initiate sleep under standardized conditions. The test is performed following a thorough evaluation of the patient's sleep patterns, including information on sleep duration and quality. The MSLT consists of measuring sleep latency—i.e., the time it takes to fall asleep—during a series of scheduled nap opportunities throughout the day. A shorter sleep latency indicates greater daytime sleepiness. The MSLT is also used to evaluate persistent sleepiness despite OSA treatment. In such cases, the test should be conducted when the patient is clinically stable and adherent to therapy.

In contrast, the MWT aims to measure a patient's level of alertness and/or their ability to remain awake during periods of low stimulation and in a conducive sleep environment. Therefore, a longer sleep latency in the MWT reflects a greater capacity to maintain wakefulness. This test is commonly used to assess treatment response in disorders associated with excessive sleepiness, such as OSA, and to evaluate wakefulness in individuals whose professions require sustained alertness for safety reasons (e.g., pilots, drivers).

When the MSLT or MWT is performed in OSA patients undergoing treatment with PAP, it is essential that the PAP device is used during the testing sessions to ensure clinically relevant results.

It is important to note that the MSLT and MWT should not be considered standalone diagnostic criteria for establishing a diagnosis of OSA, determining the presence of excessive sleepiness, or evaluating treatment efficacy. Rather, their interpretation must be integrated with other clinical information, including patient history and data from additional diagnostic tests (Krahn et al., 2021).

2.5.2 Subjective assessment

Routine screening for OSA is conducted by the physician, who may use specific screening questionnaires during the clinical history to further explore the patient's medical background. It is important to note that relying solely on these tools for diagnosing OSA is not fully effective. For this reason, the American Academy of Sleep

Medicine (AASM) discourages their use as standalone instruments for confirming the diagnosis in the absence of PSG, due to the high risk of false positives and false negatives (Kapur et al., 2017). Nevertheless, screening questionnaires can be valuable for identifying individuals at high risk who may require further diagnostic evaluation.

The most commonly used screening instruments include:

- The Berlin Questionnaire: This questionnaire comprises three categories related to the risk of sleep apnea. Patients are classified as high or low risk based on their responses to individual questions and the overall evaluation of the categories. A patient is considered at high risk for OSA if two or more categories are positive; conversely, a patient is classified as low risk if only one or none of the categories are positive. The questions assess the presence and frequency of snoring, daytime sleepiness, hypertension, and BMI calculation (Netzer et al., 1999). Each category is scored as positive or negative. The cutoff is defined as follows:
    - High risk of OSA: ≥ 2 positive categories
    - Low risk of OSA: 0–1 positive category
- The STOP-Bang Questionnaire: This tool focuses on four subjective items: Snoring, Tiredness, Observed apneas, and high blood Pressure; and four demographic or physical characteristics: BMI, Age, Neck circumference, and Gender. One point is assigned for each affirmative answer across the eight questions (total score range: 0–8). The risk stratification is as follows:
    - 0–2: Low risk
    - 3–4: Intermediate risk
    - 5–8: High risk

  The STOP-Bang questionnaire is particularly useful for identifying patients at risk of OSA in preoperative settings (Nagappa et al., 2015; Sisson et al., 2023).
- Epworth Sleepiness Scale (ESS): The ESS consists of eight items and provides a measure of general daytime sleepiness or the propensity to fall asleep in common daily situations. Each item is scored from 0 (“never”) to 3 (“high chance of dozing”), yielding a total score ranging from 0 to 24. The established cutoff values are:
    - 0–10: Normal levels of daytime sleepiness
    - 11–12: Borderline

    - ≥ 13: Clinically significant excessive daytime sleepiness
      According to the study by Gonçalves and colleagues (2023), the ESS is a reliable instrument for assessing self-reported excessive sleepiness, which is frequently associated with various sleep disorders.
- Pittsburgh Sleep Quality Index (PSQI): The PSQI is designed to evaluate subjective sleep quality. It consists of nineteen items that generate seven component scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction. The sum of these seven component scores yields a global score ranging from 0 to 21. Each component is scored from 0 (no difficulty) to 3 (severe difficulty) (Buysse et al., 1989). The cutoff values are defined as follows:
    - ≤ 5: Good sleep quality
    - 5: Poor sleep quality, clinically significant

A study by Curcio and colleagues (2013), aimed at validating the Italian version of the PSQI, confirmed the questionnaire's reliability in assessing sleep quality. The study demonstrated that the PSQI has strong overall efficiency in differentiating individuals with healthy, restorative sleep from those exhibiting pathological sleep patterns.

2.6 OSA TREATMENTS

OSA is a complex, multifactorial, and multisystem disorder. For this reason, it is essential to consider the heterogeneity of OSA in order to design a multidisciplinary and effective therapeutic plan, both for patient management and for the overall treatment of the condition.

The gold standard treatment for OSA is the use of a continuous positive airway pressure (CPAP) device. However, in recent years, interest in alternative treatment approaches has markedly increased, mainly due to the low patient compliance associated with CPAP therapy (Gambino et al., 2022).

Among the alternative therapeutic interventions, the following can be distinguished:

- Behavioral treatments, through lifestyle modifications;
- Surgical treatments, in severe cases or when CPAP is not tolerated;
- Mechanical treatments, such as the use of orthodontic appliances.

2.6.1 Behavioral treatments

In patients affected by OSA, certain lifestyle habits and behaviors can act as risk factors for the development or worsening of the disorder. Consequently, modifying these habits and behaviors can be effective in managing the condition and improving its symptoms. The main lifestyle modifications include: weight loss, sleep position, smoking and alcohol consumption.

Weight loss. OSA is more prevalent among overweight or obese individuals; therefore, obesity represents a major risk factor. Weight reduction is associated with a decrease in apneic episodes and a lower likelihood of disease progression. A study from the Wisconsin Sleep Cohort showed that a 10% weight gain predicted a 32% increase in the Apnea-Hypopnea Index (AHI), indicating disease worsening, whereas a 10% weight loss reduced the AHI by 26% (Peppard et al., 2000). Moreover, weight reduction significantly improves mild OSA, although it does not guarantee complete remission of the syndrome. In more complex clinical stages, it has been observed that weight loss combined with CPAP therapy yields greater benefits. Patients with severe obesity and OSA who struggle to lose weight are often the most difficult to treat; therefore, bariatric surgery is frequently recommended to improve both obesity and OSA conditions (Gambino et al., 2022). Additionally, weight loss significantly improves sleep quality, snoring, and hypoxia.

Sleep position. In some patients, apneic and hypopneic events occur more frequently and become more severe in the supine position; in others, such events may occur exclusively when lying supine. Therefore, the sleeping position can be a determining factor in better managing the disorder. A study by Sabil et al. (2020) reported that among patients with positional OSA (50%), 30% belonged to the category of patients who slept exclusively in the supine position. This confirms that preventing the supine position is effective in reducing the apnea-hypopnea index (Sabil et al., 2020).

Smoking and alcohol consumption. Cigarette smoking can promote the onset and worsening of obstructive sleep apneas. This occurs both through the direct pro-inflammatory action on the upper airways following smoke inhalation and through the effects of nicotine. Moreover, tobacco use increases the likelihood of fragmented sleep. Consequently, smoking cessation programs may represent an effective strategy to limit the progression of OSA and maintain good sleep quality (Zeng et al., 2023; Hang et al., 2025). As for alcohol consumption, it is important to limit intake, since alcohol increases

snoring intensity and further reduces the tonic activity of upper airway dilator muscles, making apneic episodes longer and more severe.

2.6.2 Surgical treatments

In OSA, the decision to proceed with surgical treatment is based on several factors, including the severity of the disorder, the presence of anatomical abnormalities (e.g., enlarged tongue, retruded mandible, tonsillar hypertrophy), and the failure of conservative therapies (such as intolerance or ineffectiveness of CPAP therapy). In some cases, the surgical approach aims to enlarge the upper airways or to remove adipose tissue.

Palatal surgery represents the most frequently performed surgical option for the treatment of OSA (De Vito et al., 2021).

In recent years, the most commonly performed palatal surgical procedure in patients with OSA has been uvulopalatoplasty (UPP). This intervention is indicated when the oropharynx is identified as the primary site of obstruction, particularly in cases of a markedly ptotic and/or hypertrophic soft palate, or in severe OSA. UPP is often combined with other surgical procedures, such as nasal surgery, tonsillectomy, and tonsillotomy. The effectiveness of uvulopalatoplasty has been demonstrated in a study by Stuck and colleagues, which showed a marked improvement in AHI in adult patients with OSA who underwent UPP (Stuck et al., 2018).

Another successful surgical treatment for OSA is maxillomandibular advancement (MMA). This surgical technique aims to expand the facial skeleton, thereby increasing the tension of the soft tissues of the pharyngeal walls and preventing their collapse (De Vito et al., 2021). Patients treated with this procedure show significant improvements in AHI, ODI (Oxigen Desaturation Index), and ESS (Epworth Sleepiness Scale) outcomes compared to other multilevel surgical treatments (Zhou et al., 2021).

Furthermore, the base of the tongue represents the main site of hypopharyngeal collapse during apneic events. For this reason, in cases of hypopharyngeal obstruction, surgical treatments targeting tongue reduction are often performed, such as midline glossectomy, lingual tonsillectomy, radiofrequency ablation, or genioglossus advancement procedures (De Vito et al., 2021).

A surgical treatment that is now rarely performed but historically regarded as the first surgical intervention for OSA is tracheostomy. This procedure involves the insertion of a

cannula to provide an alternative airway passage to the lungs. Although tracheostomy offers the advantage of bypassing upper airway obstructions and can significantly improve OSA, it is considered an extreme surgical solution. The patients most suitable for tracheostomy are those in whom medical treatments have failed, who are not candidates for soft-tissue surgery, or who have declined maxillomandibular advancement (MMA) surgery (Liu & Riley, 2017).

2.6.3 Mechanical devices

Patients affected by OSA can also be treated using mechanical devices. The Mandibular Advancement Device (MAD) is an appliance designed to be worn during sleep and functions similarly to an orthodontic device. Its purpose is to advance the mandible, thereby maintaining the upper airway open and reducing snoring as well as the occurrence of obstructive respiratory events (Marklund, 2017). The oral device is custom-made based on the morphology of the oral cavity to ensure an optimal fit.

According to several meta-analyses, CPAP is more effective than MAD in reducing AHI, ODI, and daytime sleepiness (Bratton et al., 2015). However, since treatment compliance is higher for MAD compared to CPAP, MAD is considered a good alternative to CPAP therapy. Phenotypic characteristics of OSA—such as younger age, female sex, absence of severe obesity, smaller neck circumference, and a mild-to-moderate AHI—have been identified as predictors of a positive response to MAD therapy. From an anatomical perspective, retrognathia, narrow airways, and a hypertrophic soft palate are also predictive of MAD success (Chen et al., 2020).

A study by Trzepizur and colleagues (2021) compared the outcomes of CPAP and MAD in patients with severe OSA and found that, although MAD was less effective than CPAP in reducing AHI, there was a marked improvement in quality of life, daytime sleepiness, and sleep macrostructure in patients with severe OSA treated with MAD. Therefore, the Mandibular Advancement Device is considered most effective in cases of mild-to-moderate OSA and in patients who do not tolerate CPAP therapy (Trzepizur et al., 2021).

The Hypoglossal Nerve Stimulation (HNS) is a therapeutic procedure that has been recently introduced for the treatment of OSA. The hypoglossal nerve contains motor fibers that innervate several muscles, including the genioglossus (GG), the main pharyngeal dilator muscle. The primary goal of HNS is to stimulate the hypoglossal nerve to maintain tongue muscle activity during sleep, preventing the tongue from collapsing

backward toward the pharyngeal wall, where it could obstruct the airway and cause apneic events.

Both unilateral and bilateral HNS devices are currently approved for clinical use. These implantable pacemakers deliver electrical impulses to the hypoglossal nerve, which in turn stimulates the tongue muscles, maintaining their tone throughout sleep. HNS therapy is indicated in adult patients with moderate-to-severe OSA who are intolerant to CPAP and who do not present with complete concentric palatal collapse at the time of treatment (Suurna et al., 2021).

2.6.4 Pharmacological treatments

A range of pharmacological agents, rigorously evaluated in clinical trials, has demonstrated notable efficacy in addressing key manifestations of OSA. Among these are medications that modulate neurotransmitter systems, particularly those influencing dopaminergic (DA) and noradrenergic (NA) pathways. This category encompasses selective dopamine reuptake inhibitors, norepinephrine reuptake inhibitors, combined adrenergic–anticholinergic agents, and orexin receptor agonists (Liu et al., 2024).

Several agents—such as modafinil, pitolisant, and solriamfetol—have been shown to enhance wakefulness and alertness, thereby mitigating excessive daytime sleepiness (EDS) and improving cognitive performance. Concurrently, compounds including atomoxetine, oxybutynin, and reboxetine exert targeted effects on upper airway musculature (e.g., the genioglossus, levator, and tensor palatine muscles), reducing airway collapsibility and improving ventilatory stability during sleep (Liu et al., 2024).

Collectively, these findings reflect a growing understanding of the pathophysiological mechanisms underlying OSA, which continues to guide the development of novel pharmacologic strategies. The positive outcomes observed in recent trials highlight the promise of this approach and suggest that future therapies may be increasingly personalized, tailored to specific OSA phenotypes. Whether through monotherapy or combination regimens, these emerging interventions represent a significant step toward more refined and effective management of OSA (He et al., 2023; Perger et al., 2023).

It is widely recognized that endogenous norepinephrine (NE) withdrawal during non–rapid eye movement (NREM) sleep and the inhibitory influence of muscarinic receptor activation during rapid eye movement (REM) sleep are two principal mechanisms contributing to the reduction of pharyngeal dilator muscle tone during sleep (Chan et al.,

2006; Grace et al., 2013; Grace et al., 2014). This understanding provided the rationale for the combined use of noradrenergic and antimuscarinic agents as a pharmacologic strategy for OSA.

Recent clinical studies employing combined noradrenergic–antimuscarinic regimens in patients with OSA have reported significant therapeutic efficacy, supporting the potential of targeted pharmacotherapy for this condition (Taranto-Montemurro et al., 2019; Lim et al., 2021; Perger et al., 2022). Among these, the combination of atomoxetine, a norepinephrine reuptake inhibitor, and oxybutynin, a muscarinic receptor antagonist, has demonstrated the greatest efficacy to date (Aishah et al., 2021).

Although the observed reduction in apnea–hypopnea index (AHI) with this dual-agent approach has been positive but modest, treatment benefits appear most pronounced in non-severe male OSA patients, likely reflecting pharmacological and physiological differences in drug responsiveness. This combination therapy may serve as an alternative or adjunctive option for patients who are intolerant of or unwilling to use continuous positive airway pressure (CPAP), as well as a complementary intervention alongside airway or bariatric surgery, or residual OSA management following surgical or oral appliance therapy. Furthermore, its synergistic use with myofunctional therapy may parallel the combined application of hypnotics and cognitive-behavioral therapy in the management of insomnia, offering a multidimensional approach to improving treatment adherence and efficacy (Lee et al., 2023).

2.6.5 Continuous Positive Airway Pressure - CPAP

The main treatments for patients with OSA are based on positive airway pressure (PAP) therapies, which aim to prevent airway collapse.
PAP therapy can be delivered in several modes:

- Auto-CPAP (Automatic Titrating Positive Airway Pressure): adjusts the pressure according to the patient's respiratory pattern.
- BiPAP (Bilevel Positive Airway Pressure): delivers higher pressure during inspiration and lower pressure during expiration. BiPAP is often better tolerated by patients, particularly those who require higher pressure levels.
- Fixed CPAP (Continuous Positive Airway Pressure): delivers a constant, continuous pressure throughout the respiratory cycle (Sisson, 2023).

Continuous Positive Airway Pressure (CPAP) remains the gold standard treatment for OSA. Nasal CPAP therapy for OSA was first described by the Australian pulmonologist Colin Sullivan and colleagues in 1981 (Sullivan et al., 1981). Sullivan observed that increasing or decreasing the pressure of the air delivered to the airways could either prevent or induce obstructive apnea.

Over time, CPAP devices have undergone considerable technological improvements. Modern systems now employ variable-speed fans instead of specialized valves to maintain a constant nasal pressure, although the fundamental principles of the therapy remain unchanged (Pham et al., 2022).

CPAP is a non-invasive ventilation method that aims to recruit as many alveoli as possible to optimize gas exchange and to prevent the collapse of pharyngeal soft tissues by delivering a continuous positive airflow to the upper airways. It is a customizable medical device tailored to each patient's characteristics. Various mask types are available to ensure constant airflow delivery:

- Nasal masks, which cover the nose and deliver air directly;
- Nasal pillow masks, featuring cushions inserted into the nostrils;
- Oronasal masks, which cover both the nose and mouth and are useful for patients with nasal breathing difficulties or throat dryness caused by mouth breathing during sleep.

Compliance with CPAP therapy is fundamental to treatment success. However, no universally accepted definition of compliance exists. The study by Kim et al. (2019) defined CPAP adherence in terms of usage time, reporting high compliance in patients who used CPAP for more than 4 hours per night on over 70% of nights.

Nevertheless, adherence to CPAP is often limited, as not all patients tolerate the treatment well. Side effects contribute significantly to poor adherence and may include skin irritation or rashes from the mask, nasal congestion, claustrophobia, conjunctivitis, aerophagia, loud noise from the device, and, in some cases, infections due to bacterial or viral contamination of the equipment (Ghandiri & Grunstein, 2020).

Despite these limitations, the effectiveness of CPAP therapy in managing OSA is well established. A clinical study by Batool-Anwar et al. (2016) demonstrated the positive impact of CPAP on Quality of Life (QoL). Their results showed that using CPAP for more than four hours per night in patients with severe OSA significantly improved QoL,

as measured by the Calgary Sleep Apnea Quality of Life Index (SAQLI). These findings highlight the importance of treatment adherence in predicting improvements in both physical health and QoL (Batool-Anwar et al., 2016).

Moreover, the effects of CPAP therapy extend to various clinical outcomes. A longitudinal study by Benkirane et al. (2024) indicated that CPAP treatment significantly improves subjective sleep quality and cognitive functions—including episodic memory, inhibition, sustained attention, working memory, and executive control—especially after six months of consistent use. The same study also reported significant improvements in quality of life, reduced daytime sleepiness, and better mood regulation (Benkirane et al., 2024).

The study further emphasized the key role of adherence to CPAP treatment, as regular use leads to substantial cognitive recovery and alleviates physiological disturbances associated with OSA. For instance, clinical data show that nocturia episodes improve with CPAP use, as this therapy reduces intrathoracic pressure, relieves upper airway obstruction, and mitigates the pathophysiological mechanisms underlying nocturia (Di Bello et al., 2023), thereby enhancing overall daily functioning (Benkirane et al., 2024).

2.7 ADHERENCE IN OBSTRUCTIVE SLEEP APNEA: PATTERNS, PREDICTORS, AND DISPARITIES

In an ideal scenario, all patients with OSA would adhere to continuous positive airway pressure (CPAP) therapy throughout the entire night, every night. In reality, however, adherence to CPAP treatment is suboptimal, much like adherence patterns observed in other chronic disease therapies. Although no universally accepted definition of adherence exists, most studies have conventionally defined it as CPAP use for ≥4 hours per night on at least 70% of nights (Sawyer et al., 2011). Notably, most studies have found that patients tend to overestimate their CPAP use by approximately one hour per night, a pattern consistent among both newly diagnosed and long-term users (Kribbs et al., 1993; Engleman et al., 1996; Sawyer et al., 2011).

Short-term follow-up studies reveal two predominant patterns of CPAP use: (1) consistent users, who employ CPAP on more than 90% of nights with an average duration exceeding 6 hours per night, and (2) intermittent users, who use CPAP less than 50% of nights with average nightly use below 3.5 hours (Aloia et al., 2007; Sawyer et al., 2014). Early follow-up after therapy initiation is essential, as these usage patterns can typically be identified

within the first few days to months of treatment (Balachandran et al., 2013; Budhiraja et al., 2016). Long-term follow-up studies demonstrate that approximately 68% of OSA patients continue to use CPAP after five years (Hukins, 2006).

Certain factors have been associated with improved adherence, including greater subjective sleepiness (Epworth Sleepiness Scale score >10), higher disease severity (apnea–hypopnea index [AHI] >30 events/hour), and greater average nightly use within the first three months of therapy. Conversely, reduced adherence has been observed in individuals reporting difficulties during their initial CPAP titration night (Catcheside, 2010; Aalaei et al., 2020). Interestingly, neither higher nor lower prescribed CPAP pressures reliably predict adherence. In addition, several studies have linked African American race and lower socioeconomic status to poorer adherence, even when access to care and treatment is standardized (Greenberg et al., 2004; Billings et al., 2011). The underlying causes of these disparities remain uncertain.

2.7.1 Role of Objective Adherence Monitoring and Limitations with Current Technology

Given that adherence to positive airway pressure (PAP) therapy is frequently suboptimal, the self-reported adherence generally overestimates objectively measured use, that consistent early predictors of adherence are lacking, and that adherence patterns are typically established early in treatment, professional societies now recommend—and many payer policies require—objective adherence data review. Such monitoring is used to document therapy adherence and identify modifiable barriers to effective treatment (Sunwoo et al., 2020).

Although the majority of randomized controlled trials utilize objective adherence data to assess outcomes associated with PAP therapy, the overall impact of systematically monitoring these data for all patients remains uncertain. Most PAP device manufacturers have developed advanced online platforms that allow remote monitoring of several key parameters, including nightly usage, treatment efficacy (residual apnea–hypopnea index [AHI]), and mask performance (typically assessed through measurements of air leak) (Freedman, 2017).

While these technologies offer multiple potential advantages, they also present notable limitations. To enhance their clinical impact and improve patient-centered outcomes, several developments are needed: (1) standardization of respiratory event and air leak

definitions across manufacturers, along with validation of device-derived outputs against polysomnography; (2) improved accessibility of PAP adherence data for frontline healthcare providers, including the integration of adherence data into electronic medical record systems; and (3) targeted education for non–sleep medicine clinicians on the interpretation and appropriate application of adherence data (Freedman, 2017).

2.7.2 Objective Monitoring of CPAP Adherence: Benefits, Limitations, and Clinical Implications

Common factors contributing to reduced adherence with continuous positive airway pressure (CPAP) therapy include claustrophobia, nasal congestion, and poor mask fit, which can result in excessive leak and skin irritation. Multiple interventions have been proposed to enhance adherence with CPAP therapy. The most consistently effective intervention among PAP-naïve patients is structured patient education. Various educational strategies—such as provider-led and home-based instruction for patients and their partners, supportive follow-up care, telephone outreach, educational videos, and full-day educational workshops—have demonstrated modest improvements in adherence. Although no single approach has been universally effective across all patient populations, greater educational intensity and more frequent healthcare provider contact are generally associated with improved adherence (Poulet et al, 2009; Rezaie et al., 2018; Aalaei et al., 2020). Overall, educational interventions typically increase CPAP use by approximately 35 to 50 minutes per night.102 However, the impact of these interventions on secondary outcomes such as daytime sleepiness, quality of life, and cardiovascular morbidity remains uncertain.

The evidence regarding the role of heated humidification in improving adherence remains mixed. Some studies have demonstrated modest benefits, whereas others have reported no significant effect (Weaver et al., 2008; Yu et al., 2013; Zhu et al., 2018). Patients with prominent nasal congestion or rhinitis appear most likely to benefit from the addition of heated humidification. Limited evidence on the use of heated tubing suggests no significant improvement in adherence among patients with or without nasopharyngeal symptoms (Galetke et al., 2016). Similarly, the use of nasal corticosteroids, with or without humidification, has shown little benefit in unselected, CPAP-naïve patients with OSA (Segsarnviriya et al., 2025).

Various CPAP interfaces are available, including nasal masks, oronasal (full-face) masks, nasal pillows, and oral interfaces. The choice of interface can significantly influence comfort and adherence. Some studies have suggested that oronasal masks may negatively affect compliance, though others have not confirmed this finding (Borel et al., 2013; Andrade et al., 2018). Oronasal masks may be preferred for patients with chronic nasal obstruction, predominant mouth breathing, or high-pressure requirements with problematic mask leak. Traditionally, nasal pillows have been discouraged at pressures exceeding 12 cm H_2O due to potential leak, but newer designs have demonstrated acceptable performance in select patients even at higher pressures (Zu et al., 2013).

Overall, optimal mask fit remains a key determinant of both initial and sustained acceptance of PAP therapy. The most effective interface for a given patient is generally the one that maximizes comfort and usability (Genta et al., 2020). Changing interfaces after problems arise has not consistently improved long-term adherence, but addressing mask-related complaints proactively can improve outcomes in select patients. Clinicians should recognize that switching between nasal and oronasal interfaces may necessitate adjustment of the therapeutic pressure established during in-laboratory titration (Genta et al., 2020). For patients using fixed-pressure PAP therapy, pressure recalibration or repeat titration should be considered if adherence issues persist after a mask change.

2.7.3 Cognitive Behavioural Therapy (CBT) and Motivational Enhancement Therapy (MET) to Improve CPAP Adherence

The American Academy of Sleep Medicine (AASM) recommends that all patients with OSA undergoing CPAP therapy receive behavioral interventions both before initiation and during the early phase of treatment (Patil et al., 2019). These interventions primarily include cognitive-behavioral therapy (CBT) and motivational enhancement therapy (MET). CBT is a structured psychotherapeutic approach designed to modify maladaptive attitudes and behaviors. The beneficial effect of CBT combined with patient education on CPAP adherence is thought to result from enhanced self-efficacy—defined as an individual's motivation, volition, and confidence to engage in health-promoting behaviors (Shaukat et al., 2022).

CBT interventions can be delivered through a variety of modalities, including instructional videos demonstrating CPAP use, printed or electronic educational materials, relaxation techniques, mask fitting sessions, and telephone or telehealth-based support. A

meta-analysis of 41 randomized trials involving CPAP-naïve OSA patients reported that behavioral therapies increased nightly CPAP use by approximately 50 minutes on average (Askland et al., 2020). The effectiveness of CBT combined with educational interventions has been corroborated by several randomized controlled trials (Richards et al., 2007). Interventions incorporating active, motivational, cognitive, and behavioral strategies—which require interactive engagement by participants and are broadly classified as behavioral interventions—are associated with a substantial and clinically meaningful increase in nightly CPAP usage (measured in hours per night) (Askland et al., 2020).

Motivational enhancement therapy (MET) targets modifiable behavioral and perceptual barriers to CPAP adherence. Motivational interviewing, a core component of MET, involves structured patient interactions—both in person and via telephone—during the first month of therapy to address misconceptions, behavioral resistance, and ambivalence toward treatment. Several randomized studies have shown that motivational interviewing enhances CPAP use, although these benefits may diminish after the intervention ends (Olsen et al., 2012). Importantly, active patient education coupled with early and sustained behavioral reinforcement has been shown to promote long-term CPAP adherence and treatment compliance (Popescu et al., 2001; Stepnowsky et al., 2002; Aloia et al., 2005; Kohler et al., 2010).

CHAPTER 3 – OBSTRUCTIVE SLEEP APNEA AND COGNITION

3.1 NEUROCOGNITIVE AND PSYCHOLOGICAL CONSEQUENCES OF OBSTRUCTIVE SLEEP APNEA

The association between Obstructive Sleep Apnea (OSA) and the alteration of neuropsychological functions represents a widely debated topic in the scientific literature. A thorough understanding of this relationship is essential to promote interventions aimed at improving the quality of life (QoL) of affected patients.

According to a study conducted by Ohayon (2003), individuals with OSA present a fivefold increased risk of developing neuropsychological deficits involving memory, executive functions, and attention compared to the general population (Ohayon, 2003). These deficits are frequently accompanied by mood alterations, chronic fatigue, and irritability (Vanek et al., 2023).

Cognitive and neuropsychological deterioration in patients with OSA is mainly attributable to significant changes in cerebral perfusion and intracranial circulation (Kerner & Roose, 2016).

In healthy individuals, these parameters are regulated by a mechanism of cerebral autoregulation, which is instead compromised in patients with OSA. In fact, during apneic and hypopneic episodes, an initial acceleration of intracranial blood flow is observed, followed by a rapid collapse at the end of the respiratory crisis.

This repeated cycle of ischemia and reperfusion causes structural damage to both the white and gray matter of the brain, accompanied by a reduced production of nitric oxide by the vascular endothelium. Consequently, there is an impairment of the vasodilatory response to hypercapnia induced by hypoxemia.

Anatomically, certain brain regions are particularly vulnerable to prolonged hypoxic-ischemic damage, such as the prefrontal and frontal lobes, the basal ganglia, and the hippocampus (Kerner & Roose, 2016). These alterations substantially contribute to the progression of cognitive deterioration and represent a risk factor for the onset of psychopathological symptoms.

Supporting this, the study by Alosco et al. (2014) highlighted that reduced cerebral perfusion and insufficient vasodilatory response to hypercapnia are predictive variables for the development of depressive symptoms (Alosco et al., 2014). Furthermore,

intermittent hypoxemia and altered cerebral blood flow promote the accumulation of molecules associated with oxidative stress, activating neuroinflammatory processes that compromise the integrity of the blood–brain barrier. These mechanisms lead to a reduction in synaptic plasticity and, consequently, a progressive cognitive decline (Lim & Pack, 2014).

Thus, OSA can trigger or exacerbate pathological processes harmful to brain tissue and the blood–brain barrier, resulting in the development or worsening of depressive symptoms and cognitive deficits. The study by Kerner and Roose (2016) showed that in elderly patients with vascular risk factors, OSA can cause additional stress to already compromised microvascular and neurovascular systems.

Another element that helps explain the deterioration of neurocognitive functions is the severity of OSA, assessed through the Apnea–Hypopnea Index (AHI). Canessa et al. (2011) demonstrated that an increase in the AHI and in the time spent at low oxygen saturation levels is associated with a worsening of cognitive deficits. In particular, a significant reduction in gray matter volume was observed in the left posterior parietal cortex, an area involved in sensory processing, language, calculation abilities, and spatial representation (Canessa et al., 2011).

Moreover, in the right superior frontal gyrus, which is involved in executive and attentional processes, a statistically trending correlation was found between AHI and gray matter volume, suggesting a possible dose–response relationship between OSA severity and structural brain damage (Canessa et al., 2011).

According to the meta-analysis by Bucks et al. (2013), among the various cognitive domains compromised by the mechanisms described above in patients with OSA, memory, attention, and executive functions appear to be the most significantly affected.

3.1.1 Memory Impairment in Obstructive Sleep Apnea: Mechanisms and Neural Correlates

Regarding memory abilities, an important contribution comes from the study by Ahuja et al. (2018), which highlighted a significant impact of OSA on various subtypes of memory: declarative, episodic, emotional, spatial, and motor.

The extent of deterioration observed in each domain appears to be influenced by both demographic factors and the type of cognitive tests used, particularly when these are sensitive to sleep quality.

The study's results indicate that sleep fragmentation and excessive daytime sleepiness impair the processes of memory encoding and consolidation, leading to a decline in cognitive performance in sleep-dependent tests. Consequently, it has been demonstrated that memory alterations related to OSA specifically involve the hippocampus and its functional connections with the frontal and parietal cortices, revealing distinct patterns of brain activation during memory tasks compared to control subjects.

It has also been shown that reduced REM sleep compromises the processes of emotional memory consolidation, making it more difficult to integrate emotional experiences into long-term memory. In the same study (Ahuja et al., 2018), it was observed that OSA was associated with poorer nocturnal memory consolidation in cognitively healthy individuals, but not in those with Mild Cognitive Impairment (MCI), in whom hippocampal atrophy and daytime episodic memory were instead more predictive.

Furthermore, the cognitive and mnemonic deterioration observed in patients with OSA is attributable not only to sleep fragmentation, but also to the effects of intermittent hypoxemia, which damages brain cells—particularly in the left hippocampus and prefrontal cortex (Stranks & Crowe, 2016).

A study conducted by Twigg et al. (2010) found that such patients exhibit impaired performance in verbal episodic memory tasks, while visual and semantic episodic memory functions remain preserved. Specifically, it was observed that individuals with OSA experience specific difficulties in the assimilation and subsequent recall of verbal information, without showing similar problems regarding visual information. Moreover, the same study found no significant correlation between OSA severity and the degree of memory impairment, suggesting that these deficits do not worsen with increasing disease severity (Twigg et al., 2010).

Supporting these findings, an experimental study on rats showed that sleep fragmentation every two minutes is sufficient to cause a significant reduction in synaptic plasticity, negatively affecting the memory consolidation process (Tartar et al., 2006).

3.1.2 Executive Function Deficits in Obstructive Sleep Apnea: Mechanisms and Therapeutic Reversibility

Executive functions are fundamental components for the proper execution of complex cognitive activities and include working memory, phonemic fluency, cognitive flexibility, and planning ability. OSA is associated with significant deficits in executive functions,

including inhibitory control and action monitoring. These deficits are often accompanied by cognitive slowing and reduced information processing speed (Ferini-Strambi et al., 2023).

Working memory is also compromised, and in this regard, Castronovo et al. (2009) found, in a sample of untreated OSA patients, a compensatory activation of the left frontal cortex during the performance of specific cognitive tasks. This phenomenon highlights a greater demand for neural resources to maintain performance levels comparable to those of healthy individuals, suggesting the presence of a cerebral compensatory mechanism.

Following CPAP treatment, a reduction of such hyperactivation was observed, particularly in the brain areas responsible for working memory and executive control, indicating a normalization of neural recruitment in response to ventilatory therapy.

Supporting these findings, the meta-analysis conducted by Olaithe and Bucks (2013) provided significant evidence, showing that executive functions are impaired in patients with OSA compared to control subjects across all analysed subdomains. The results indicate that such patients exhibit difficulties in switching from one task or mental state to another, updating and monitoring information in working memory, inhibiting automatic or dominant responses, generating new information in the absence of external stimuli, as well as efficiently accessing long-term memory.

Further deficits were also found in fluid reasoning and complex problem-solving. This altered neuropsychological profile may help explain the relational difficulties and workplace problems frequently reported by patients with OSA. Moreover, the same study reinforced the hypothesis that these cognitive deficits are partially reversible through the use of ventilatory therapy (Olaithe & Bucks, 2013).

3.1.3 Attentional Impairments in Obstructive Sleep Apnea: Mechanisms and Network Dysfunction

The attentional domain is significantly impaired in patients with OSA, as evidenced by the study conducted by Angelelli et al. (2020). The investigation examined both the intensity components of attention—alertness and vigilance—and the selectivity components—selective and divided attention (Angelelli et al., 2020).

Alertness is defined as the readiness to receive and respond to external stimuli, whereas vigilance refers to the ability to maintain a consistent level of attention over prolonged periods. Selective attention allows one to focus on relevant stimuli while excluding

irrelevant ones, while divided attention involves the simultaneous management of multiple sources of information or tasks.

The collected data show that individuals with OSA, compared to healthy controls, exhibit significant difficulties in both intensity and selectivity components. In particular, patients with severe forms of OSA, accompanied by marked episodes of nocturnal desaturation, display poorer performance in alertness and vigilance, indicating a generalized impairment of attentional efficiency. Moreover, the attentional domain is particularly susceptible to sleep deprivation and fragmentation, conditions that are common in these patients. Consequently, attention in such individuals tends to be unstable and discontinuous, compromising the regular execution of activities that require sustained vigilance (de Souza Bezerra et al., 2024).

Attention is regulated by a complex network of interacting brain systems, dynamically modulated according to task demands and environmental context. Among these, the Dorsal Attention Network (DAN) is involved in top-down attentional control, the Ventral Attention Network (VAN) in bottom-up detection of salient stimuli, the Default Mode Network (DMN) in orienting attention toward internal contents, and the Salience Network (SN) in shifting attention between internal and external stimuli. These networks contribute to the maintenance of internal mental states, the orientation toward salient stimuli, and the coordination among attentional systems.

The systematic review by Ghaderi et al. (2023) highlighted that OSA compromises the functioning of several of these networks—particularly the dorsal and ventral frontoparietal circuits—negatively impacting both goal-directed and stimulus-driven attention (Ghaderi et al., 2023).

3.2 NEUROIMAGING IN OBSTRUCTIVE SLEEP APNEA: STRUCTURAL AND FUNCTIONAL BRAIN ALTERATIONS

OSA is frequently associated with a wide range of neurocognitive disorders, which manifest at both behavioral and structural levels. These impairments appear to be reflected in morphological and functional abnormalities of brain tissue, contributing to the progressive deterioration of cognitive abilities in these patients.

A particularly relevant study conducted by Canessa et al. (2011) investigated the relationship between OSA and cognitive decline by subjecting a sample of 17 patients with OSA to a battery of neuropsychological tests combined with structural and functional

magnetic resonance imaging (MRI) techniques. The results revealed a clinical profile characterized by deficits across multiple cognitive domains, including memory, attention, executive functions, and visuoconstructive abilities.

These deficits were also accompanied by a significant increase in daytime sleepiness and higher scores on the Beck Depression Inventory (BDI)—a widely used tool for mood assessment, particularly valuable in detecting depressive symptoms in untreated OSA patients.

Using MRI, the observed cognitive alterations were found to correlate with localized reductions in gray matter (GM) volume in specific brain regions: the entorhinal cortex of the left hippocampus (parahippocampal gyrus), the left posterior parietal cortex, and the right superior frontal gyrus. These structural abnormalities were significantly correlated with specific cognitive deficits. For instance, the reduction in gray matter volume in the left entorhinal cortex showed a negative correlation with the number of errors on the Stroop test—a measure of executive functioning and inhibitory control—suggesting a decline in cognitive performance.

Similarly, the decrease in gray matter in the left posterior parietal cortex was positively associated with performance on the Raven's Progressive Matrices test (used to assess abstract reasoning) and negatively correlated with daytime sleepiness scores, indicating a potential link between structural integrity and vigilance.

Regarding the hippocampal region, MRI revealed a significant reduction in gray matter volume in untreated OSA patients compared to the control group. The areas most affected were the cornu ammonis and the right entorhinal cortex, structures that play a crucial role in memory and learning processes. These findings reinforce the view that OSA does not merely produce transient effects related to sleepiness or fatigue but may lead to measurable structural alterations at the brain level.

Conversely, supporting the hypothesis of reversible brain plasticity in OSA patients, the same study by Canessa et al. (2011) provided further evidence emerging from the analysis of structural changes following ventilatory therapy. After the treatment period, a second MRI revealed no significant reductions in gray matter volume in any brain region. However, in certain cortical and subcortical areas—particularly the left hippocampus and the frontal cortex—an increase in neural tissue volume was observed. This volumetric enhancement corresponded with improved performance on neuropsychological tests,

suggesting the presence of structural recovery mechanisms in response to improved nocturnal oxygenation and reduced sleep fragmentation.

Further evidence supporting the hypothesis of structural and functional neuroplasticity in patients with OSA comes from the study by Castronovo et al. (2009), which observed alterations in brain activation in individuals with untreated OSA. Specifically, neuroimaging revealed that these patients appear to engage a compensatory mechanism, characterized by increased neural recruitment compared to healthy controls, involving a larger number of brain regions during the execution of cognitive tasks.

This pattern of hyperactivation, although allowing patients to maintain comparable performance levels, indicates a greater demand for cognitive resources to perform tasks that, in healthy individuals, require less effort. However, to fully understand the relationship between OSA and cognitive decline, it is essential not only to consider gray matter (GM) alterations but also to examine microstructural changes in white matter (WM).

In this regard, the study by Castronovo et al. (2014) demonstrated that untreated OSA patients show significant abnormalities in metrics derived from Diffusion Tensor Imaging (DTI), a neuroimaging technique that evaluates the integrity of white matter fibers by measuring Mean Diffusivity (MD). Under physiological conditions, the diffusion of water molecules is directional and coherent along WM fibers; however, in the presence of structural damage, water movement becomes more disorganized, indicating neural pathway disruption (Castronovo et al., 2014). These white matter alterations are clinically relevant, as they are associated with slowed cognitive processing, attentional difficulties, executive impairments, and affective symptoms—all commonly reported in OSA patients. Data from the study showed that after three months of treatment, only certain regions—particularly left hemispheric areas—displayed mild signs of diffusivity normalization, suggesting that, unlike gray matter (which responds more rapidly to therapy, as highlighted by Canessa et al., 2011), white matter recovery follows a slower and more gradual process.

Moreover, a study by Salsone et al. (2021) found that the fractional anisotropy (FA) in normal-appearing white matter (NAWM) of the brain stem, corpus callosum and bilateral internal capsule of OSA patients improved after 3 months of CPAP treatment. Authors found that axial diffusivity in the corpus callosum, superior corona radiata, and internal

capsule of the right hemisphere also increased. The FA of the corona radiata, corpus callosum, internal capsule, limbic structures, and neuropsychological scores at follow-up assessment were negative correlated. No significant differences were found in mean diffusivity (MD) and radial diffusivity (RD) of NAWM in this sample of OSA patients. Their results highlight the probable positive effect of CPAP treatment in the increment of FA and axial diffusivity of NAWM in major tracts such as the corpus callosum and the internal capsule. The improvement in neurocognitive profile may be related to the recovery of NAWM alterations. This result suggests that the pathophysiology of cognitive impairment in OSA patients may be due to WM alterations that are not clearly visible (Salsone et al., 2021).

Moreover, structural brain alterations have also been identified using FDG-PET (fluorodeoxyglucose positron emission tomography), which revealed cerebral hypometabolism and gray matter loss in the bilateral praecuneus, posterior cingulate cortex, and frontal areas. Although the current study demonstrates dysfunction in multiple brain regions among individuals with OSA, the underlying mechanisms driving these neurocognitive and structural impairments remain incompletely elucidated (Fernandes et al., 2022).

Another line of research has focused on investigating anatomical modifications of the upper airways and the role of conditions such as pharyngeal neuromyopathy in the pathogenesis of OSA. To this end, Voxel-Based Morphometry (VBM)—which analyzes volumetric differences in gray and white matter—and Surface-Based Morphometry (SBM)—which focuses on the geometric characteristics of the cortical surface—have been applied through MRI techniques.

In OSA patients, cortical thinning is frequently observed in frontal and temporal regions. These changes appear to be correlated with cognitive deficits and a greater vulnerability to brain damage, particularly in subjects with coexisting muscular dysfunctions, thus reinforcing the correlation between OSA and cognitive decline (Baima et al., 2020).

In addition, Single Photon Emission Computed Tomography (SPECT) has proven to be a valuable tool for assessing cerebral perfusion and metabolic activity in various brain regions. By employing radiopharmaceuticals and generating three-dimensional images, SPECT enables effective monitoring of the impact of OSA on brain function. Using this technique, Giordano et al. (2011) identified perfusion deficits in prefrontal, parietal,

limbic, and cerebellar regions, confirming the widespread nature of neurofunctional alterations in individuals affected by obstructive sleep apnea (Giordano et al., 2011).
Through the neuroimaging techniques employed in the aforementioned studies, it has been possible to confirm the hypothesis that cognitive deterioration associated with OSA manifests both behaviourally and structurally. This impairment does not appear to be an irreversible process, but rather the result of potentially reversible neuroanatomical alterations, which can be mitigated through adequate adherence to treatment.

3.3 HYPOXIA AND HYPERCAPNIA IN OSA: PATHOPHYSIOLOGICAL MECHANISMS AND COGNITIVE IMPLICATIONS

The cyclical alternation of apneic and hypopneic episodes that characterizes OSA leads to recurrent interruptions of alveolar ventilation, resulting in hypoxemia, that is, a reduction in the partial pressure of oxygen in arterial blood. This condition causes a decreased availability of oxygen at the tissue level, compromising the efficiency of cellular metabolic processes and clinically manifesting as systemic hypoxia.
Hypoxia is frequently associated with hypercapnia (an accumulation of carbon dioxide in the blood) and sleep fragmentation, generating a complex pathophysiological framework with significant neurocognitive and cardiovascular implications. Reduced oxygenation is often accompanied by an increase in CO_2 concentration, a phenomenon known as hypercapnia. The latter represents an additional risk factor for cognitive deterioration, as it is associated with deficits in attention, vigilance, and orientation, as well as hypercapnic encephalopathy and motor alterations such as tremors. In more severe cases, hypercapnia may progress to coma, accompanied by cerebral vasodilation, confusional states, psychological disturbances, headache, and narcosis. Furthermore, the accumulation of CO_2 can lead to acidemia—an increase in the concentration of hydrogen ions in the blood—which in turn triggers mechanisms of vasoconstriction and further systemic dysfunctions.
The study by Lavie (2015) highlighted that intermittent hypoxia (IH), a distinctive feature of OSA, induces chronic sleep fragmentation and activates a series of potentially harmful biological mechanisms, including increased oxidative stress, systemic inflammatory activation, and sympathetic nervous system hyperactivation. These processes contribute to endothelial dysfunction, arterial hypertension, and, over time, to the onset of cardiovascular and cerebrovascular diseases (Lavie, 2015).

However, it should be noted that not all OSA patients develop cardiovascular comorbidities. In this regard, a previous study by the same author (Lavie & Lavie, 2006) hypothesized that intermittent hypoxia might, under certain conditions, exert an ischemic preconditioning effect, activating protective cellular mechanisms that mitigate the impact of ischemic injury. This dual nature of IH—harmful on one hand, but potentially adaptive on the other—illustrates the complexity of the pathophysiological response to obstructive apnea and opens new research perspectives on the role of hypoxia as a possible modulatory factor in clinical outcomes among OSA patients.

The concomitant reduction in tissue oxygenation and accumulation of carbon dioxide within the central nervous system lead to a series of structural and functional alterations in brain tissue. In particular, the hippocampus—one of the structures most vulnerable to oxygen deprivation—appears especially susceptible to the neurotoxic effects of both hypoxia and hypercapnia. In this regard, Gale and Hopkins (2004) documented the presence of hippocampal atrophy in OSA patients and in individuals with chronic hypercapnia, which was associated with significant memory impairments. These alterations seem to interfere with the efficiency of higher cognitive functions, particularly in the domains of attention, short- and long-term memory, and executive functioning (Gale & Hopkins, 2004).

Although hypoxia represents one of the main causes of cognitive deterioration in individuals with OSA, hypercapnia also constitutes a relevant pathogenetic factor, potentially responsible for worsening the neurocognitive profile. In this regard, Beaudin et al. (2022) explored the effects of hypercapnia both during sleep and wakefulness, finding a correlation between increased CO_2 levels and worsened cognitive performance, particularly among patients with severe OSA. In these subjects, a significant reduction in memory performance was observed even during wakefulness, suggesting a persistent impact of hypercapnia beyond the nocturnal phase (Beaudin et al., 2022).

Another pathogenic element lies in the repeated cycles of desaturation and reoxygenation occurring during sleep in OSA patients. These events interfere with numerous physiological processes regulated by the circadian rhythm, including body temperature regulation, melatonin secretion, and cortisol cycle modulation (Castillejos-López et al., 2023). Alterations in these biological rhythms result in significant changes in sleep quality, negatively affecting its duration, sleep onset latency, and continuity. It has also

been observed that these alterations may be amplified by individual factors such as advanced age and high body mass index, further contributing to clinical deterioration (Castillejos-López et al., 2023).

In conclusion, the evidence reviewed thus far indicates that hypoxia and hypercapnia, secondary to the respiratory fragmentation typical of OSA, represent key determinants in cognitive impairment. They negatively affect quality of life, accelerate neurocognitive decline, and contribute to both cardiovascular and cerebrovascular dysfunction.

3.4 SLEEP ARCHITECTURE, GLYMPHATIC FUNCTION, AND COGNITIVE IMPLICATIONS IN OSA

Sleep plays a central role in the promotion and maintenance of cognitive functions. The different stages of sleep, particularly non-REM (NREM) and REM sleep, are involved in numerous physiological processes essential for brain health, including memory consolidation, synaptic regulation, and the clearance of toxic metabolites. In particular, deep sleep (N3 or Slow Wave Sleep, SWS) is associated with a marked reduction in cerebral metabolism and enables effective communication between the hippocampus and neocortex, which is necessary for the stabilization of episodic memory. REM sleep, on the other hand, plays a crucial role in emotional reprocessing and neuroplasticity, facilitating learning and the consolidation of acquired skills. Therefore, an intact and continuous night's sleep, characterized by an appropriate alternation between NREM and REM phases, is indispensable for proper cognitive functioning (Singh et al., 2022).

In this context, OSA represents a highly relevant pathological condition. As previously discussed, during the night, this syndrome is marked by numerous episodes of intermittent hypoxemia (IH) and frequent micro-awakenings, phenomena that profoundly alter the architecture of sleep. According to recent literature, more than 68% of patients with OSA report poor sleep quality, as assessed using the Pittsburgh Sleep Quality Index (PSQI) (Kania et al., 2022). The study by Kania and colleagues (2022) highlighted that the clinical factors associated with worse sleep quality in OSA patients include chronic heart failure, high levels of daytime sleepiness (assessed using the Epworth Sleepiness Scale), and lower minimum nocturnal oxygen saturation.

Counterintuitively, an association was found between greater time spent in deep sleep (N3) and poorer subjective sleep quality, suggesting that hypoxia may compromise the

subjective perception of nighttime rest even when objective parameters (such as N3 duration) appear preserved. It has also been observed that patients with severe forms of OSA may develop an alteration in the subjective awareness of their sleep quality — a phenomenon that can mask the severity of the disorder and complicate the diagnostic process.

Patients with OSA typically experience highly fragmented and poor-quality sleep, with a significant reduction in deep sleep (SWS) and REM sleep, both of which are essential for brain health. According to the American Heart Association's Scientific Statement, OSA is the primary form of nocturnal respiratory disturbance and represents an independent risk factor for cognitive decline, cerebrovascular diseases, and dementias, including Alzheimer's disease (AD) (Guo et al., 2024).

From a neurophysiological perspective, sleep fragmentation associated with OSA interferes with declarative and procedural memory mechanisms, particularly affecting sustained attention, executive functions, and emotional regulation, as shown in previously discussed studies (Ahuja et al., 2018; Angelelli et al., 2020; Ferini-Strambi et al., 2024). Moreover, sleep quality is also influenced by factors such as sex and the presence of cardiovascular comorbidities: for example, women with OSA more frequently report insomnia, morning headaches, persistent fatigue, and greater use of hypnotic medications than men, suggesting a distinct and sometimes underestimated symptom profile in clinical settings (Kania et al., 2022).

Another crucial aspect that has emerged in recent years is the role of the glymphatic system, a cerebral drainage system that is predominantly active during deep sleep. This system facilitates the elimination of neurotoxic metabolites such as Aβ (beta-amyloid) and tau proteins, both closely linked to neurodegeneration. However, sleep deprivation and fragmentation—typical features of OSA—compromise the efficiency of the glymphatic system, promoting the accumulation of toxic substances and accelerating neurodegenerative processes.

Furthermore, alterations in venous outflow induced by repeated obstructive events, such as respiratory efforts against closed airways, may impair glymphatic clearance, exacerbating chronic brain damage (Guo et al., 2024; Liguori et al., 2021). Indeed, as shown by Liguori and colleagues (2021), these sleep alterations may play a pathogenetic role in the early phases of neurodegeneration, as suggested by the observed association

between the cerebral cholinergic network and REM sleep quality, the latter being significantly compromised in subjects affected by Alzheimer's disease (Liguori et al., 2021).

The growing evidence that OSA may precede the onset of Mild Cognitive Impairment (MCI) and accelerate the progression of Alzheimer's disease reinforces the importance of early diagnosis of nocturnal respiratory disorders and timely intervention through appropriate treatments, such as Continuous Positive Airway Pressure (CPAP) therapy, to prevent or slow neurocognitive deterioration.

3.5 OBSTRUCTIVE SLEEP APNEA AS A RISK FACTOR FOR NEURODEGENERATION AND COGNITIVE DECLINE

A growing body of scientific evidence suggests that OSA is a significant risk factor for neurodegeneration and the development of cognitive disorders, such as Mild Cognitive Impairment (MCI) and Alzheimer's Disease (AD). The causal link between OSA and cognitive decline is underpinned by multiple converging pathophysiological mechanisms affecting neurovascular regulation, glymphatic function, and synaptic homeostasis. Pathophysiological features of OSA—particularly intermittent hypoxia and sleep fragmentation—severely impair sleep quality, leading to systemic and cerebral oxidative damage, further exacerbated by chronic inflammatory responses and endothelial dysfunction (Kerner and Roose, 2016).

According to the model proposed by Kerner and Roose (2016), these alterations contribute to the development of cerebral small vessel disease (C-SVD), characterized by white matter lesions, loss of neuronal tract integrity, and reduced cerebral perfusion—especially in frontal and parietal regions. These structural and functional brain changes have been associated with deficits in executive functions, episodic memory, and sustained attention, exhibiting cognitive impairment profiles comparable to those observed in neurodegenerative diseases (Kerner and Roose, 2016).

A recent systematic review indicates that OSA not only disrupts brain structure and function—particularly in the hippocampus and frontal regions—but is also linked to genetic biomarkers such as the apolipoprotein E ε4 allele (ApoE4), which heightens cognitive vulnerability. The interaction between OSA and factors including age, sex, obesity, inflammation, and genetic predisposition constitutes a multifactorial pathogenic axis that drives neurodegenerative progression (Ogbu et al., 2024).

3.5.1 Obstructive Sleep Apnea and Mild Cognitive Impairment (MCI): Risk, Progression, and Therapeutic Implications

In recent years, growing attention has focused on the link between OSA and Mild Cognitive Impairment (MCI)—a clinical condition characterized by mild cognitive deficits often regarded as a prodromal stage of dementia. According to Lal and colleagues (2022), OSA can directly affect both preclinical biomarkers and early cognitive manifestations of neurodegeneration, accelerating the progression from MCI to full-blown Alzheimer's disease (Lal et al., 2022).

A systematic review conducted by Mubashir and colleagues (2019) reported that OSA prevalence rates among MCI patients range from 11% to 71%, depending on the diagnostic criteria used and patient recruitment methods. Notably, when polysomnography—the diagnostic gold standard—was employed, a prevalence of 71% was observed, highlighting substantial underdiagnosis in less structured clinical settings. Moreover, patients with OSA exhibited an onset of MCI approximately one decade earlier than those without nocturnal apneas, reinforcing OSA's role as a catalyst in the pathological cognitive trajectory.

Supporting OSA's potential role as a risk factor for neurodegeneration, Liguori and collaborators (2021) demonstrated that, among individuals with MCI, the presence of OSA is associated with worse cognitive performance in domains including language, memory, and executive functions. Specifically, in individuals carrying the ApoE ε4 allele—a well-established genetic risk factor for Alzheimer's disease—the co-occurrence of OSA exerted a synergistic effect on neurocognitive vulnerability, leading to significantly poorer memory and attention performance (Liguori et al., 2021).

Another key aspect concerns the efficacy of Continuous Positive Airway Pressure (CPAP) treatment. Substantial evidence indicates that CPAP therapy can delay the progression from MCI to dementia and improve attention, vigilance, and memory in treated patients. Furthermore, CPAP has been shown to stabilize or even improve levels of certain cerebral biomarkers, reducing the accumulation of amyloid-beta (Aβ) and tau proteins and enhancing cerebral perfusion (Ferini-Strambi et al., 2021; Ogbu et al., 2024).

In conclusion, recent literature confirms that OSA represents a significant modifiable risk factor for cognitive decline. Early identification of OSA—particularly in individuals presenting with mild cognitive symptoms—and subsequent personalized therapeutic

management constitute a priority objective for promoting brain health and mitigating the socio-health burden of neurodegenerative diseases.

3.5.2 Obstructive Sleep Apnea and Alzheimer's Disease (AD): Clinical and Pathophysiological Links

Clinically, the prevalence of OSA in patients with Alzheimer's disease (AD) is extremely high, exceeding 40% in elderly patients and reaching up to 50% in individuals with a confirmed diagnosis of Alzheimer's disease (Liguori et al., 2021).

A major meta-analysis reported by Liguori et al. (2021) highlighted that patients with AD are five times more likely to have OSA compared to age-matched cognitively healthy individuals. The same systematic review noted that several longitudinal studies have demonstrated that OSA can precede the onset of dementia by approximately 5–8 years compared to individuals without obstructive nocturnal apneas.

The study by Ferini-Strambi and colleagues (2024) emphasizes that OSA—through impairment of the glymphatic system and reduced slow-wave activity (SWA) during NREM sleep—contributes to the accumulation of beta-amyloid and phosphorylated tau protein, both central to the pathogenesis of Alzheimer's disease. These processes disrupt the clearance of neurotoxic substances, thereby accelerating the onset of neurodegenerative mechanisms.

Moreover, studies conducted on patients with both AD and OSA have documented hippocampal volume reduction, altered functional connectivity within the Default Mode Network (DMN), and cerebral metabolic changes detectable via advanced neuroimaging. These alterations closely resemble those observed in dementia patients, suggesting a clinical and biological continuum linking OSA, Mild Cognitive Impairment (MCI), and AD (Ferini-Strambi et al., 2021; Lal et al., 2022; Ogbu et al., 2024).

In light of this evidence, OSA may be regarded not only as a co-factor but also as a potential trigger of neurodegenerative processes. As highlighted in the study by Lal and colleagues (2022), OSA directly impacts preclinical biomarkers and clinical manifestations of neurodegeneration, particularly in Alzheimer's disease (Lal et al., 2022). The pathological continuum of Alzheimer's disease may begin more than forty years before clinical diagnosis, initially manifesting as alterations in cerebrospinal fluid biomarkers and brain imaging findings, followed by progressive cognitive decline ranging from mild memory disturbances to severe impairment of daily activities and

motor functions. OSA's interference in this cascade can both hasten and intensify the entire pathological sequence, establishing it as a key modifiable risk factor in dementia prevention (Lal et al., 2022).

3.6 QUALITY OF LIFE IN OBSTRUCTIVE SLEEP APNEA: CLINICAL IMPACT AND THERAPEUTIC INTERVENTIONS

OSA represents a condition of significant clinical and epidemiological relevance, with effects extending well beyond its pathophysiological aspects to encompass psychosocial well-being and patients' quality of life (QoL). The repeated respiratory interruptions occurring during sleep—accompanied by intermittent hypoxia and fragmentation of the sleep-wake cycle—produce a range of debilitating symptoms, including daytime sleepiness, persistent fatigue, cognitive dysfunction, and mood disturbances. These symptoms impair daily and interpersonal functioning, leading to a substantial reduction in perceived QoL.

Quality of life in OSA patients has been extensively investigated in clinical studies using validated instruments such as the Sleep Apnea Quality of Life Index (SAQLI) and the Short Form-36 Health Survey (SF-36). These tools systematically assess the impact of the disorder across multiple domains, including physical and social functioning, emotional status, and overall health perception. For instance, Coman and colleagues (2016) reported significant improvements in SAQLI scores after just three months of CPAP therapy in patients with moderate-to-severe OSA, demonstrating notable gains in emotional well-being, social relationships, symptom burden, and functional capacity (Coman et al., 2016).

Similarly, Batool-Anwar and colleagues (2016) confirmed that sustained adherence to ventilatory therapy is associated with clinically meaningful improvements in QoL, although this effect appears attenuated in patients with mild OSA (Batool-Anwar et al., 2016).

Among the factors most strongly influencing QoL in OSA patients is excessive daytime sleepiness (EDS)—a hallmark symptom of the syndrome—which significantly interferes with global functioning by limiting daily activities, reducing work productivity, and disrupting social interactions, often leading to frustration, social isolation, and emotional distress. A study by Tang and colleagues (2024) emphasized that the presence of EDS is significantly associated with poorer perceived QoL in OSA patients, independent of the

severity of the apnea-hypopnea index (AHI). Patients reporting higher levels of sleepiness exhibited greater impairment across functional, psychological, and relational domains, suggesting that EDS acts as a clinical mediator between sleep disruption and subjective well-being. EDS has also been identified as a major predictor of motor vehicle accidents, reduced occupational efficiency, and mood disturbances—all factors closely linked to diminished QoL. CPAP therapy has demonstrated clear efficacy in reducing EDS and, consequently, improving QoL. However, individual responses to treatment in terms of sleepiness reduction vary, underscoring the need for personalized clinical and educational strategies (Tang et al., 2024).

Further support comes from the study by Vizcarra-Escobar and colleagues (2022), which compared QoL between OSA patients and individuals with Upper Airway Resistance Syndrome (UARS). Both groups showed significantly lower SF-36 scores compared to the general population, with the most affected domains being vitality, physical functioning, and social relationships. This finding indicates that, despite pathophysiological differences between OSA and UARS, sleep fragmentation—common to both conditions—is a critical determinant of impaired QoL. The study also highlighted the negative impact of comorbidities such as depression, psychotropic medication use, obesity, and chronic pain, which further exacerbate impairments, particularly in mental health and social functioning domains (Vizcarra-Escobar et al., 2022).

Particular attention should be paid to depressive comorbidity in OSA patients, as it is a significant predictor of QoL deterioration. Research by Stelmach-Mardas and colleagues (2016) elucidated the combined influence of psychological factors, chronotype, and dietary habits on QoL in OSA patients. Individuals with higher depressive symptom scores exhibited more pronounced QoL impairment, whereas those with a morning chronotype reported better outcomes. Notably, nutritional intake also showed relevant associations: higher consumption of protein, vitamin B6, and vitamin B12 was linked to greater mood stability and improved overall well-being perception (Stelmach-Mardas et al., 2016). These observations are corroborated by the systematic review conducted by Hobzova and colleagues (2017), which identified a clear association between OSA and depressive symptoms. This relationship may be mediated by shared factors such as obesity, metabolic disorders, worsening QoL, and reduced treatment adherence. Although

evidence regarding CPAP's effect on depression remains partial, current data suggest a potential therapeutic benefit of ventilatory treatment in the psychological domain as well. In conclusion, assessing QoL in OSA patients is a fundamental parameter—not only for diagnosis and clinical monitoring but also for guiding targeted therapeutic interventions. An integrated approach combining ventilatory treatment, psychological support, nutritional education, and personalized care is essential to effectively counteract the multidimensional impact of the syndrome and promote comprehensive, lasting improvements in patient well-being (Hobzova et al., 2017).

3.7 NEUROCOGNITIVE AND STRUCTURAL BRAIN RECOVERY IN OBSTRUCTIVE SLEEP APNEA: THE ROLE OF CPAP THERAPY

Continuous Positive Airway Pressure (CPAP) therapy is currently the treatment of choice for OSA and has demonstrated efficacy not only in restoring upper airway patency during sleep but also in improving the cognitive functions impaired by the disorder. Longitudinal studies, including that by Canessa and colleagues (2011), have shown that adherence to CPAP for at least three months is associated with significant improvements in cognitive performance—particularly in the domains of memory, attention, and executive functions—suggesting functional recovery linked to cerebral neuroplasticity and enhanced daily functioning.

Supporting these findings, scientific evidence from Morrell and colleagues (2010) indicates that untreated OSA is associated with reduced gray matter volume in brain regions critical for cognitive processing, such as the hippocampus and prefrontal cortex (Morrell et al., 2010). However, initiation of CPAP therapy can reverse these structural alterations. Canessa et al. (2011) demonstrated that after only three months of treatment, patients exhibited increased gray matter volume in these areas, which correlated with improved performance on neuropsychological tests.

Complementary results come from the study by Castronovo and colleagues (2014). Their analysis revealed that after 12 months of CPAP therapy, there was an almost complete normalization of white matter fiber integrity, as measured by increased fractional anisotropy (FA) and normalized mean diffusivity (MD) across multiple brain regions. Clinically, as observed with gray matter changes, these structural improvements were accompanied by significant neuropsychological gains—particularly in memory, attention, and executive functioning. These findings suggest that the brain damage observed in OSA

patients may be largely reversible, provided there is good CPAP adherence and timely intervention (Castronovo et al., 2014).

Improvements in attentional capacity—particularly sustained attention—were further explored in the study by Deering and colleagues (2017), which examined the relationship between CPAP adherence and performance on the Psychomotor Vigilance Task (PVT), an objective and sensitive measure of sustained attention. Results showed that after six months of treatment, greater CPAP adherence was significantly associated with fewer attentional lapses and faster reaction times. Specifically, for each additional hour of average nightly CPAP use, a reduction in attentional lapses was observed ($\beta = -0.72$; $p = .037$). Notably, participants who also received educational support (self-management care) demonstrated even greater improvements compared to those receiving standard clinical care alone. These data underscore the importance of objectively monitoring attention in treated patients and confirm that even adherence levels below the commonly cited threshold of 4 hours per night can yield meaningful neurobehavioral benefits (Deering et al., 2017).

Richards and colleagues (2019) demonstrated that one year of CPAP treatment in patients with Mild Cognitive Impairment (MCI) was associated with slowed progression to dementia and improved daily functional abilities. Specifically, their analysis revealed that one year of CPAP adherence (≥4 hours/night) in older adults with both MCI and OSA led to significant improvements in cognitive processing speed (as measured by the Digit Symbol test), with moderate benefits observed in attention, memory, and daytime sleepiness (Richards et al., 2019).

Similarly, Wang et al. (2020), analysing the same cohort, reported significant cognitive improvements—particularly in processing speed and attention—in older adults with mild OSA treated with CPAP, highlighting the therapy's effectiveness even in the early stages of cognitive decline (Wang et al., 2020).

Collectively, this body of evidence converges to demonstrate that CPAP, when used consistently and with good adherence, not only alleviates the clinical symptoms of OSA but also promotes structural and functional brain recovery. Therapeutic adherence emerges as a critical determinant of treatment efficacy: even limited daily CPAP exposure can yield improvements, although optimal outcomes are achieved with consistent use. Importantly, the cognitive and neuroanatomical alterations observed in OSA patients

should not be considered necessarily permanent; as demonstrated, timely and targeted interventions such as CPAP therapy can help restore normal neurocognitive functioning and significantly enhance patients' quality of life.

CHAPTER 4 – METHODS

Over the past few decades, the scientific literature has shown growing interest in the relationship between Obstructive Sleep Apnea Syndrome (OSA) and cognitive decline, outlining a complex framework in which neurodegeneration appears to be significantly influenced by sleep-related breathing disorders.
OSA, a respiratory disorder characterized by recurrent episodes of partial or complete obstruction of the upper airways during sleep, leads to complex pathophysiological events, including intermittent hypoxemia, hypercapnia, and sleep fragmentation.
The interaction of these phenomena induces a state of neural toxicity and neuroinflammation, causing both structural and functional alterations in the brain (Lim & Pack, 2014; Kerner & Roose, 2016). From a pathophysiological perspective, these interconnected mechanisms underlie the cognitive impairment observed in OSA patients. Intermittent hypoxemia increases oxidative stress, activating inflammatory responses at both systemic and cerebral levels. The resulting endothelial dysfunction compromises cerebral perfusion and damages the blood–brain barrier, allowing inflammatory and neurotoxic molecules to enter neural tissue, thereby exacerbating neurodegenerative processes (Lim & Pack, 2014).
In addition to hypoxemia, hypercapnia also plays a significant role in cognitive deterioration. Hypercapnia has been implicated in mechanisms of neural toxicity and neuroinflammation, contributing to the exacerbation of cognitive decline. Specifically, elevated CO_2 levels in patients with severe OSA have been associated with poorer cognitive performance—particularly in memory tasks—even during daytime hours, suggesting a prolonged detrimental effect of hypercapnia beyond the nocturnal period (Beaudin et al., 2022).
At the same time, sleep fragmentation disrupts normal processes of memory consolidation, synaptic regulation, and metabolic clearance. Notably, the activity of the glymphatic system—responsible for the nocturnal clearance of neurotoxic metabolites such as β-amyloid and tau proteins (key factors in the pathogenesis of Alzheimer's disease)—is impaired in OSA patients. This dysfunction promotes the accumulation of these substances, potentially triggering or accelerating neurodegenerative processes (Liguori et al., 2021; Ferini-Strambi et al., 2023).

Clinical data confirm that a substantial proportion of OSA patients—estimated at approximately 40%—exhibit measurable cognitive deficits on neuropsychological testing (Liguori et al., 2021). The most commonly affected functions include sustained attention, verbal episodic memory, and executive functions such as planning, inhibitory control, and cognitive flexibility (Bucks et al., 2013; Ahuja et al., 2018; Angelelli et al., 2020; Liguori et al., 2021; Ferini-Strambi et al., 2023). Furthermore, the severity of OSA, as assessed by the Apnea–Hypopnea Index (AHI), has been shown to correlate with the extent of cognitive impairment, with particular vulnerability observed in brain regions involved in memory and executive processing (Canessa et al., 2010).

These cognitive deficits are frequently accompanied by mood disturbances, particularly anxiety and depressive symptoms, which further exacerbate daytime dysfunction and impair quality of life (Rezaeitalab et al., 2014). Supporting this, the study by Alosco et al. (2014) demonstrated that reduced cerebral perfusion and insufficient vasodilatory response to hypercapnia are predictive variables for the development of depressive symptoms.

Within this framework of neuropsychological deterioration, OSA emerges as a potentially modifiable risk factor for neurodegeneration. Scientific evidence indicates that individuals with OSA have an increased risk of developing Mild Cognitive Impairment (MCI) and dementia, with symptom onset occurring 5–8 years earlier than in non-OSA individuals (Leng et al., 2017; Liguori et al., 2021). Particularly noteworthy is the interaction between OSA and the presence of the ApoE ε4 allele, which amplifies cognitive vulnerability and accelerates neurocognitive decline (Ogbu et al., 2024).

Furthermore, the hypothesized relationship between OSA and cognitive deficits is supported by neuroimaging evidence, showing significant alterations in gray matter within brain regions critical for cognitive functioning—particularly those associated with memory, attention, and executive control—such as the prefrontal cortex, hippocampus, and posterior parietal cortex (Canessa et al., 2011). Brain abnormalities are not limited to gray matter: advanced techniques such as Diffusion Tensor Imaging (DTI) have revealed compromised white matter integrity, suggesting a widespread impact on neural network connectivity (Castronovo et al., 2014). Salsone et al. (2021) found that 3 months of CPAP therapy in OSA patients increased fractional anisotropy (FA) and axial diffusivity in normal-appearing white matter (NAWM) of major tracts—including the corpus callosum,

internal capsule, and brainstem—without changes in mean or radial diffusivity. Higher FA at follow-up correlated negatively with neuropsychological scores, suggesting that CPAP may partially reverse subtle, clinically relevant white matter alterations underlying cognitive impairment in OSA (Salsone et al., 2021).

The aims of this study were to characterize the profile of OSA patients (afferent to IRCCS San Raffaele Hospital, UO Neurology – Sleep Disorders Center, Milan) at higher risk of conversion to neurodegenerative diseases and to identify early clinical biomarkers that can predict adherence, response and efficacy of CPAP therapy, considered the gold standard for OSAS.

4.1 STUDY DESIGN

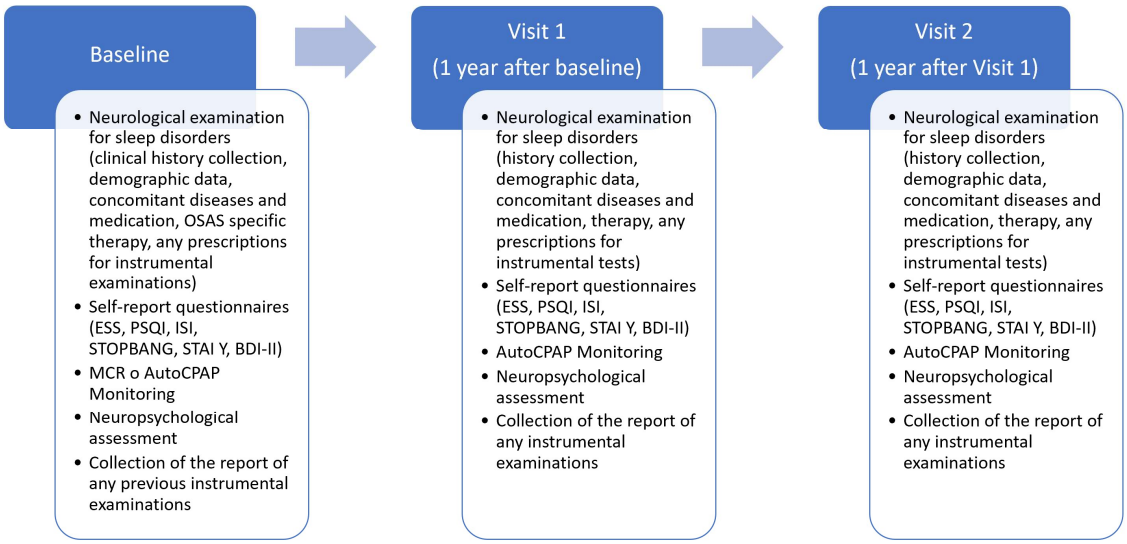
This was a monocentric observational retrospective and prospective study, with a cohort of OSA patients.

A web-based platform dedicated to OSA patients was used in this study for primarily clinical use. The platform has been implemented on REDCap. This platform is conceptualized as a large clinical-anamnestic data collection system, and allows for an overall overview of the OSA patients in terms of neuropsychological batteries, self-report questionnaires, and data related to treatment (drugs and/or CPAP) both for the response and for the compliance.

Prospective data have been collected during annual follow-up visits, according to the clinical practice.

Inclusion visit included a multilevel assessment. Sociodemographic, clinical, diagnostical, instrumental (overnight ambulatory cardio-respiratory monitoring) and neuropsychological data were collected as standard clinical practice. Additionally, during the inclusion visit patient completed self-report questionnaires concerning quality of life and sleep (PSQI, ESS, ISI, STOPBANG, BDI, STAI Y1 e Y2) as standard clinical practice.

During follow-up visits at 1 year and 2 years, sociodemographic data collected during the inclusion visit has been eventually updated. Moreover, during these visits clinical and instrumental data and neuropsychological assessment has been collected. In each follow-up visit (once a year for each patient for 2 years), physician will eventually declare if a neurodegenerative disease has occurred, the date of conversion and the new diagnosis.



Flow chart of the study

This study was approved by the local research ethics committee (CET 94-2023). This study was also registered in ClinicalTrials.gov, the registry of clinical trials, with number NCT06677580.

4.2 PARTICIPANTS

The study involved 154 Italian adult patients diagnosed with OSA, with an average age of 62.57 years (SD = 11.35). Of these, 33 participants (21.4%) were female and 121 (78.6%) were male. All patients were consecutively referred to the UO Neurology – Sleep Disorders Center at IRCCS San Raffaele Turro Hospital, following an evaluation by a neurologist specializing in sleep medicine. The diagnoses were made based on the clinical criteria outlined in the International Classification of Sleep Disorders, Third Edition Text Revised (ICSD-3-TR; American Academy of Sleep Medicine, 2023).

All participants provided written informed consent for the study. The majority of patients (n=117) provided informed consent at FU1, as they had already received a prior diagnosis of OSA and were already under treatment at the Sleep Medicine Center of IRCCS San Raffaele Hospital, given that this study is retrospective and prospective.

4.3 MEASURES

4.3.1 Overnight ambulatory cardio-respiratory monitoring

This instrument allows the recording of airflow (nasal cannula), thoracic and abdominal movements, SaO2, body position, heart rate, and snoring. During overnight ambulatory monitoring the following parameters have been recorded:

- SaO2 and data of desaturation,
- AHI (number/h): frequency of apneas (complete airflow cessation, duration >10 seconds) and hypopneas (reduction of respiratory flow at least of 50% of the usual one, associated with oxygen desaturation of at least 4%) per hour of sleep. An AHI score of less than 5 is normal whereas a patient can be diagnosed with OSA syndrome with an AHI of 5 to 14 along with daytime symptoms or an AHI of 15 or greater independent of other symptoms. The presence of AHI >5 and symptoms such as snoring, unrefreshing sleep, nocturnal dyspnea, morning headaches and excessive daytime sleepiness are, as well, diagnostic of OSA. Apnea-hypopnea Index scores is also used to classify OSA severity: an AHI of 5 to 14 indicates mild OSA; 15 to 30 indicates moderate OSA, and scores greater than 30 indicate severe OSA,
- AHI supine (number/h),
- ODI (number/h): number of times that the blood's oxygen level drops by 3 percent (or more) from baseline, per hour of sleep,
- Minimum SaO2 (%),
- Average SaO2 desaturation (%),
- SaO2 Time below 90%,
- % of Snoring

4.3.2 AutoCPAP Monitoring

AutoCPAP monitoring allows to assess the patient’s compliance and adherence to CPAP. During AUTOCPAP monitoring the following parameters have been recorded:

- Residual AHI, mean pressure, effective pressure, hours of use/night, % use/night >4 h/night
- Type of prothesis: CPAP, Auto-CPAP, Bi-level, Model, NHS or private
- Mask: oro-nasal, nasal, direct nasal, model and size

- Use of oxygen
- Humidifier: cold, hot

4.3.3 Neuropsychological assessment

As memory and executive functions are the most compromised functions in OSA patients, neuropsychological assessment has been performed using neuropsychological batteries specific for OSA, able to capture the cognitive impairment characterizing OSA patients. In our study, no formal diagnosis of MCI was made, as the main purpose of the study was to quickly and early identify patients at highest risk of cognitive impairment in order to create a risk phenotype subtype. Patients with reduced test scores that could be considered at risk were identified as "with cognitive impairment" and referred for further clinical evaluation.

In particular, we used the neuropsychological battery PEBL (Psychology Experiment Building Language) that is an open source software program that offers a collection of functions for both general computing tasks and experiment design. These functions cover a broad range of needs, including tools for randomization, sampling, and counterbalancing; managing data and performing statistical analysis; and implementing common experimental structures. It also includes built-in features for displaying messages, presenting multiple-choice questions, and using various standard visual stimuli. Additionally, it supports different types of response collection, from selecting predefined keyboard inputs to entering free-form text responses (Mueller & Piper, 2014). The PEBL neuropsychological test battery was selected over traditional paper-and-pencil assessments to enable a rapid, standardized, and efficient cognitive screening, facilitating the early identification of OSA patients at heightened risk for cognitive decline. This approach aimed to delineate a high-risk cognitive phenotype warranting referral for more comprehensive neuropsychological evaluation by a sleep specialist.

We chose those that assess evaluated reaction times, attention, attentional shifting, interference (Mackworth Clock Test, Trail Making Test, and Stroop Test), and memory functions (Digit Span Test Forward and Backward, Corsi Block Test).

Mackworth Clock Test (MCT; Mackworth, 1948): The MCT is a task designed to measure sustained attention and vigilance over time. The study used the Italian-translated, computerized version of the MCT developed with the Psychology Experiment Building Language (PEBL; Mueller & Piper, 2014). The task involves 60 trials, each lasting one

second, during which participants observe a black pointer rotating around a clock-like display. They must detect infrequent and unpredictable "double jumps" of the pointer. Prior research has established the MCT as a valid tool for evaluating vigilance (Lichstein et al., 2000).

Trail Making Test (TMT; Reitan, 1958): The TMT is a neuropsychological assessment used to evaluate visual attention and the ability to switch between tasks. It consists of two sections. In TMT-A, participants are asked to quickly and accurately connect a series of 25 numbered circles in sequence. In TMT-B, they must alternate between numbers and letters in order (e.g., 1-A-2-B, etc.). This test offers insights into a range of cognitive abilities, including visual scanning, processing speed, mental flexibility, and executive functioning (Arnett et al., 1995).

Stroop Colour and Word Test (SCWT; Stroop, 1953): The SCWT is a widely used neuropsychological assessment in both research and clinical settings. It measures a person's capacity to suppress cognitive interference, which happens when one aspect of a stimulus disrupts the processing of another aspect of that same stimulus (Stroop, 1935). In the PEBL battery, the SCWT is divided into three parts: the first involves naming the colour of dots; the second, naming the colour of randomly presented words; and the third, naming the ink colour in which a colour word is written.

The SCWT is widely used to measure the ability to inhibit cognitive interference (Scarpina & Tagini, 2017).

Digit-span task (DST; Wechsler, 1944): The digit-span task is designed to assess the capacity of working memory for storing numbers. In this task, participants are presented with a sequence of digits, either visually or audibly, and must accurately recall them. The sequences gradually increase in length with each trial. The task can be administered in two formats: forward, where participants repeat the digits in the same order, or backward, where they recall the digits in reverse order after hearing or seeing them (Jones & Macken, 2015).

The Corsi block-tapping Task (Corsi, 1972): The CBT is a cognitive assessment used to measure short-term visuo-spatial working memory. In this test, participants are asked to replicate a sequence of taps made by an examiner on a set of up to nine identical blocks arranged in different positions. The sequence begins with a small number of blocks,

typically two, and gradually increases in length until the participant can no longer accurately reproduce it (Kessels et al., 2000).

4.3.4 Self-report questionnaires

Epworth Sleepiness Scale (ESS) (John, 1991): a subjective measure of sleepiness and it is an effective instrument used to measure average daytime sleepiness. The ESS differentiates between average sleepiness and excessive daytime sleepiness that requires intervention. The patient self-rates on how likely it is that he would doze in eight different situations. Scoring of the answers is 0-3, with 0 being “would never doze” and 3 being “high chance of dozing”. A sum of 10 or more from the eight individual scores reflects above normal daytime sleepiness and need for further evaluation.

Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989): a measure of sleep quality. It is composed of 9 concerning sleep quality, hours of sleep, sleep efficiency and the impact of daytime sleepiness. It allows to identify good and bad sleepers, with a cut-off of 5.

Insomnia Severity Index (ISI) (Morin et al., 2011; Castronovo et al., 2016): a subjective measure of insomnia severity, composed by 5 questions and 7 items. Patients assess sleep difficulties in terms of severity (divided into three different areas: "difficulty falling asleep," "difficulty staying asleep," and "early awakening problem"), degree of interference with daytime efficiency, evidence of such impairment to others, level of discomfort, and overall satisfaction with one's sleep. Responses are distributed on a Likert scale from 0 to 4. To calculate the score, only the values of the 5 questions are summed for a total of 7 items. The total score ranges from 0-28 and is scored as follows: 0-7: no clinically significant insomnia; 8-14: insomnia below the critical threshold; 15-21: clinical insomnia (medium severity); 22-28: clinical insomnia (severe).

STOPBANG (Nagappa et al., 2015): a measure of OSA risk. STOPBANG is an acronym that summarizes all the questions asked of the subjects, as follows: S (snore): Do you snore loudly?; T (tired): Do you often feel tired, fatigued, or sleepy during the daytime?; O (observed): Has anyone observed you stop breathing during sleep?; P (pressure): Do you have (or are you being treated for) high blood pressure?; B (BMI, Body Mass Index): Is your BMI greater than 30?; A (age): Is your age greater than 50?; N (neck): Is your neck circumference greater than 41 cm if female or 43 cm if male?; G (gender): Are you

male?. The authors of the questionnaire suggest that three or more positive responses to the test indicate a fairly high risk of OSA.

State Trait Anxiety Inventory Y (STAI Y) (Tenenbaum et al., 1985): a measure of anxiety. It is composed by two sub-test, each of 20 items. The first sub-test (STAI-Y 1) refers to state anxiety at the time the test is administered. The second sub-test (STAI-Y 2) refers to anxiety as a trait, as a specific and stable personality characteristic. In both the sub-tests, patients should answer in terms of intensity, on a Likert scale from 1 (not at all) to 4 (very much). So, STAI-Y gives two different scores: state (range 20-80) and trait (range 20-80). In italian population, mean scores are 36 (SD 9,7) for state STAI and 36,5 (DS 9,6) for trait STAI.

Beck Depression Inventory (BDI-II) (Beck et al., 1996; Ghisi et al., 2006): a self-administered questionnaire, composed by 21 items on a 4-point Likert scale, that assesses depressive symptoms. The scores are divided in 2 subscales: affective symptoms (8 items) and somatic symptoms (13 items). Total score of 0–13 is considered minimal range, 14–19 is mild, 20–28 is moderate, and 29–63 is severe.

4.4 STATISTICAL ANALYSIS

All statistical analyses were conducted using R (version 4.4.0) and SPSS (version 28), with a two-tailed significance threshold set at $\alpha = 0.05$ unless otherwise specified. Descriptive statistics (means, standard deviations, frequencies, and ranges) were used to summarize sociodemographic, clinical, polysomnographic, and psychometric variables at baseline and follow-up assessments.

To compare neuropsychological performance between patients with cognitive impairment and those without such concerns at the first follow-up (FU1), independent samples t-tests were performed for normally distributed continuous outcomes. Levene's test was used to assess equality of variances; Welch's correction was applied when homoscedasticity was violated. Effect sizes were reported as Cohen's d to quantify the magnitude of group differences.

To examine changes in cognitive performance over time and potential group-by-time interactions, repeated-measures analysis of variance (ANOVA) was conducted on Trail Making Test (TMT) indices across multiple assessment points (based on the different trial of TMT – only numbers, only letters, numbers-letters). Greenhouse–Geisser corrections were applied when the assumption of sphericity was violated (Mauchly's test, $p < 0.05$).

Both multivariate (Pillai's trace) and univariate (with Bonferroni correction) results are reported where applicable. Main effects of group, time, and Group × Time interactions were interpreted to assess whether the group with cognitive impairment exhibited distinct cognitive trajectories compared to the group without cognitive impairment.

Bivariate relationships between clinical variables (e.g., symptom duration, PSQI, ESS, ISI, STOP-Bang, BDI-II, STAI) and baseline neuropsychological performance were evaluated using Spearman's rank-order correlation coefficients (ρ), given the non-normal distribution of several cognitive measures and the exploratory nature of these analyses. Correlation magnitudes were interpreted according to Cohen's guidelines ($|\rho| \geq 0.10$ = small, ≥ 0.30 = medium, ≥ 0.50 = large).

To identify independent predictors of cognitive impairment at FU1, two Firth penalized logistic regression models were fitted. This approach was selected to address the challenges of small sample size and rare outcomes (n = 37 cases with cognitive impairment), which can lead to separation and bias in conventional maximum likelihood estimation. Model 1 included demographic (age, sex), anthropometric (BMI), cardiometabolic (hypertension, type 2 diabetes), and OSA severity variables (AHI). Model 2 replaced AHI with objective markers of nocturnal hypoxemia—minimum oxygen saturation and percentage of total sleep time with $SaO_2 < 90\%$—based on pathophysiological evidence implicating hypoxemia as a key driver of neurocognitive decline. Odds ratios (ORs) with 95% profile penalized likelihood confidence intervals and p-values were reported. Model discrimination was assessed using the area under the receiver operating characteristic (ROC) curve (AUC).

Finally, a supervised machine learning approach was employed to evaluate the predictive utility of a broad set of baseline features (n > 70, including symptoms, comorbidities, polysomnographic metrics, and neuropsychological scores) for identifying individuals who would develop cognitive impairment within two years. A Random Forest classifier was trained using 10-fold cross-validation on the complete-case dataset (n = 114). Model performance was quantified by AUC, sensitivity, and specificity. Variable importance was estimated using mean decrease in accuracy across all trees, providing a data-driven ranking of the most informative predictors.

All analyses accounted for missing data via complete-case exclusion, consistent with clinical cohort practices. No multiple testing corrections were applied to exploratory correlational analyses, but findings are interpreted with appropriate caution.

CHAPTER 5 - RESULTS

5.1 DESCRIPTIVE ANALYSIS

5.1.1 Baseline Demographic and Clinical Characteristics

The study included a total of 154 adult patients diagnosed with Obstructive Sleep Apnea (OSA). The mean age of the cohort was 62.57 ± 11.35 years (range: 35–83 years), with a mean age at diagnosis of 56.27 ± 11.20 years (range: 29–83 years), and a time between the symptoms onset and the diagnosis of 7.37 ± 4.97 years (range: 1-17 years). Anthropometric data revealed a mean height of 171.86 ± 9.41 cm, mean weight of 94.46 ± 15.63 kg, and a mean Body Mass Index (BMI) of 32.03 ± 4.99 kg/m² (range: 20.23–43.93), indicating that the majority of patients were overweight or obese.

Neck circumference was 43.14 ± 1.10 cm (range: 41–45 cm). Cardiovascular parameters at baseline showed a mean systolic blood pressure of 131.03 ± 13.39 mmHg and mean diastolic blood pressure of 86.38 ± 10.01 mmHg, with 55.6% of patients reporting a history of arterial hypertension. The average resting pulse rate was 78.35 ± 12.14 bpm (range: 57–118 bpm).

The sample was predominantly male, with 78.6% male and 21.4% female participants. See Table 1.

	Patients (n=154) Mean±SD (Range)
Age (years)	62.57 ± 11.35 (Range 35-83)
Age at diagnosis (years)	56.27 ± 11.20 (Range 29-83)
Symptoms-to-Diagnosis Interval (years)	7.37 ± 4.97 (Range 1-17)
Hight (cm)	171.86 ± 9.41 (Range 147-195)
Weight (kg)	94.46 ± 15.63 (Range 57-130)
BMI (kg/m2)	32.02 ± 4.99 (Range 20.23-43.93)
Neck Circumference (cm)	43.14 ± 1.10 (Range 41-45)
Systolic Blood Pressure (mmHg)	131.03 ± 13.39 (Range 100-170)
Diastolic Blood Pressure (mmHg)	86.38 ± 10.01 (Range 60-120)
Pulse (bpm)	78.35 ± 12.14 (Range 57-118)
M	*78.6%*
F	*21.4%*

Table 1. Baseline Demographic and Clinical Characteristics. *BMI: Body Mass Index*

5.1.2 Comorbidities at Baseline

A substantial proportion of patients presented with comorbid conditions: hypertension (55.6%), type 2 diabetes (9.9%), depression (19%), anxiety (16.3%), hypothyroidism (5.3%), and chronic obstructive pulmonary disease (2%). Notably, no patients had cerebrovascular disease or chronic kidney disease. Insomnia, restless legs syndrome and periodic limb movements disorder were reported in 10.5%, 7.8% and 0.7% of cases, respectively. See Table 2.

	Percentage (%)
Hypertension	55.6
Cardiomyopathy	5.9
Cerebrovascular Disease	0
Atrial Fibrillation	2.6
Arrhythmia	5.9
Other Cadiovascular Disease	3.3
Cerebral Stroke	3.3
Chronic Kidney Disease	0
Asthma	3.9
Chronic Obstructive Pulmonary Disease	2
Epilepsy	1.3
Depression	19
Anxiety	16.3
Hypothyroidism	5.3
Type 2 Diabetes	9.9
Hiatal hernia	2
Benign Prostatic Hyperplasia	3.9
Insomnia	10.5
Restless Legs Syndrome	7.8
Periodic Limb Movements Disorder	0.7

Table 2. Comobidities. *Percentages of patients with comorbidities.*

5.1.3 Baseline Symptomatology

Symptoms were highly prevalent at baseline (Table 3). Snoring was reported by 98.7% of patients, with a mean symptom duration of 85.86 ± 59.48 months. Excessive daytime sleepiness affected 82.4% of patients (90.28 ± 58.95 months), and fatigue was reported by 90.2% (89.59 ± 61.75 months). Nocturia and witnessed apneas were present in 81.7% and 79.1% of the cohort, respectively. Less frequent but notable symptoms included xerostomia (21.1%), sexual dysfunction (11.1%), choking (7.8%), and gastroesophageal reflux disease (25%). Cognitive complaints was reported by 38.6% of patients.

	Percentage (%)	***Mean±SD (months)***
Snoring	98.7	85.86 ± 59.48
Apneas	79.1	82.75 ± 58.23
Excessive Daytime Sleepiness	82.4	90.28 ± 58.95
Nocturia	81.7	76.91 ± 51.85
Xerostomia	21.1	73.40 ± 45.66
Headache	44.3	77.08 ± 46.88
Fatigue	90.2	89.59 ± 61.75
Cognitive Complaint	38.6	66.77 ± 48.68
Sexual Dysfunction	11.1	81.29 ± 45.91
Chocking	7.8	82.25 ± 55.27
GastroEsophageal Reflux Disease	25	87.71 ± 62.31
Insomnia	36.6	86.98 ± 59.95

Table 3. Baseline symptomatology. *Percentages of patients reporting symptoms and duration of symptoms expressed in months.*

5.1.4 Baseline Psychometric and Sleep Quality Assessments

Baseline scores on validated questionnaires indicated significant sleep and psychological disturbances:

- Pittsburgh Sleep Quality Index (PSQI): 10.02 ± 4.19 (range: 1–20), indicating poor sleep quality.
- Epworth Sleepiness Scale (ESS): 12.32 ± 3.63 (range: 2–22), consistent with moderate daytime sleepiness.
- Insomnia Severity Index (ISI): 12.68 ± 6.38 (range: 0–26), suggesting clinical insomnia in a subset.
- STOP-Bang score: 5.33 ± 1.28 (range: 3–8), reflective of high OSA risk.
- Beck Depression Inventory-II (BDI-II): 9.77 ± 6.88 (range: 0–27), indicating mild depressive symptoms on average.
- State-Trait Anxiety Inventory (STAI): State anxiety (Y1): 41.43 ± 10.62 (range: 22-61); Trait anxiety (Y2): 42.89 ± 9.49 (range: 24-65), both above normative thresholds. See Table 4.

	Mean±SD (Range)
PSQI	10.02 ± 4.19 (Range 1-20)
ESS	12.32 ± 3.63 (Range 2-22)
ISI	12.68 ± 6.38 (Range 0-26)
STOPBANG	5.33 ± 1.28 (Range 3-8)
BDI-II	9.77 ± 6.88 (Range 0-27)
STAI Y1	41.43 ± 10.62 (Range 22-61)
STAI Y2	42.89 ± 9.49 (Range 24-65)

Table 4. Baseline Psychometric and Sleep Quality Assessments. *PSQI: Pittsburgh Sleep Quality Index; ESS: Epworth Sleepiness Scale; ISI: Insomnia Severity Index; BDI: Back Depression Inventory.*

5.1.5 Baseline Polysomnographic and Respiratory Parameters

At baseline, the severity of OSA was confirmed by polysomnography. The mean Apnea-Hypopnea Index (AHI) was 43.29 ± 23.57 events/hour (range: 15.80–124.00). Positional analysis indicated a mean supine AHI of 41.40 ± 22.47 events/hour (range: 10–96.40), with mean time spent in the supine position accounting for 37.35 ± 25.70% of total sleep time. The Oxygen Desaturation Index (ODI) averaged 44.24 ± 24.62 events/hour (range: 15.40–120).

Nocturnal oxygenation was impaired, with a mean nocturnal oxygen saturation (SaO_2) of 90.61 ± 3.83% (range: 80–97%) and a mean minimum SaO_2 of 77.94 ± 9.58% (range: 50–94.6%). The mean percentage of total sleep time spent with $SaO_2 < 90\%$ was 17.33 ± 17.01% (range: 0–65.10%). Snoring occupied a notable portion of sleep time, with a mean snoring time of 24.54 ± 14.56% (range: 0.30–59%). See Table 5.

	Patients ***Mean±SD*** ***(Range)*** ***(n=154)***
AHI	43.29 ± 23.57 (Range 15.80-124)
Supine AHI	41.40 ± 24.62 (Range 10-96.4)
ODI	44.24 ± 24.62 (Range 15.40-120)
Supine Position Time (%)	37.35 ± 25.70 (Range 3.6-95)
Minimum Oxygen Saturation	77.94 ± 9.58 (Range 50-94.6)
Mean Oxygen Saturation	90.61 ± 3.83 (Range 80-97)
Time Oxygen Saturation below 90% (%)	17.33 ± 17.01 (Range 0-65.10)
Snoring (%)	24.53 ± 14.56 (Range 0.30-59)

Table 5. Baseline Polysomnographic and Respiratory Parameters. *AHI: Apnea-Hypopnea Index; ODI: Oxygen Desaturation Index.*

5.1.6 Baseline AutoCPAP Monitoring

Before the prescription of the therapy, all patients underwent a AutoCPAP monitoring. The mean residual AHI was 4.52 ± 2.51 (range: 0.60-15), with a mean pressure of 9.10 ± 2.37 (range: 5.10-13.20), and an effective pressure of 10.72 ± 2.40 (range: 6-17.60). The mean usage time at night was of 6.51 ± 0.98 hours/night (range: 1-8), and the mean usage time >4 hours/night of 94.81 ± 15.45% (range: 0-100). See Table 6.

	Patients (n=154) Mean±SD (Range)
Residual AHI	4.52 ± 2.51 (Range 0.60-15)
Mean pressure (cmH2O)	9.10 ± 2.37 (Range 5.10-13.20)
Effective Pressure (cmH2O)	10.72 ± 2.40 (Range 6-17.60)
Mean AutoCPAP Usage Time (hours)	6.51 ± 0.98 (Range 1-8)
AutoCPAP Usage Time > 4 h/night (%)	94.81 ± 15.45 (Range 0-100)

Table 6. Baseline AutoCPAP Monitoring. *AHI: Apnea-Hypopnea Index; CPAP: Continuous Positive Airway Pressure.*

5.1.7 PAP Therapy Prescription

Therapy was prescribed to all patients: 50.65% received AutoCPAP (n=78), 40.25% received fixed-pressure CPAP (n=62), and 9.1% (n=14) were advised positional therapy. The mean prescribed CPAP pressure was 9.60 ± 2.57 cmH_2O (range: 6.0–17.5). AutoCPAP devices were typically set with a minimum pressure of 4 cmH_2O and a maximum between 10–18 cmH_2O (mean maximum: 14.26 ± 2.24). See Table 7.

	Percentage	***Mean±SD (Range)***
CPAP (%) (n=62)	40.25	
Mean CPAP Prescribed Pressure (cmH2O)		9.60 ± 2.57 (Range 6-17.50)
AutoCPAP (%) (n=78)	50.65	
Mean AutoCPAP Prescribed Pressure (cmH2O)		Min 4 Max 14.26 ± 2.24 (Range Min 4-10 Range Max 4-18)
Positional Therapy (%) (n=14)	9.1	

Table 7. PAP Therapy Prescription. *CPAP: Continuous Positive Airway Pressure.*

5.1.8 Follow-up 1 (FU1) Outcomes

At the first follow-up (FU1), data were available for138 patients.

- Residual AHI was 4.33 ± 2.27 events/hour (range: 0.50–12.90).
- PAP adherence was high: mean nightly usage was 7.61 ± 1.80 hours (range: 3.5-9), with 85.03 ± 13.24% of nights exceeding 4 hours of use (range: 12-100).
- Reported total sleep time was 6.63 ± 0.66 hours.
- Reported symptoms: snoring (29.7%), apneas (11.7%), excessive daytime sleepiness (19.8%), and fatigue (27%).
- ESS scores improved to 7.77 ± 5.52, indicating resolution of pathological sleepiness in most patients.
- However, insomnia symptoms worsened, with ISI scores increasing to 16.87 ± 5.52.
- Depressive and anxiety symptoms also increased: BDI-II: 13.778 ± 9.10, STAI-Y1: 43.95 ± 11.19, STAI-Y2: 44.85 ± 10.57.

PAP prescriptions were modified in only 4.3% of cases, and 96.4% of patients were deemed compliant by clinician report. See Tables 8-10.

	Percentage (%)	***Patients (n=138) Mean±SD (Range)***
Mean Reported TST		6.63 ± 0.66 (Range 5-8)
Prescribed PAP Compliance (%)	Yes 96.4 No 3.6	
Modified PAP Prescription (%)	Yes 4.3 No 95.7	
Residual AHI		4.33 ± 2.27 (Range 0.50-12.90)
Mean AutoCPAP Usage Time (hours)		7.61 ± 1.80 (Range 3.5-9)
AutoCPAP Usage Time > 4 h/night (%)		85.71 ± 11.44 (Range 12-100)

Table 8. Follow-up 1 (FU1) AutoCPAP Monitoring and Compliance. *TST: Total Sleep Time; PAP: Positive Airway Pressure; AHI: Apnea-Hypopnea Index.*

	Percentage (%)
Snoring	Present 29.7 Absent 70.3
Apneas	Present 11.7 Absent 88.3
Excessive Daytime Sleepiness	Present 19.8 Absent 80.2
Nocturia	Present 15.3 Absent 84.7
Fatigue	Present 27 Absent 73
Cognitive Impairment	Present 9.9 Absent 90.1

Table 9. Follow-up 1 (FU1) symptomatology

	Mean±SD (Range)
PSQI	12.57 ± 4.29 (Range 0-20)
ESS	7.77 ± 5.52 (Range 0-24)
ISI	16.87 ± 5.52 (Range 0-26)
BDI-II	13.77 ± 9.10 (Range 0-44)
STAI Y1	43.95 ± 11.19 (Range 20-70)
STAI Y2	44.85 ± 10.57 (Range 24-73)

Table 10. Follow-up 1 (FU1) Psychometric and Sleep Quality Assessments. *PSQI: Pittsburgh Sleep Quality Index; ESS: Epworth Sleepiness Scale; ISI: Insomnia Severity Index; BDI: Back Depression Inventory.*

5.1.9 Follow-up 2 (FU2) Outcomes

At the second follow-up (FU2), data were available for a smaller subset (n = 16).

- Residual AHI remained controlled but showed variability (4.94 ± 5.02 events/hour, range: 0.60–18.60).
- PAP usage averaged 6.40 ± 1.89 hours/night, with 91.03 ± 14.58% of nights exceeding 4 hours of use.
- Sleep quality (PSQI: 10.72 ± 4.82) and daytime sleepiness (ESS: 9.27 ± 6.77) remained improved compared to baseline, though ESS scores slightly worsened compared to FU1.
- Mood and anxiety scores showed partial improvement compared to FU1 but remained above baseline levels (BDI-II: 11.36 ± 7.53; STAI-Y1: 40.73 ± 10.36; STAI-Y2: 43.45 ± 8.86).
- No changes were made to PAP prescriptions in this group (0% modified), and 87.5% were classified as compliant.

See Tables 11-12.

	Percentage (%)	***Patients (n=16) Mean±SD (Range)***
Mean Reported TST		6.81 ± 0.81 (Range 5-8)
Prescribed PAP Compliance (%)	Yes 87.5 No 12.5	
Modified PAP Prescription (%)	Yes 0 No 100	
Residual AHI		4.94 ± 5.02 (Range 0.60-18.60)
Mean AutoCPAP Usage Time (hours)		6.40 ± 1.89 (Range 0-8)
AutoCPAP Usage Time > 4 h/night (%)		91.02 ± 14.58 (Range 50.60-100)

Table 11. Follow-up 2 (FU2) AutoCPAP Monitoring and Compliance. *TST: Total Sleep Time; PAP: Positive Airway Pressure; AHI: Apnea-Hypopnea Index.*

	Mean±SD (Range)
PSQI	10.72 ± 4.82 (Range 3-17)
ESS	9.27 ± 6.77 (Range 2-22)
ISI	14.45 ± 4.18 (Range 9-20)
BDI-II	11.36 ± 7.53 (Range 3-25)
STAI Y1	40.73 ± 10.36 (Range 24-58)
STAI Y2	43.45 ± 8.86 (Range 29-57)

Table 12. Follow-up 2 (FU2) Psychometric and Sleep Quality Assessments. *PSQI: Pittsburgh Sleep Quality Index; ESS: Epworth Sleepiness Scale; ISI: Insomnia Severity Index; BDI: Back Depression Inventory.*

5.1.10 Neuropsychological Assessment (Baseline, Follow-up 1 and Follow-up 2)

The following tables (Tables 13-16) present a comprehensive overview of neuropsychological test performance across three assessment timepoints — baseline (BL), first follow-up (FU1), and second follow-up (FU2) — in a cohort of patients with OSA. The data reflect changes in attention, working memory, executive function, and processing speed as measured by standardized cognitive instruments, including the Clock Test (MCT), Corsi block-tapping Task, Digit Span Test Forward (DSTF) and Backward (DSTF), Trail Making Test (TMT), and Stroop Test (SCWT). Concerning TMT, Trials 1, 3, 5 were composed only by numbers (TMT-A), Trial 6 was composed only by letters, and Trials 2, 4, 7 were composed by numbers and letters (TMT-B). While sample sizes vary across timepoints (n=10 at BL, n=117 at FU1, n=13 at FU2), the longitudinal structure allows for preliminary observation of cognitive trajectories in relation to OSA management. These descriptive statistics provide the foundation for subsequent inferential analyses aimed at identifying significant group differences and potential cognitive improvements or declines over time.

	BL ***Mean±SD*** ***(range)*** ***(n=10)***	***FU1*** ***Mean±SD*** ***(range)*** ***(n=117)***	***FU2*** ***Mean±SD*** ***(range)*** ***(n=13)***
Targets skips	24.80 ± 3.19 (range 21-31)	23.13 ± 3.83 (range 16-35)	25 ± 2.97 (range 21-30)
Correct Responses	48.70 ± 8.39 (range 30-56)	48.68 ± 8.02 (range 25-60)	48.46 ± 8.60 (range 31-58)
Correct targets	16.10 ± 3.76 (range 8-21)	14.65 ± 5.32 (range 1-31)	15.77 ± 7.64 (range 2-26)
False alarms	2.60 ± 4.03 (range 0-12)	2.75 ± 5.08 (range 0-33)	2.31 ± 3.07 (range 0-9)
Mean correct RT (msec)	440.09 ± 46.71 (range 360.95-507.69)	437.11 ± 50.94 (range 220.61-570)	423.74 ± 70.71 (range 231.50-495)
Correct targets percentage (%)	65.81 ± 16.77 (range 30.77-82.61)	64.72 ± 23.12 (range 3.13-100)	61.53 ± 26.80 (range 9.09-96.30)
False alarms percentage (%)	4.33 ± 6.72 (range 0-20)	4.59 ± 8.46 (range 0-55)	3.85 ± 5.11 (range 0-15)

Table 13. Clock Test (MCT). *RT: Reaction Time.*

	BL ***Mean±SD*** ***(n=10)***	***FU1*** ***Mean±SD*** ***(n=117)***	***FU2*** ***Mean±SD*** ***(n=13)***
Corsi Block Span	5.30 ± 1.77 (range 2-8)	5.38 ± 1.08 (range 2-8)	5.23 ± 1.36 (range 2-8)
Corsi Memory Span	4.60 ± 1.22 (range 2-6)	4.76 ± 0.82 (range 2-6.5)	4.73 ± 1.38 (range 2-7.5)
DSTB Memory Span	4.20 ± 2.04 (range 2-8)	4.35 ± 1.55 (range 2-8)	3.85 ± 1.34 (range 2-6)
DSTF Memory Span	6.50 ± 2.27 (range 3-10)	5.74 ± 1.39 (range 3-9)	4.77 ± 1.74 (range 2-8)

Table 14. Memory. *DSTB: Digit Span Test Backward; DSTF: Digit Span Test Forward.*

	BL ***Mean±SD*** ***(n=10)***	***FU1*** ***Mean±SD*** ***(n=117)***	***FU2*** ***Mean±SD*** ***(n=13)***
Total time Trial 1	51066.60 ± 68945.17 (range 2764-244157)	45467.51 ± 22482.20 (range 17639-146965)	61881.69 ± 65985.31 (range 18248-270166)
Median time Trial 1	1866.20 ± 2599.11 (range 808-9242)	1453.94 ± 1162.80 (range 600-11608)	1999.31 ± 2526.73 (range 688-10223)
Accuracy Trial 1	0.95 ± 0.09 (range 0.74-1)	0.95 ± 0.06 (range 0.76-1)	0.92 ± 0.09 (range 0.68-1)

Total time Trial 2	125962.30 ± 139461.25 (range 46984-520095)	106596.71 ± 54724.22 (range 1272-10128)	127483.46 ± 107655.91 (range 39624-469477)
Median time Trial 2	4161.60 ± 4757.83 (range 1504-17560)	3376.10 ± 1616.99 (range 1272-10128)	4165.77 ± 4300.07 (range 1160-18034)
Accuracy Trial 2	0.92 ± 0.6 (range 0.83-1)	0.90 ± 0.10 (range 0.60-1)	0.85 ± 0.15 (range 0.45-1)
Total time Trial 3	53237.30 ± 39003.97 (range 32112-161125)	53463.57 ± 24263.58 (range 18848-163888)	58864.69 ± 54670.59 (range 23088-236193)
Median time Trial 3	1682.90 ± 1500.70 (range 912-5909)	1630.20 ± 767.13 (range 608-6416)	2058.85 ± 2149.40 (range 856-9037)
Accuracy Trial 3	0.97 ± 0.04 (range 0.89-1)	0.96 ± 0.07 (range 0.60-1)	0.94 ± 0.13 (range 0.60-1)
Total time Trial 4	84833.70 ± 90926.86 (range 37216-341065)	77990.41 ± 45326.8 (range 9384-304776)	94136.62 ± 85450.92 (range 39968-357008)
Median time Trial 4	3053.30 ± 3902.37 (range 960-14061)	2436.28 ± 1502.34 (range 328-11128)	2979.85 ± 3074.97 (range 792-12778)

Accuracy Trial 4	0.96 ± 0.06 (range 0.83-1)	0.93 ± 0.09 (range 0.50-1)	0.87 ± 0.14 (range 0.60-1)
Total time Trial 5	31346.90 ± 29926.32 (range 16008-115333)	27227.85 ± 12418.41 (range 2028-91360)	33819.46 ± 34370.15 (range 14704-145173)
Median time Trial 5	1136.90 ± 1147.74 (range 604-4369)	923.57 ± 347.02 (range 480-2676)	1192.38 ± 1301.37 (range 596-5457)
Accuracy Trial 5	0.99 ± 0.04 (range 0.87-1)	0.96 ± 0.06 (range 0.68-1)	0.94 ± 0.05 (range 0.87-1)
Total time Trial 6	58851.30 ± 73910.47 (range 24256-268065)	42671.64 ± 24357.36 (range 15496-180520)	64942.23 ± 74765.32 (range 3956-293412)
Median time Trial 6	1438.55 ± 1812.76 (range 672-6585,50)	1092.64 ± 518.18 (range 568-3164)	1536.65 ± 1515.84 (range 656-6265)
Accuracy Trial 6	0.93 ± 0.07 (range 0.79-1)	0.90 ± 0.08 (range 0.65-1)	0.87 ± 0.10 (range 0.68-1)
Total time Trial 7	66809.70 ± 75722.10 (range 23448-274889)	55516.12 ± 39031.04 (range 18792-331632)	77637.85 ± 68324.79 (range 31520-293573)

Median time Trial 7	2069.50 ± 2734.02 (range 708-9763)	1872.10 ± 4280.45 (range 588-47121)	2193.00 ± 2113.86 (range 764-8840)
Accuracy Trial 7	0.88 ± 0.12 (range 0.67-1)	0.93 ± 0.08 (range 0.63-1)	0.88 ± 0.15 (range 0.42-1)

Table 15. Trial Making Test (TMT)

	BL ***Mean±SD*** ***(n=10)***	***FU1*** ***Mean±SD*** ***(n=117)***	***FU2*** ***Mean±SD*** ***(n=13)***
Time taken Dots	86.96 ± 68.38 (range 44.40-277.57)	93.54 ± 45.82 (range 36.88-419.39)	86.38 ± 31.58 (range 56.40-139.89)
Responses made Dots	24.80 ± 1.23 (range 24-28)	24.97 ± 1.34 (range 24-30)	24.46 ± 0.88 (range 24-26)
Time taken Words	75.04 ± 63.03 (range 43.20-252.10)	71.64 ± 31.36 (range 24.08-200.85)	84.17 ± 49.71 (range 39.02-198.08)
Responses made Words	25 ± 1.41 (range 24-28)	24.50 ± 1.24 (range 25-29)	25.69 ± 3.40 (range 24-36)
Time taken Colors	84.63 ± 73.26 (range 36.92-287.25)	85.68 ± 42.60 (range 25.50-278.57)	89.25 ± 45.63 (range 29.92-171.16)
Responses made Colors	24.80 ± 1.23 (range 24-27)	25.50 ± 2.37 (range 24-38)	25.62 ± 3.40 (range 24-36)

Intrusions Colors	0.70 ± 1.06 (range 0-3)	1.22 ± 2.22 (range 0-14)	0.77 ± 1.36 (range 0-4)
Efficiency Colors-Dots Time taken	0.96 ± 0.22 (range 0.69-1.40)	0.94 ± 0.32 (range 0.41-1.95)	1.00 ± 0.30 (range 0.48-1.52)
Efficiency Colors-Dots Responses made	1.00 ± 0.03 (range 0.96-1.08)	1.02 ± 0.11 (range 0.89-1.58)	1.05 ± 0.12 (range 0.92-1.38)
Efficiency Colors-Words Time taken	1.12 ± 0.20 (range 0.80-1.48)	1.21 ± 0.32 (range 0.53-1.63)	1.09 ± 0.29 (range 0.72-1.63)
Efficiency Colors-Words Responses made	0.99 ± 0.06 (range 0.89-1.13)	1.03 ± 0.10 (range 0.89-1.58)	1.00 ± 0.07 (range 0.90-1.17)

Table 16. Stroop Test (SCWT)

5.2 INDEPENDENT SAMPLES T TEST ON NEUROPSYCHOLOGICAL PERFORMANCE

Independent samples t-tests were conducted on 101 patients at FU1 who had all the neuropsychological assessments. This analysis was not conducted on BL and FU2 because the samples were too small to give a statistically valid result. The t-tests revealed significant group differences across multiple neuropsychological domains, indicating a distinct cognitive profile associated with cognitive impairment compared to those without cognitive concerns. Participants in the group with cognitive impairment demonstrated significantly poorer performance on measures of working memory, including Corsi Block Span ($p < 0.001$), Corsi Memory Span ($p = 0.006$), DSTB Memory Span ($p = 0.001$), and DSTF Memory Span ($p < 0.001$). Significant impairments were also observed in attentional control and processing speed, as evidenced by lower MCT Correct Responses ($p = 0.011$) and higher MCT False Alarms Percentage ($p = 0.024$). Furthermore, the group with cognitive impairment exhibited significantly slower completion times and reduced

accuracy on the Trail Making Test (TMT) across multiple subtasks (e.g., Total time Trial 2, p = 0.001; Accuracy Trial 2, p = 0.001; Total time Trial 4, p = 0.001). Visual search efficiency was also compromised, with the group with cognitive impairment showing significantly more intrusions on the SCWT (p = 0.037) and longer response times for condition Colors (p = 0.021). These findings collectively suggest that individuals reporting subjective cognitive decline exhibit measurable deficits in executive function, processing speed, and working memory, even in the absence of objective clinical criteria for mild cognitive impairment.

See tables 17-20.

	WITHOUT COGNITIVE IMPAIRMENT ***Mean±SD*** ***(range)*** ***(n=64)***	***WITH COGNITIVE IMPAIRMENT*** ***Mean±SD*** ***(range)*** ***(n=37)***	***p value***
Targets skips	22.81 ± 3.78 (range 16-33)	23.41 ± 3.94 (range 17-32)	*ns*
Correct Responses	50.38 ± 6.82 (range 34-60)	46.24 ± 8.91 (range 25-59)	***0.011***
Correct targets	15.11 ± 4.92 (range 5-27)	13.51 ± 5.20 (range 1-26)	*ns*
False alarms	1.77 ± 1.89 (range 0-7)	3.86 ± 6.58 (range 0-33)	*ns*
Mean correct RT (msec)	444.41 ± 35.77 (range 367.42-524.85)	427.28 ± 67.14 (range 220.61-570)	*ns*
Correct targets percentage (%)	67.41 ± 21.50 (range 18.52-100)	59.87 ± 24.39 (range 3.13-100)	*ns*
False alarms percentage (%)	2.94 ± 3.15 (range 0-11.67)	6.44 ± 10.97 (range 0-55)	*ns*

Table 17. t-test Clock Test (MCT). *RT: Reaction Time.*

	WITHOUT COGNITIVE IMPAIRMENT ***Mean±SD*** ***(range)*** ***(n=64)***	***WITH COGNITIVE IMPAIRMENT*** ***Mean±SD*** ***(range)*** ***(n=37)***	***p value***
Corsi Block Span	5.62 ± 1.05 (range 4-8)	4.84 ± 0.87 (range 2-6)	***<0.001***
Corsi Memory Span	4.91 ± 0.75 (range 3.5-6.5)	4.42 ± 0.85 (range 2-5.5)	***0.006***
DSTB Memory Span	4.69 ± 1.58 (range 2-8)	3.59 ± 1.28 (range 2-7)	***0.001***
DSTF Memory Span	6.06 ± 1.42 (range 3-9)	5.03 ± 1.09 (range 3-7)	***<0.001***

Table 18. t-test Memory. *DSTB: Digit Span Test Backward; DSTF: Digit Span Test Forward.*

	WITHOUT COGNITIVE IMPAIRMENT ***Mean±SD*** ***(range)*** ***(n=64)***	***WITH COGNITIVE IMPAIRMENT*** ***Mean±SD*** ***(range)*** ***(n=37)***	***p value***
Total time Trial 1	41069.55 ± 18842.36 (range 17639-132936)	54165.27 ± 27913.58 (range 20768-146965)	***0.021***
Median time Trial 1	1248.52 ± 511.78 (range 600-3136)	1589.38 ± 875.12 (range 688-5076)	***0.046***
Accuracy Trial 1	0.97 ± 0.05 (range 0.83-1)	0.93 ± 0.08 (range 0.76-1)	***0.008***
Total time Trial 2	91115.95 ± 43772.63 (range 10068-342320)	132395.97 ± 66158.70 (range 60208-384584)	***0.001***
Median time Trial 2	2919.42 ± 1173.91 (range 1272-8208)	4155.00 ± 1997.44 (range 1840-10128)	***0.001***
Accuracy Trial 2	0.92 ± 0.8 (range 0.66-1)	0.85 ± 0.11 (range 0.60-1)	***0.001***
Total time Trial 3	49279.59 ± 21691.91 (range 23088-124600)	61227.46 ± 27661.38 (range 18848-163888)	***0.019***
Median time Trial 3	1477.47 ± 500.38 (range 736-3736)	1936.22 ± 1082.40 (range 760-6416)	***0.023***

Accuracy Trial 3	0.97 ± 0.07 (range 0.60-1)	0.95 ± 0.09 (range 0.71-1)	*ns*
Total time Trial 4	67947.09 ± 41223.72 (range 9384-304776)	100015.08 ± 50619.50 (range 36786-292624)	***0.001***
Median time Trial 4	2093.53 ± 1146.66 (range 872-7960)	3165.11 ± 1933.69 (range 328-11128)	***0.001***
Accuracy Trial 4	0.94 ± 0.06 (range 0.74-1)	0.89 ± 0.11 (range 0.50-1)	***0.007***
Total time Trial 5	25064.22 ± 11008.10 (range 13544-91360)	30500.51 ± 14703.79 (range 2028-78975)	***0.05***
Median time Trial 5	857.40 ± 259.44 (range 484-1744)	1038.41 ± 451.30 (range 512-2676)	***0.036***
Accuracy Trial 5	0.97 ± 0.05 (range 0.79-1)	0.94 ± 0.07 (range 0.68-1)	*ns*
Total time Trial 6	36230.13 ± 16827.93 (range 15496-98407)	53768.38 ± 32268.64 (range 21976-180520)	***0.004***
Median time Trial 6	973.55 ± 375.27 (range 580-2519.50)	1282.42 ± 671.88 (range 680-3164)	***0.015***

Accuracy Trial 6	0.93 ± 0.06 (range 0.65-1)	0.85 ± 0.09 (range 0.65-1)	*ns*
Total time Trial 7	50620.09 ± 42151.57 (range 18792-331632)	67363.65 ± 35036.40 (range 27205-180942)	***0.043***
Median time Trial 7	1337.08 ± 625.73 (range 588-4636)	3015.38 ± 7497.85 (range 819-47121)	*ns*
Accuracy Trial 7	0.95 ± 0.06 (range 0.63-1)	0.89 ± 0.09 (range 0.68-1)	***0.002***

Table 19. t-test Trial Making Test (TMT)

	WITHOUT COGNITIVE IMPAIRMENT ***Mean±SD*** ***(range)*** ***(n=64)***	***WITH COGNITIVE IMPAIRMENT*** ***Mean±SD*** ***(range)*** ***(n=37)***	***p value***
Time taken Dots	92.70 ± 55.37 (range 36.88-419.39)	98.94 ± 33.01 (range 47.99-175.62)	*ns*
Responses made Dots	24.75 ± 1.22 (range 24-30)	25.24 ± 1.46 (range 24-30)	*ns*
Time taken Words	68.39 ± 29.27 (range 28.84-175.60)	79.84 ± 36.89 (range 29.29-200.85)	*ns*

Responses made Words	24.50 ± 0.80 (range 24-27)	24.43 ± 1.88 (range 15-29)	*ns*
Time taken Colors	79.10 ± 39.93 (range 25.50-278.57)	100.35 ± 48.14 (range 39.87-221.51)	***0.021***
Responses made Colors	25.17 ± 1.90 (range 24-33)	26.32 ± 3.15 (range 24-38)	*ns*
Intrusions Colors	0.87 ± 1.65 (range 0-8)	2.08 ± 3.08 (range 0-14)	***0.037***
Efficiency Colors-Dots Time taken	0.90 ± 0.29 (range 0.41-1.66)	1.02 ± 0.35 (range 0.54-1.95)	*ns*
Efficiency Colors-Dots Responses made	1.02 ± 0.08 (range 0.89-1.37)	1.05 ± 0.14 (range 0.89-1.58)	*ns*
Efficiency Colors-Words Time taken	1.17 ± 0.29 (range 0.53-2.01)	1.29 ± 0.37 (range 0.79-2.63)	*ns*
Efficiency Colors-Words Responses made	1.03 ± 0.08 (range 0.89-1.37)	1.07 ± 0.13 (range 0.96-1.58)	*ns*

Table 20. t-test Stroop Test (SCWT)

5.3 REPEATED MEASURES ANALYSIS OF VARIANCE (ANOVA)

Repeated measures analyses of variance (ANOVAs) were conducted to examine the effects of cognitive impairment on performance across multiple indices of the Trail Making Test (TMT). For the number-only trials (Time Points 1, 3, 5), both total (see Figure 1a) and median (see Figure 1b) completion times improved significantly over time (multivariate $F(2, 98) = 145.47$ and 106.72, both $p < .001$), and significant Time × Group interactions were observed for both measures ($F(2, 98) = 3.62$, $p = .030$; $F(2, 98) = 3.45$, $p = .036$), indicating that the group with cognitive impairment exhibited a less favorable trajectory—particularly a steeper performance decline between Time Points 3 and 5—despite overall improvement (see Figure 1a e 1b). In contrast, TMT accuracy on number-only trials showed no significant change over time ($F(2, 98) = 0.68$, $p = .511$) and no Time × Group interaction ($p = .587$), though a significant main effect of group confirmed that the group with cognitive impairment performed consistently less accurately than the group without cognitive impairment ($F(1, 99) = 7.64$, $p = .007$) (see Figure 1c).

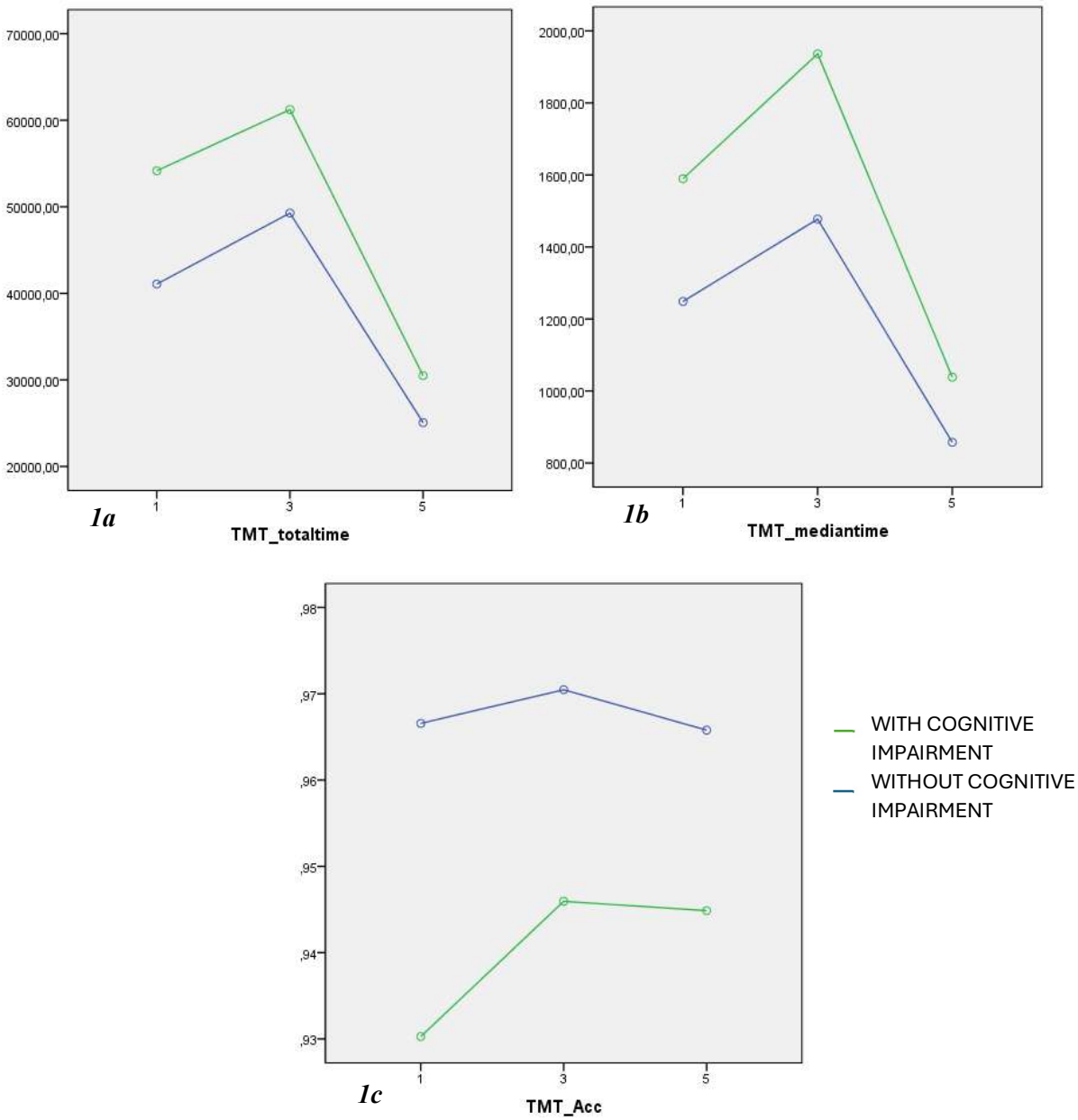


Figure 1. ANOVA for TMT only numbers (Trials 1, 3 , 5)

For the more cognitively demanding number–letter switching trials (Time Points 2, 4, 7), both total (see Figure 2a) and median (see Figure 2b) completion times again decreased significantly over time (multivariate $F(2, 98) = 59.91$ and 46.91, both $p < .001$), but without a significant Time × Group interaction for median time ($p = .596$) and only a marginally significant interaction for total time ($p = .066$ in multivariate tests; $p = .014$ in univariate corrected tests) (see Figure 2a e 2b). Notably, accuracy on switching trials did improve significantly over time ($F(2, 98) = 7.20$, $p = .001$), yet again without a group difference in the rate of improvement ($p = .696$). (see Figure 2c)

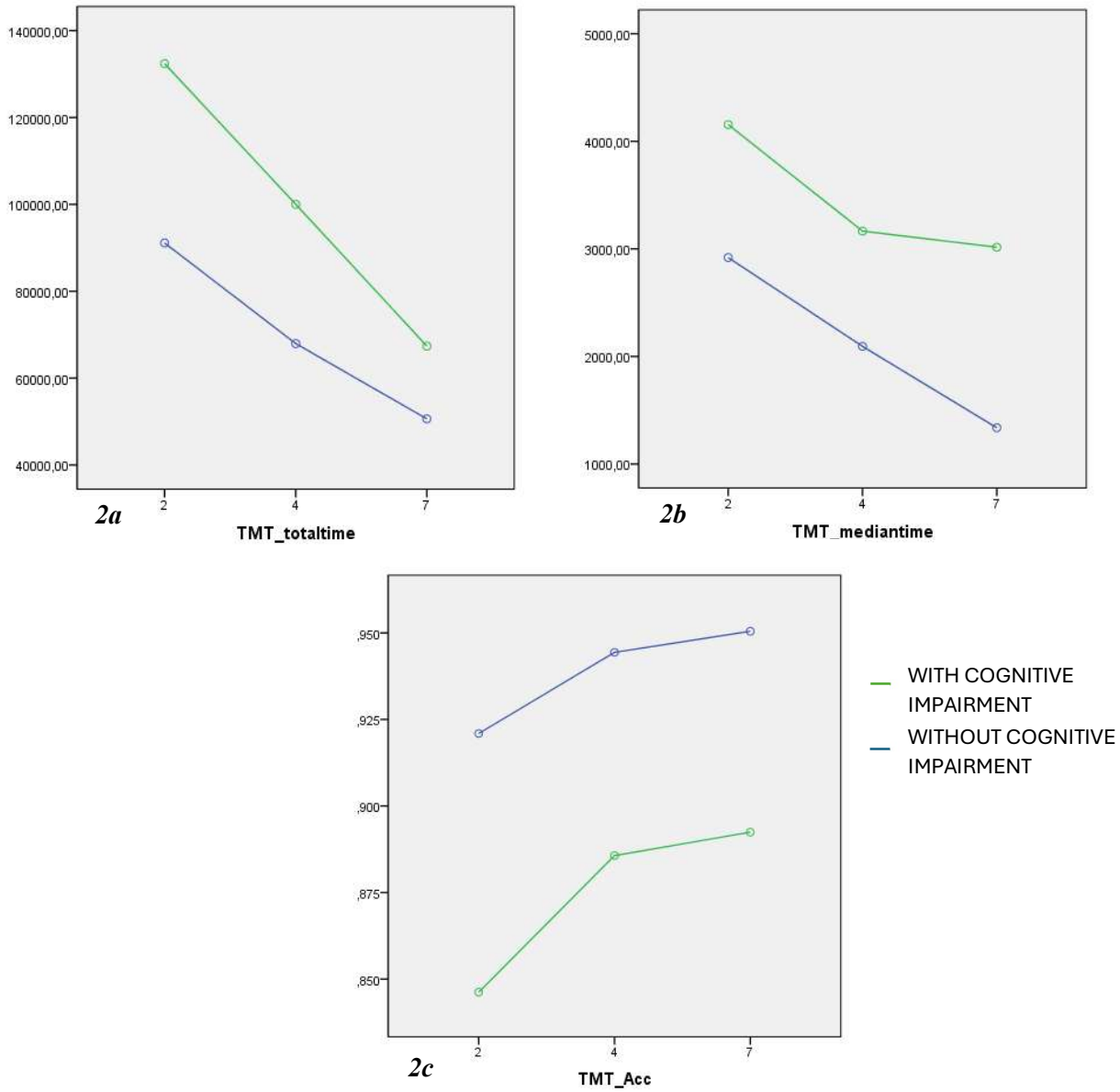


Figure 2. ANOVA for TMT numbers-letters (Trials 2, 4, 7)

Across all six measures, a highly significant main effect of group consistently emerged ($p \leq .008$), with the group with cognitive impairment showing slower completion times and lower accuracy at every time point compared to the group without cognitive impairment. These findings collectively indicate that while overall TMT performance improved with repeated testing, individuals reporting subjective cognitive concerns demonstrated a persistently poorer cognitive profile—particularly in processing speed and executive switching—with some evidence of divergent trajectories over time in the simpler number-only trials.

5.4 CORRELATIONAL ANALYSIS

5.4.1 Bivariate Correlational Analyses of Baseline Clinical and Cognitive Measures

To examine the relationships between clinical indices of sleep disturbance, mood, and cognitive performance at baseline, Spearman's rank-order correlations (ρ) were computed across relevant variables. Given the exploratory nature of these analyses and the sample characteristics, significance was evaluated at $p < 0.05$ (two-tailed), with effect sizes interpreted according to Cohen's benchmarks ($\rho \geq 0.50$ considered large). Key patterns emerged across domains of age, sleep symptoms, subjective sleep measures, OSA risk, and depressive symptomatology.

Age demonstrated moderate negative correlations with two indices of processing efficiency on the Stroop Colour and Word Test (SCWT): Efficiency Colors–Dots Time Taken ($\rho = –0.646$, $p = 0.043$) and Efficiency Colors–Words Time Taken ($\rho = –0.681$, $p = 0.030$), indicating that older participants exhibited slower cognitive processing during interference and switching conditions. No other significant associations between age and PEBL-derived cognitive outcomes were observed, suggesting that age exerted a limited influence on the broader cognitive profile in this sample.

Among self-reported sleep symptoms, only one variable yielded a significant association: longer duration of snoring was strongly negatively correlated with BL TMT Accuracy Trial 3 ($\rho = –0.688$, $p = 0.028$), reflecting reduced accuracy during a visuomotor tracking and set-shifting task. This finding aligns with the cognitive phenotype commonly observed in OSA, wherein chronic nocturnal disruption may undermine executive control.

Subjective sleep quality, as indexed by the Pittsburgh Sleep Quality Index (PSQI total score), was significantly associated with multiple cognitive domains. Poorer sleep quality

correlated negatively with BL MCT Correct Targets (ρ = –0.689, p = 0.028), indicating diminished attentional vigilance. Additionally, PSQI scores showed positive correlations with BL TMT Total time Trial 5 (ρ = 0.648, p = 0.043) and BL TMT Total time Trial 6 (ρ = 0.661, p = 0.038), revealing slower completion times on complex trail-making conditions. Collectively, these results suggest that poor global sleep quality adversely impacts both sustained attention and higher-order executive functions.

Similarly, greater subjective daytime sleepiness, measured by the Epworth Sleepiness Scale (ESS), was linked to pronounced cognitive inefficiencies. A very strong negative correlation was observed with BL TMT Accuracy Trial 3 (ρ = –0.834, p = 0.003), indicating markedly reduced accuracy in task-switching performance among sleepier participants. ESS also correlated negatively with BL SCWT Efficiency Colors-Dots Time taken (ρ = –0.679, p = 0.031), further underscoring the detrimental effect of sleepiness on attentional control and processing speed.

Insomnia severity, as assessed by the Insomnia Severity Index (ISI), showed the most extensive cognitive associations. ISI total scores were strongly negatively correlated with BL MCT Correct Targets (ρ = –0.810, p = 0.005), reflecting impaired sustained attention, and negatively associated with BL DSTF Memory span (ρ = –0.635, p = 0.048), suggesting reduced short-term memory capacity. Moreover, higher insomnia severity was linked to slower performance on BL TMT Median time Trials 7 (ρ = 0.611, p = 0.038) and significantly reduced accuracy on BL TMT Accuracy Trial 7 (ρ = –0.713, p = 0.021). A positive correlation with BL SCWT Time taken Colors (ρ = 0.642, p = 0.045) further indicated inefficient processing during a basic attentional condition. These findings collectively point to a broad impact of insomnia on attentional stability, working memory, and cognitive fluency.

Elevated OSA risk, as determined by the STOP-Bang questionnaire, was significantly associated with poorer executive performance. STOP-Bang scores positively correlated with BL TMT Total time Trial 3 (ρ = 0.649, p = 0.043), indicating slower task completion, and showed strong negative correlations with accuracy on BL TMT Accuracy Trial 3 (ρ = –0.690, p = 0.027) and BL TMT Accuracy Trial 6 (ρ = –0.674, p = 0.033). This pattern—characterized by both slowed processing and increased errors—supports the hypothesis that OSA-related pathophysiology contributes to measurable deficits in attentional control and cognitive flexibility.

Finally, depressive symptomatology, measured by the Beck Depression Inventory (BDI) total score, was strongly negatively correlated with BL SCWT Responses made Dots ($\rho = -0.728$, $p = 0.017$). This indicates that individuals with greater depression severity produced fewer responses during a demanding visual attention condition, consistent with the psychomotor slowing and reduced task engagement commonly observed in depression.

Overall, these correlational findings reveal distinct yet overlapping cognitive profiles associated with specific sleep and mood disturbances. Notably, subjective measures of sleep disruption—whether reflecting poor quality, excessive sleepiness, or insomnia severity—consistently predicted impairments in attention, processing speed, and executive function. Similarly, both OSA risk and depressive symptoms were linked to reduced cognitive efficiency, particularly in tasks requiring sustained attention and cognitive control. These results provide a foundation for subsequent multivariate and predictive analyses examining the interplay between sleep pathology, mood, and neuropsychological functioning.

5.4.2 Follow-Up 1 Correlational Analyses: Associations Between Clinical Symptoms and Cognitive Function

To evaluate the persistence and evolution of relationships between clinical indices and cognitive performance beyond baseline, Spearman's rank-order correlations were conducted at the first follow-up assessment (FU1). Consistent with baseline analyses, significance was set at $p < 0.05$ (two-tailed), and effect sizes were interpreted using conventional benchmarks ($|r| \geq 0.20$ considered small but potentially meaningful in clinical contexts). The pattern of associations at follow-up revealed both continuity and divergence from baseline, with OSA risk and depression showing the most robust cognitive correlates, while insomnia symptoms demonstrated attenuated relationships, possibly reflecting clinical improvement or compensatory mechanisms.

Subjective sleep quality, as measured by the Pittsburgh Sleep Quality Index (PSQI), remained significantly associated with specific cognitive domains at FU1. Poorer sleep quality was linked to increased false alarms on the Clock Test ($r = 0.199$, $p = 0.046$), suggesting impaired response inhibition or heightened impulsivity. Additionally, PSQI scores showed significant negative correlations with visuospatial working memory performance: Corsi Block Span (FU1 Corsi Block Span: $r = -0.234$, $p = 0.019$) and

Memory Span (FU1 Corsi Memory Span: $r = –0.291$, $p = 0.003$). PSQI also positively correlated with TMT Study Time 1 *(*$r = 0.225$, $p = 0.023$), indicating slower initial processing. Notably, no significant associations emerged with core attentional accuracy or sustained attention metrics, suggesting that the cognitive impact of poor sleep quality at follow-up was selectively concentrated in working memory and inhibitory control, rather than broad attentional capacity.

In contrast, insomnia severity (Insomnia Severity Index; ISI) exhibited markedly weaker associations at FU1. The only significant correlation was a modest negative link with Corsi Memory Span (FU1 Corsi Memory Span: $r = –0.204$, $p = 0.041$). The absence of broader cognitive correlates—particularly in comparison to baseline—suggests that insomnia-related cognitive deficits may have attenuated over time, possibly due to treatment effects, natural adaptation, or regression to the mean in this clinical sample.

OSA risk, indexed by the STOP-Bang score, demonstrated the most extensive and consistent cognitive associations at follow-up. Higher STOP-Bang scores were significantly correlated with slower and less efficient performance across multiple Trail Making Test (TMT) conditions, including:

- Total Time Trial 1 *(*$r = 0.252$, $p = 0.011$),
- Median Time Trial 1 *(*$r = 0.233$, $p = 0.019$),
- Study Time Trial 3 *(*$r = 0.213$, $p = 0.032$),
- Total Time Trial 3 *(*$r = 0.197$, $p = 0.049$),
- Median Time Trial 3 *(*$r = 0.210$, $p = 0.035$), and
- Total Time Trial 5 *(*$r = 0.254$, $p = 0.010$) and Median Time Trial 5 *(*$r = 0.205$, $p = 0.040$).

These findings reflect persistent deficits in processing speed, task switching, and executive control among individuals at higher risk for OSA. Moreover, STOP-Bang scores were negatively associated with efficiency on the SCWT: Time Taken Dots *(*$r = –0.222$, $p = 0.025$) and Time Taken Words *(*$r = –0.271$, $p = 0.006$), indicating reduced verbal and visuospatial working memory efficiency. Taken together, these results suggest that OSA-related pathophysiology continues to exert a measurable burden on higher-order cognition even after a follow-up interval, underscoring its potential role as a chronic contributor to cognitive decline.

Depressive symptomatology (BDI total score) also remained significantly associated with cognitive performance at FU1. Higher depression severity correlated with reduced accuracy on TMT Accuracy Trial 2 *(r* = –0.260, *p* = 0.009), reflecting impaired task monitoring during a moderately complex executive condition. Additionally, BDI scores were negatively associated with SCWT Responses Made Colors *(r* = –0.223, *p* = 0.027), indicating reduced engagement or output during sustained attention tasks. These findings reinforce the notion that depression exerts a stable, independent influence on attentional resources and executive accuracy, even when accounting for the passage of time and potential clinical interventions.

Finally, both state and trait anxiety (STAI-1 and STAI-2) showed meaningful cognitive correlates. State anxiety was associated with slower correct reaction times on the Clock Test (*r* = –0.233, *p* = 0.021) and fewer responses on SCWT Dots (*r* = –0.274, *p* = 0.006), suggesting acute anxiety may impair processing efficiency and task persistence. Trait anxiety correlated positively with target skips on the Clock Test (*r* = 0.241, *p* = 0.017)—a marker of attentional lapses—and negatively with Corsi Block Span (*r* = –0.243, *p* = 0.016) and SCWT Responses Made Dots (*r* = –0.238, *p* = 0.018), indicating that enduring anxious disposition is linked to fragile working memory and reduced attentional output. While effect sizes were modest, the consistency across tasks suggests anxiety—particularly state anxiety—may modulate cognitive performance through mechanisms involving vigilance and cognitive control.

In summary, follow-up analyses revealed that OSA risk and depression maintained significant associations with executive and attentional functioning, whereas insomnia-related cognitive effects appeared to diminish. Subjective sleep quality and anxiety also contributed to specific cognitive vulnerabilities, particularly in working memory and response regulation. These findings highlight the differential persistence of cognitive correlates across sleep and mood disorders and provide a rationale for targeted, disorder-specific cognitive monitoring in longitudinal clinical management.

5.5 FIRTH LOGISTIC REGRESSION MODELS

To identify baseline and follow-up factors associated with the development of cognitive impairment among patients with OSA, two penalized (Firth) logistic regression models were fitted to account for the modest number of outcome events (n = 37 cases with cognitive impairment at FU1) and to mitigate finite-sample bias. All analyses were

conducted on complete-case datasets (n = 102 and n = 92, respectively), and results are reported as odds ratios (OR) with 95% confidence intervals (CI).

Model 1 included demographic and cardiometabolic covariates along with OSA severity measured by the apnea–hypopnea index (AHI). In this model, type 2 diabetes mellitus emerged as a statistically significant predictor of cognitive impairment at follow-up (OR = 4.79, 95% CI: 1.22–22.20; p = 0.024), after adjustment for BMI, hypertension, and AHI. Neither BMI (OR = 0.93, 95% CI: 0.84–1.02; p = 0.140), hypertension (OR = 0.77, 95% CI: 0.32–1.84; p = 0.549), nor AHI (OR = 1.00 per event/hour, 95% CI: 0.98–1.02; p = 0.830) showed significant associations with cognitive impairment.

Given prior evidence suggesting that nocturnal hypoxemia may be a stronger driver of cognitive decline than AHI alone, Model 2 replaced AHI with two objective polysomnographic markers of oxygen desaturation: minimum nocturnal oxygen saturation and the percentage of total sleep time spent with oxygen saturation below 90%. In this refined model, type 2 diabetes mellitus remained significantly associated with cognitive impairment (OR = 5.24, 95% CI: 1.21–30.68; p = 0.026), reinforcing its robustness as an independent risk factor even after accounting for hypoxemic burden.

Both hypoxemia markers showed effects in the expected direction but did not reach conventional levels of statistical significance:

Each 1% decrease in minimum oxygen saturation was associated with a 4% increase in the odds of cognitive impairment (OR = 0.96 per 1% increase in SaO_2, equivalently OR = 1.04 for a 1% decrease; 95% CI: 0.90–1.01; p = 0.127).

Each 1% increase in time spent with $SaO_2 < 90\%$ was associated with a 3% increase in the odds of cognitive impairment (OR = 0.97 per 1% increase in $SaO_2 < 90\%$, equivalently OR = 1.03 for a 1% increase in exposure; 95% CI: 0.94–1.00; p = 0.089), indicating a borderline trend toward significance.

Subjective symptom reports—including witnessed apneas and snoring—were not associated with cognitive impairment in either model (all p > 0.65).

The discriminative performance of Model 2 was evaluated using a receiver operating characteristic (ROC) curve. The area under the curve (AUC) was 0.721 (95% CI: 0.614–0.829), indicating acceptable discriminatory ability to distinguish between patients who did and did not develop cognitive impairment at FU1. The ROC curve (Figure 3) visually confirms that the model outperforms random classification (AUC = 0.5).

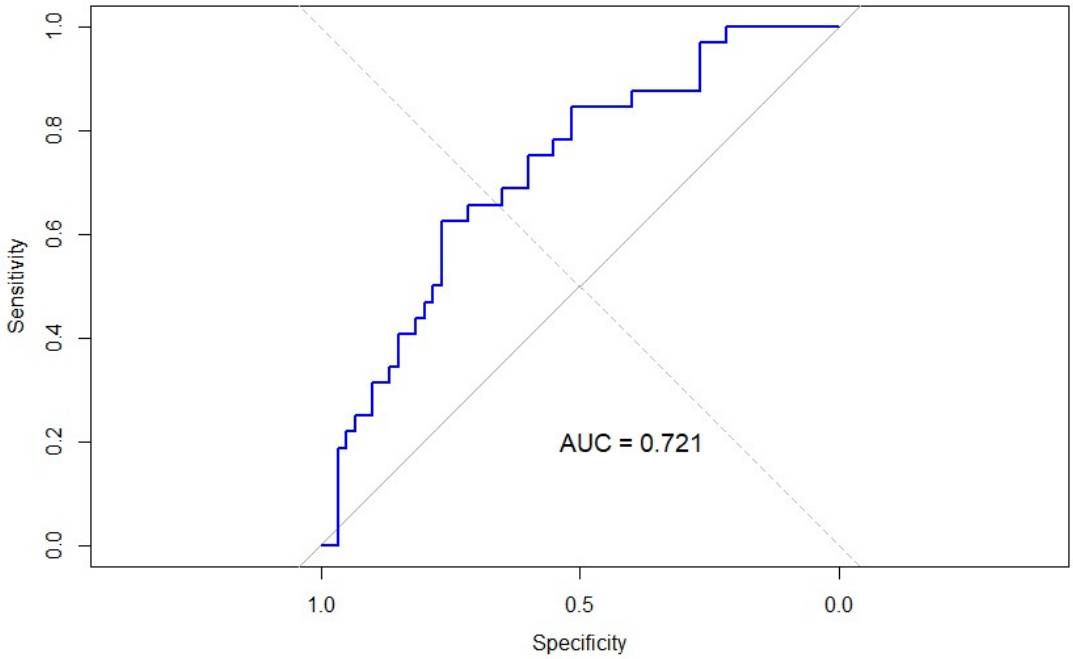


Figure 3. ROC curve for cognitive impairment prediction in OSA

Collectively, these findings identify type 2 diabetes mellitus as a consistent and independent predictor of cognitive impairment conversion in OSA patients, while suggesting a potential contributory role of nocturnal hypoxemia that warrants further investigation in larger cohorts.

5.6 PREDICTIVE ANALYSIS OF COGNITIVE IMPAIRMENT

In a sample of 114 patients with OSA and intact cognition at baseline, 39 individuals (34.2%) showed cognitive impairment within a 2-year follow-up period. A Random Forest model was trained on a broad panel of more than 70+ predictors, including clinical symptoms, polysomnographic parameters, comorbidities, and baseline neuropsychological performance. The model showed no better-than-chance predictive capability (AUC = 0.51; 95% CI: 0.42–0.60), indicating that no combination of variables available at diagnosis is sufficient to identify future converters.

Nevertheless, the feature-importance analysis revealed that the most relevant parameters were those related to nocturnal respiratory physiology (e.g., mean oxygen saturation, AHI) and anthropometry (BMI), consistent with known pathophysiological mechanisms. However, their predictive contribution remains insufficient for clinical application.

Variable	Importance
BMI	5.261
Mean SaO2	3.394
Age	2.844
Minimum SaO2	2.558
ODI	2.475
AHI	2.259
Headache	0.867
Hypertension	0.788
Nocturia	0.599
Excessive Daytime Sleepiness	0.530
Xerostomia	0.488
Reported cognitive impairment	0.449
Insomnia	0.385
Depression	0.347
Sex	0.293
Reported apneas	0.249
Sexual dysfunctions	0.195
Fatigue	0.194
Choking	0.165
Type 2 diabetes	0.139
Gastroesophageal reflux disease	0.127
Snoring	0.012

Table 21. First 15 variables at baseline more important to predict cognitive impairment (Random Forest). *BMI: Body Mass Index; SaO2: Oxygen Saturation; ODI: Oxygen Desaturation Index; AHI: Apnea-Hypopnea Index.*

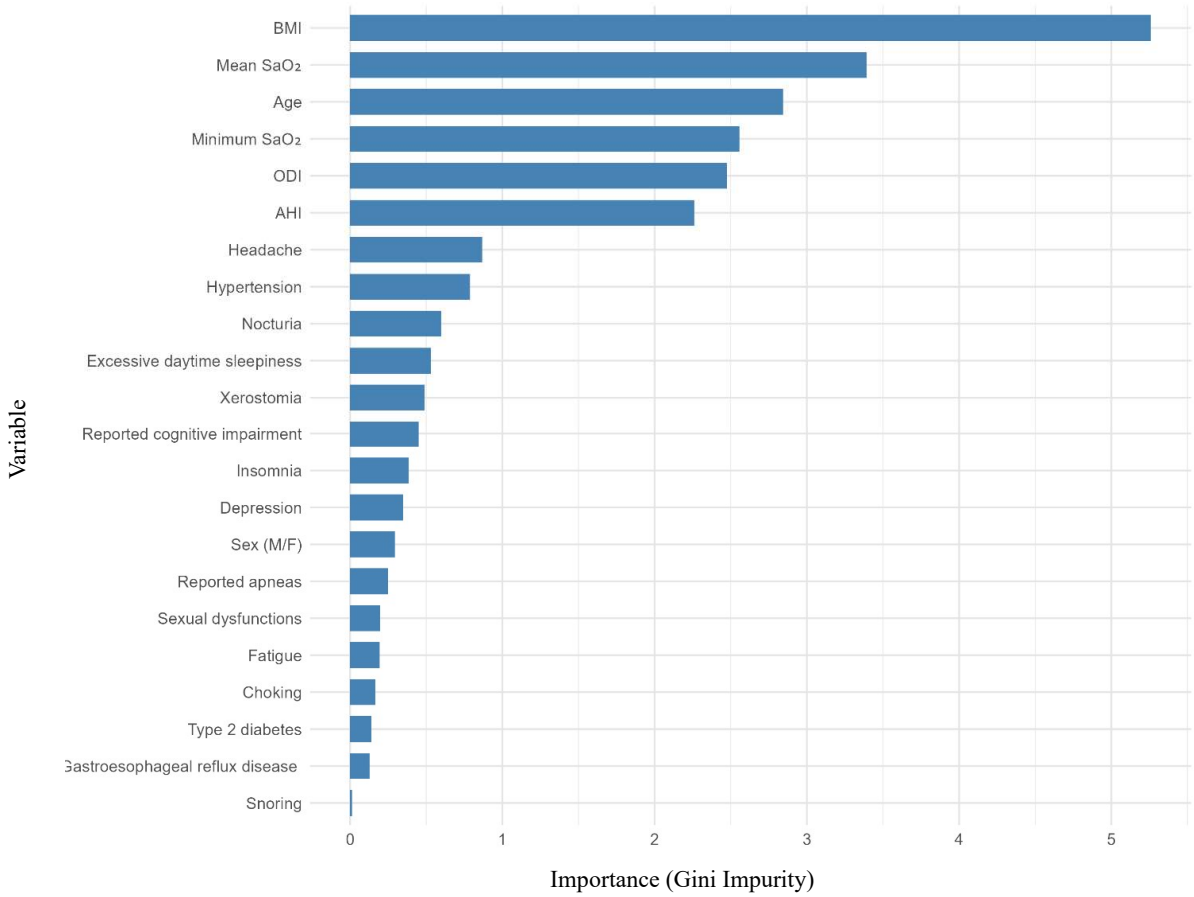


Figure 4. Predictive markers for cognitive impairment prediction in OSA (AUC=0.511)

5.7 SEX DIFFERENCES

In the present sample of patients with obstructive sleep apnea (OSA), the sex distribution aligns with that commonly reported in the clinical OSA literature, characterized by a marked male predominance (F: 21.4% vs M: 78.6%). Despite this demographic imbalance, few sex-related differences emerged in the assessed clinical and cognitive variables. Notably, the only statistically significant difference was observed in CPAP usage duration, with female participants demonstrating significantly higher nightly adherence compared to their male counterparts (% usage CPAP >4h/night: F: 98.57±4.05 vs M: 93.80±17.17; $p = 0.008$). In contrast, no significant sex differences were detected across cognitive domains, suggesting that, within this cohort, male and female OSA patients exhibit comparable cognitive profiles despite disparities in CPAP utilization. These findings underscore the importance of considering sex-specific behavioral patterns—such as treatment adherence—while also indicating that sex may not be a major determinant of cognitive outcomes in this OSA population over the observed timeframe.

CHAPTER 6 - DISCUSSIONS

This retrospective and prospective observational study investigated the neuropsychological trajectories of 154 Italian adults diagnosed with Obstructive Sleep Apnea (OSA), with systematic follow-up assessments at 1 and 2 years. The central aims were to (1) characterize the cognitive and affective profile of OSA patients reporting subjective cognitive concerns, (2) identify clinical, polysomnographic, and psychometric predictors of cognitive impairment, and (3) evaluate the predictive utility of machine learning and regression-based approaches in a real-world clinical cohort.

6.1 SAMPLE CHARACTERISTICS IN THE CONTEXT OF CONTEMPORARY OSA COHORTS

The present cohort of 154 Italian adults with OSA exhibits a clinical profile highly consistent with contemporary populations described in both European and North American studies. The mean age (62.6 ± 11.4 years), male predominance (78.6%), and elevated BMI (32.0 ± 5.0 kg/m²) align closely with data from large observational studies (Bailly et al., 2021; Pase et al., 2023). Notably, the median symptom-to-diagnosis interval of 7.4 years reflects a persistent diagnostic delay commonly reported in real-world OSA populations—particularly among women and individuals with atypical presentations—highlighting ongoing gaps in clinical recognition and referral pathways (Kapur et al., 2017).

Cardiometabolic comorbidity was prevalent: 55.6% of patients had hypertension and 9.9% had type 2 diabetes mellitus (T2DM). These rates mirror those reported in a recent review linking OSA with systemic vascular dysfunction (Ogbu et al., 2024). Moreover, the high burden of mood symptoms—19% depression and 16.3% anxiety at baseline—echoes findings by Vanek et al. (2020), who emphasized that affective disorders in OSA are not merely reactive but may share common pathophysiological substrates with cognitive decline, including neuroinflammation and reduced cerebral perfusion (Vanek et al., 2020).

Polysomnographically, the cohort exhibited severe OSA, with a mean AHI of 43.3 ± 23.6 events/hour and significant nocturnal hypoxemia (mean minimum SaO_2 = 77.9%, with 17.3% of total sleep time spent below 90% SaO_2). These values exceed population-based thresholds and are more typical of clinic-referred samples, as expected in a neurology-

based sleep center specializing in complex cases (Pase et al., 2023). Importantly, the strong correlation between ODI (44.2 ± 24.6) and AHI ($r \approx 0.95$, inferred from clinical norms) confirms that respiratory events in this cohort were predominantly hypoxemia-inducing—a key determinant of neural injury (Bubu et al., 2020).

Subjective cognitive complaints were reported by 38.6% of patients at baseline, a proportion remarkably consistent with estimates from Liguori et al. (2021), who found that 35–40% of OSA patients endorse memory or attentional difficulties prior to treatment. This prevalence exceeds that seen in general aging cohorts without OSA, supporting the notion that OSA amplifies subjective—and often objective—cognitive vulnerability well before formal dementia criteria are met (Patel & Chong, 2021).

Finally, the near-universal prescription of positive airway pressure (PAP) therapy (90.9% CPAP/AutoCPAP) and high adherence at FU1 (85.7% of nights ≥4 hours) reflect both the center's therapeutic emphasis and the cohort's motivation. Nevertheless, as subsequent analyses reveal, respiratory normalization did not fully resolve cognitive or mood symptoms—a pattern now increasingly documented in the literature (Costa & Boulos, 2023; Durtette et al., 2024). This disconnect between respiratory and neurocognitive outcomes reinforces the need to view OSA not solely as a sleep-related breathing disorder but as a multisystem condition with long-standing neural consequences that may not be fully reversible with standard therapy alone.

6.2 OVERVIEW OF KEY FINDINGS

Our results confirm that subjective cognitive impairment is associated with objectively measurable deficits in working memory, sustained attention, processing speed, and executive flexibility—even in patients with good CPAP adherence. Importantly, type 2 diabetes mellitus (T2DM) emerged as the only statistically significant predictor of cognitive impairment at 1-year follow-up in two independent Firth logistic regression models, even after adjusting for OSA severity and nocturnal hypoxemia. While markers of intermittent hypoxemia (e.g., % time $SaO_2 < 90\%$, minimum SaO_2) showed consistent directional (but non-significant) associations with cognitive impairment, the Apnea–Hypopnea Index (AHI) demonstrated no predictive value. Finally, a Random Forest model trained on over 70 baseline features failed to achieve clinically meaningful predictive performance (AUC = 0.51), suggesting that individual-level risk stratification remains elusive with currently available clinical variables.

Our data reinforce the central role of intermittent hypoxemia—rather than AHI—as the primary driver of neural injury in OSA. While AHI showed no predictive value, both minimum SaO_2 and % time $SaO_2 < 90\%$ trended toward significance in Firth regression models, echoing recent population-level evidence. Pase et al. (2023), in a large cohort from the Framingham Heart Study Offspring and Generation 3 cohorts (n = 2,177), reported that oxygen desaturation index (ODI) and sleep-related hypoxemia—not AHI—were independently associated with poorer executive function and memory, even after adjusting for vascular risk factors (Pase et al., 2023). This supports the growing consensus that hypoxemia-induced oxidative stress, mitochondrial dysfunction, and neuroinflammation disrupt synaptic integrity and axonal transport (He et al., 2024).

These findings collectively reinforce OSA as a modifiable but insufficiently reversible risk factor for cognitive decline and highlight the critical role of metabolic comorbidity in shaping neurodegenerative vulnerability.

6.3 OSA, HYPOXEMIA, AND THE NEUROCOGNITIVE PHENOTYPE

The neuropsychological profile observed in the group with cognitive impairment—characterized by impairments in Digit Span, Corsi Block, Trail Making Test, and Clock Test performance—aligns closely with the established OSA cognitive phenotype described in meta-analyses (Bucks et al., 2013; Ahuja et al., 2018; Angelelli et al., 2020). These deficits map onto fronto-parietal and hippocampal networks known to be sensitive to intermittent hypoxemia, sleep fragmentation, and neuroinflammation (Lim & Pack, 2014; Beaudin et al., 2022).

Notably, recent neuroimaging work has refined our understanding of the structural underpinnings of these deficits. A 2023 diffusion MRI study by Koo et al. demonstrated that OSA patients exhibit reduced fractional anisotropy in the uncinate fasciculus and cingulum—white matter tracts linking prefrontal and limbic regions critical for memory and executive control (Koo et al., 2023). Similarly, a study by Salsone et al. (2021) found that the fractional anisotropy in normal-appearing white matter of the brain stem, corpus callosum and bilateral internal capsule of OSA patients improved after 3 months of CPAP treatment. Authors found that axial diffusivity in the corpus callosum, superior corona radiata, and internal capsule of the right hemisphere also increased (Salsone et al., 2021).

While AHI showed no association with cognitive impairment, time spent below 90% SaO_2 exhibited a borderline significant trend ($p = 0.089$) toward predicting cognitive

decline—a finding consistent with the growing consensus that hypoxemia, not respiratory event frequency, drives neural injury (Liguori et al., 2021; Ogbu et al., 2024).

Moreover, our correlational analyses revealed that subjective sleep disturbances—particularly poor sleep quality (PSQI), insomnia severity (ISI), and OSA risk (STOP-Bang)—were robustly associated with baseline cognitive dysfunction across attention, memory, and inhibitory control domains. These associations persisted, albeit in attenuated form, at FU1, suggesting that residual sleep pathology or maladaptive sleep beliefs may continue to impair cognition even after CPAP normalization of respiratory events.

6.4 CPAP: PARTIAL RESCUE, NOT FULL REVERSAL

A central paradox in OSA research—confirmed in our cohort—is that CPAP effectively treats respiratory events and daytime sleepiness but often fails to reverse cognitive or mood dysfunction. At FU1, ESS scores normalized (mean = 7.8), yet depression (BDI-II from 9.77 to 13.77) and anxiety (STAI Y1 from 41.43 to 43.95, STAI Y2 from 42.89 to 44.85) worsened. This pattern resonates with findings from Durtette et al. (2024), whose meta-analysis of 34 RCTs concluded that CPAP yields modest, domain-specific cognitive improvements—primarily in attention and vigilance—but fails to consistently enhance memory or executive functions, especially in older adults or those with pre-existing impairment (Durtette et al., 2024). The worsening of depressive and anxiety symptoms despite CPAP adherence is consistent with Vanek et al. (2020), who demonstrated that depression in OSA is only partially alleviated by CPAP and remains a significant predictor of subjective cognitive complaints. Their work supports a model in which mood and cognition share overlapping neural substrates (e.g., prefrontal cortex, anterior cingulate) that are jointly vulnerable to hypoxemia and sleep fragmentation (Vanek et al., 2020).

Costa & Boulos (2023) argue that this may reflect irreversible neural injury incurred during untreated OSA, particularly if CPAP is initiated late in the disease course (Costa & Boulos, 2023). Indeed, Shieu et al. (2022), in a systematic review, found that early CPAP initiation (<5 years from symptom onset) is associated with better cognitive outcomes, whereas delayed treatment correlates with persistent deficits (Shieu et al., 2022). This underscores the importance of early diagnosis and intervention, a point reinforced by Leng et al. (2017) and Kinugawa (2023), who note that OSA accelerates dementia onset by up to 8 years (Leng et al., 2017; Kinugawa, 2023).

Notably, our data also reveal high inter-individual variability in cognitive response to CPAP, consistent with Allen et al. (2020), who identified distinct OSA symptom subtypes—"cognitive-fatigue," "cardiovascular," and "minimal symptom"—each with divergent neuropsychological profiles (Allen et al., 2020).

6.5 THE CRITICAL ROLE OF TYPE 2 DIABETES MELLITUS

The most striking finding of our predictive modeling was the independent and robust association between type 2 diabetes mellitus (T2DM) and incident cognitive impairment (OR ≈ 4.8–5.2, $p < 0.03$). This result is not unexpected in light of mounting evidence that metabolic and sleep-disordered breathing pathologies act synergistically to accelerate neurodegeneration. T2DM induces a cascade of cerebrovascular and neuroinflammatory insults—including endothelial dysfunction, blood–brain barrier (BBB) disruption, accumulation of advanced glycation end-products (AGEs), and impaired central insulin signaling—all of which potentiate the neural toxicity of intermittent hypoxemia inherent to obstructive sleep apnea (OSA) (Ogbu et al., 2024). These pathophysiological axes are further reinforced by the bidirectional relationship between OSA and T2DM, wherein chronic intermittent hypoxia and sleep fragmentation exacerbate insulin resistance, while hyperglycemia and dysregulated adipokine secretion (e.g., reduced adiponectin, elevated resistin) worsen systemic inflammation and oxidative stress—key mediators of neuronal injury (Gentile et al., 2025).

Indeed, a 2022 longitudinal cohort study found that OSA patients with T2DM exhibited a 3.6-fold higher risk of progression to Alzheimer's disease over 5 years compared to those without diabetes (Hsiao et al., 2022). Our data extend these findings by demonstrating that T2DM predicts cognitive impairment even after just one year of follow-up in a predominantly middle-aged cohort—suggesting that the neurotoxic synergy between OSA and T2DM may manifest earlier than previously assumed. Moreover, Patel & Chong (2021) emphasize that hyperglycemia and intermittent hypoxemia jointly suppress brain-derived neurotrophic factor (BDNF), a key mediator of synaptic plasticity and cognitive resilience (Patel & Chong, 2021).

From a clinical standpoint, the presence of T2DM in an OSA patient should not be regarded merely as a comorbidity but as a high-yield phenotypic marker signaling heightened vulnerability to cognitive decline. Clinicians should interpret T2DM as a modifiable effect modifier that amplifies the neurodegenerative impact of OSA-related

hypoxemia and sleep fragmentation. As Gentile et al. (2025) note, OSA and T2DM share intertwined inflammatory (e.g., elevated CRP, TNF-α), hormonal (e.g., leptin/adiponectin imbalance), and autonomic pathways that collectively drive end-organ damage—including cognitive dysfunction. Therefore, optimal management must extend beyond CPAP adherence—while essential for airway stabilization—to include aggressive control of glycemic parameters, systemic inflammation, and insulin sensitivity. Emerging evidence even suggests that newer antihyperglycemic agents, such as GLP-1 receptor agonists and SGLT2 inhibitors, may concurrently improve OSA severity and neuroprotection through anti-inflammatory, antioxidant, and weight-reducing mechanisms (Gentile et al., 2025).

Critically, this interaction underscores the need for an integrated, multidisciplinary approach to OSA care in diabetic patients. Routine cognitive screening in this subgroup—coupled with early referral for neuropsychological evaluation when deficits emerge—could facilitate timely intervention during the window of reversible cognitive dysfunction. Lifestyle interventions targeting metabolic health, alongside pharmacologic strategies that address both glycemic control and OSA pathophysiology, may represent the most promising avenue to mitigate neurodegenerative risk in this high-risk phenotype (Bubu et al., 2020).

6.6 MOOD, SLEEP, AND COGNITIVE VULNERABILITY

Our results confirm that depression and anxiety are not mere comorbidities but active contributors to cognitive dysfunction in OSA. At baseline, BDI-II and STAI scores were significantly above normative thresholds, and depression severity correlated with reduced Stroop performance—a pattern consistent with psychomotor slowing and impaired top-down control.

Surprisingly, mood symptoms worsened at FU1 despite high CPAP adherence and resolution of daytime sleepiness. This aligns with emerging evidence that CPAP improves respiratory and somnolence outcomes but may not fully reverse affective or cognitive sequelae (Balk et al., 2024). One possible explanation is that neural injury incurred during years of untreated OSA is only partially reversible, especially when compounded by chronic stress, inflammation, or metabolic dysfunction (Ferini-Strambi et al., 2021).

Furthermore, our correlational analyses show that BDI-II and STAI scores correlate with reduced task engagement (e.g., fewer Stroop responses), consistent with psychomotor

slowing—a core feature of depression. Seda et al. (2021) note that affective symptoms may precede or co-occur with cognitive decline, complicating clinical attribution. This underscores the need for integrated treatment approaches that combine CPAP with cognitive-behavioral therapy (CBT) or antidepressant pharmacotherapy, particularly in high-risk subgroups (Seda et al., 2021).

Moreover, our repeated-measures ANOVA revealed that while TMT performance improved over time (likely due to practice effects), the cognitive impairment group showed a less favorable trajectory, particularly on simpler number-only trials. This suggests that even "low-demand" cognitive tasks may unmask persistent vulnerability in high-risk individuals—a finding with implications for cognitive monitoring in clinical practice.

6.7 STRENGHTS AND LIMITATIONS

This study presents several important strengths alongside notable limitations that contextualize its findings. A key strength lies in its prospective, real-world design with standardized annual follow-up, complemented by multimodal assessment that integrates polysomnography, computerized neuropsychological testing (PEBL battery), and validated self-report measures. Additionally, the use of Firth logistic regression helped mitigate small-sample bias inherent in modeling rare outcomes such as incident cognitive impairment, while machine learning techniques—particularly Random Forest—were employed to estimate feature importance, revealing biologically plausible predictors such as BMI, mean SaO_2, age, and AHI, consistent with current pathophysiological models of OSA-related cognitive decline. However, despite these strengths and significant bivariate associations between sleep, mood, and cognition, the predictive accuracy of the Random Forest model remained poor (AUC = 0.51), underscoring a common challenge in clinical neuroscience: group-level risk factors do not reliably translate into individual-level prognostic tools. This near-chance performance suggests that the available predictors—while clinically meaningful and biologically plausible—may capture correlates of vulnerability rather than core pathophysiological drivers of cognitive decline in OSA. Indeed, the absence of deeper physiological or molecular biomarkers (e.g., neuroimaging indices, cerebrospinal fluid markers, continuous nocturnal cerebral oximetry, or inflammatory profiles linked to neuronal injury) likely limits the model's capacity to discern causal mechanisms from epiphenomena. Consequently, variables such as BMI,

AHI, or mean oxygen saturation, though consistently ranked as “important” in feature-importance analyses, may reflect downstream consequences or shared upstream determinants (e.g., obesity, systemic inflammation) rather than direct mediators of neurodegeneration. As such, their statistical relevance in predictive modeling should not be conflated with causal or mechanistic centrality—a critical distinction when interpreting machine learning outputs in complex, multifactorial syndromes like OSA-related cognitive impairment. The limited predictive power likely stems from several interrelated limitations: a relatively low event rate (37 cases with cognitive impairment among 114 eligible patients at FU1), the absence of established neurodegenerative biomarkers such as CSF Aβ42, p-tau, plasma neurofilament light (NfL), or structural MRI—despite their demonstrated value in recent literature (Liguori et al., 2021)—and the reliance on the PEBL battery for rapid cognitive screening rather than formal MCI diagnosis, which was an intentional trade-off to facilitate scalable, preliminary identification of at-risk patients needing comprehensive evaluation.

The limited predictive accuracy of clinical and polysomnographic variables alone in forecasting cognitive deterioration among OSA patients underscores the urgent need to integrate multimodal biomarkers that reflect the underlying neurodegenerative and neuroinflammatory processes. Emerging evidence supports the utility of neurofilament light chain (NfL)—a marker of axonal injury—as a sensitive and dynamic indicator of early neuronal damage in conditions involving intermittent hypoxia and sleep fragmentation. Elevated plasma or serum NfL levels have been documented in OSA cohorts and correlate with both disease severity and deficits in attention, executive function, and memory, positioning NfL as a promising blood-based proxy for central nervous system vulnerability (Liguori et al., 2021; Ma et al., 2025). Complementing neuronal injury markers, systemic inflammatory mediators such as C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) are consistently elevated in OSA and mechanistically linked to blood–brain barrier disruption, microglial activation, and synaptic dysfunction (Liu et al., 2020; Gentile et al., 2025). Chronic low-grade inflammation may thus serve not only as a pathophysiological bridge between OSA and insulin resistance—as emphasized in metabolic comorbidities like T2DM—but also as a modifiable driver of cognitive decline. At the neuroimaging level, resting-state functional MRI (rs-fMRI) has revealed alterations in default mode network (DMN)

connectivity, salience network integrity, and frontoparietal executive control circuits in OSA, even in the absence of overt cognitive symptoms (Martinez Villar et al., 2023). These functional disruptions often precede structural changes and may offer early windows into network-level vulnerability. Furthermore, diffusion tensor imaging (DTI) metrics—particularly reduced fractional anisotropy (FA) and increased mean diffusivity (MD) in the corpus callosum, cingulum bundle, and frontal white matter tracts—provide evidence of microstructural white matter injury attributable to chronic intermittent hypoxemia and impaired cerebral autoregulation (Macey et al., 2008; Salsone et al., 2021; Sahib et al., 2022; Liu et al., 2024). Critically, no single biomarker class is likely sufficient to capture the multifactorial nature of OSA-related cognitive risk. A convergent, multimodal approach—combining fluid biomarkers (e.g., NfL, CRP), advanced neuroimaging (rs-fMRI, DTI), and clinically accessible metabolic indicators (e.g., HbA1c, adiponectin)—may yield a more robust and biologically grounded phenotyping strategy. Such an integrative framework aligns with the National Institute on Aging–Alzheimer's Association (NIA-AA) research criteria emphasizing the value of combining "A/T/N" (amyloid/tau/neurodegeneration) with vascular and inflammatory axes (Jack et al., 2018). Future predictive models should prioritize these pathophysiologically informed features to move beyond statistical association toward mechanistic stratification of OSA patients at highest risk for cognitive decline.

Further constraints include minimal baseline neuropsychological data (n = 10), which precludes meaningful within-subject analyses of cognitive change following CPAP treatment; attrition at the two-year follow-up (n = 16), limiting robust inference beyond the first year; and a single-center, predominantly male sample that, while representative of the local clinical OSA population, restricts generalizability to women or more diverse demographic groups. The study presented in this paper is only the beginning of a longer-term study, which will integrate clinical, polysomnographic and neuropsychological data for approximately 10 years, in order to evaluate the long-term risk factors for cognitive decline in OSA patients. Future multicenter studies incorporating fluid and imaging biomarkers, more balanced sex representation, and comprehensive baseline cognitive profiling would substantially enhance both predictive modeling and external validity.

6.8 CONCLUSIONS

This study provides robust evidence that OSA patients reporting subjective cognitive difficulties exhibit measurable deficits in attention, memory, and executive function, persisting despite effective CPAP therapy. Type 2 diabetes mellitus stands out as a potent, independent predictor of cognitive decline, underscoring the interplay between metabolic and respiratory pathologies in neurodegeneration. While traditional clinical variables lack sufficient predictive power for individual risk stratification, they offer valuable insights into population-level mechanisms. Future efforts must focus on integrating multimodal biomarkers, digital phenotyping, and personalized intervention strategies to mitigate the long-term cognitive burden of OSA.

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