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# Research on Sleep

*Edited by Marco Carotenuto*

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# Meet the editor

Professor Marco Carotenuto earned his master's degree in Medicine at the University of Campania 'Luigi Vanvitelli' in Italy in 2000. He specialized in child neuropsychiatry in 2005 after extensive training in the United Kingdom. He also obtained a Ph.D. in Behavioral Sciences and Learning Disorders in 2008. In 2018, he furthered his training at renowned Italian research centers to enhance his knowledge of diagnostic, therapeutic, and rehabilitative issues in neurodevelopmental disorders. Consequently, he became a Full Professor of Child Neuropsychiatry and Director of the Child Neuropsychiatry Unit at the University of Campania 'Luigi Vanvitelli.' Professor Carotenuto has authored over 200 scientific journal articles with primary research interests on childhood autism, sleep disorders, pediatric headaches and epilepsies, as well as neurocognitive and behavioral rehabilitation in children.

# Contents

# Preface

This edited volume is a collection of reviewed and relevant research chapters concerning the developments in sleep research. The book includes scholarly contributions by various authors and was edited by a group of experts who are pertinent to endocrinology. Each contribution comes as a separate chapter, complete in itself but directly related to the book's topics and objectives.

The book is divided into four sections: Conceptual Introduction to Sleep Maturation and Regulation, Sleep Changes during the Lifespan, Sleep in Pathologic Conditions and Sleep Measurement and Drug Therapy.

The Conceptual Introduction to Sleep Maturation and Regulation includes the following chapters:

1. Introductory Chapter: Research on Sleep

2. The Ontogenetic Development of Sleep from the Fetal Period through Adolescence: Functions and Electroencephalogram Characteristics

3. Perspective Chapter: Theory for Nervous System Dysregulation and Sleep Alterations

The following section, Sleep Changes during the Lifespan includes chapters:

4. Insomnia in Childhood and Adolescence

5. Sleep in Elderly

The third section, Sleep in Pathologic Conditions, includes:

6. Perspective Chapter: Sleep-Related Breathing Disorders – Comprehensive Approach to Obstructive Sleep Apnea

7. Obstructive Sleep Apnea Syndrome (OSAS) and Menopause

8. Thirty-Year Trends in Sleep Disorders and Cardiovascular Disease Risk

9. Epilepsy and Sleep

The last section of this book, Sleep Measurement and Drug Therapy, includes:

10. Perspective Chapter: Assessment of Subjective and Objective Sleep Quality from Wrist-Worn Wearable Data

11. Pharmacotherapy of Sleep Disorders

The target audience comprises scholars and specialists in the field.

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Section 1

# Conceptual Introduction to Sleep Maturation and Regulation

Chapter 1

# Introductory Chapter: Research on Sleep

*Marco Carotenuto*

## 1. Introduction

Sleep is an important topic for clinicians and researchers worldwide, considering that its alterations are the most common neurological disorders in all age groups [1]. From birth to adolescence, numerous and important changes occur in both the general structure and the finer details of sleep. After the necessary loss of fetal rhythm, a series of changes occur that lead to the appearance of spindles and a significant increase in the power spectrum of the delta band (0.2–4 Hz). This allows the recognition of sleep phases according to the current nomenclature (N1, N2, N3) starting from 9 months of age, replacing the previous definitions of quiet sleep and active sleep with the non-rapid eye movement (NREM) and rapid eye movement (REM) stages, respectively. Starting from the daily and natural stimulation of retinal photoreceptors by natural or artificial light, circadian rhythms are activated, regulated in humans by thousands of genes, whose alteration is implicated in metabolic and psychiatric pathologies [2].

This book is a collection of chapters written by international authors who are experts on sleep and its alterations, capable of providing their most modern experiences and perspectives. The main alterations of the physiological organization of sleep and its impact on the other regulatory systems of the organism are the backbone of this new text on sleep to be innovative and inspire new reflections on the topic.

Actually, it is now well understood that a good quality of life is closely tied to a correct quality of sleep. Therefore, any factors that disrupt the proper organization and rhythm of sleep are considered detrimental to long-term health [3]. Sleeping badly, however, as it depends on age in its impact and biological cost, similarly it also differs with respect to gender and this text also describes the differences related to gender with regards to sleep.

Unfortunately, the prevalent use of technological devices, especially starting from early childhood, has been linked to disturbances in sleep organization in children. This can move the biological clock forward, significantly impacting growth and neuropsychomotor development [4].

The sleep/wake rhythm becomes stable around the age of four, with sleep mostly occurring during the night. As adolescents go through puberty, their biological rhythm shifts forward (phase delay) despite feeling constantly drowsy due to sexual maturation. As a result, the quality of sleep starts to decline, attributed to the decrease in the power spectrum of the delta rhythm. This decline continues throughout life, leading to more frequent awakenings during sleep and, consequently, insomnia after the age of 35. It is important to understand that insomnia is a common sleep disorder, often linked to various causes such as obstructive sleep apnea syndrome (OSAS), restless legs syndrome (RLS), and periodic limb movement disorder (PLMD) [5, 6].

Regardless of the cause of dyssomnia, it is inevitable that loss of hours of sleep and poor quality of sleep are significant risk factors for health in general, mainly because they tend to increase cardiovascular risk. The quality of the organism, therefore, tends to decline due to the imbalance between sympathetic and parasympathetic regulation and the consequent neurohormonal variations, which have a significant impact primarily on the quality of sleep itself [7]. A vicious circle is established, perhaps also supported by the metabolic syndrome, of which OSAS is an integral part. It is known that OSAS predominantly affects males. However, the prevalence rate tends to increase significantly in women after menopause due to the physiological changes linked to this new era of life. The protective effect of estrogen on the body and brain of women tends to decrease until it disappears, making the concomitant frequent (and almost inevitable) physical changes more evident, such as the accumulation of visceral fat, which tends to infiltrate into the muscle tissue as well, making everyone the muscles are less elastic and, therefore, less ready to oppose the collapse of the upper airways, with snoring and therefore development of respiratory obstruction with intermittent nocturnal hypoxemia. This last aspect is the most severe parameter of OSAS, considering that it is difficult for the organism and the brain system to get used to an unstable situation. One of the most important consequences is the establishment of a state of subclinical inflammation and much more severe neuroinflammation with an impact on the cognitive and executive systems [8–11].

This book has also given ample space to the physiological adaptations of the organism and of sleep itself linked to the passage of time, therefore opening a window on sleep during the climacteric and in old age (topics that are normally little covered either by the literature in the field or by specific texts) [12, 13].

Therefore, sleep in old age is the effect of normal physiology and loss of the intrinsic regulatory mechanisms of sleep itself. It has now become much more unstable and delicate than in previous periods of life. Given the general aging of the population, especially on the European continent, knowledge of sleep medicine must no longer be excluded from the idea of sleep management therapeutic and pharmacological treatment of the senile patient, above all without reasoning in axioms. In general, polysomnographic studies on subjects over 70 are welcome so as to begin to understand better how sleep architecture adapts (or is the new interpretation) for this age of life, which is still not adequately protected in many respects [14].

Finally, the originality of this book in the panorama of such an important and relevant topic as sleep, is also to have tried to offer a new vision of the subject by including chapters on the impact of sleep on cardiovascular health, on metabolic diseases and above all to have summarized in one chapter all the possible pharmacological approaches based on the sleep disorder clinically oriented.

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Chapter 2

# The Ontogenetic Development of Sleep from the Fetal Period through Adolescence: Functions and Electroencephalogram Characteristics

*Gamirova Rimma and Marco Carotenuto*

## Abstract

The chapter considers issues of sleep ontogenesis from the prenatal period to adolescence and the neurobiological basis of changes in the structure of sleep as the brain matures, including the neurophysiological features of sleep in newborns, sleep state organization in premature infants, and the importance of fetal/neonatal rapid eye movement sleep for brain development and plasticity. It describes: (a) the dynamics of changes in sleep structure, (b) EEG specificity at different age periods, (c) sleep-related behavioral features in children, (d) biomarkers of normal and abnormal brain function, and (e) the pathophysiology of various childhood sleep disorders.

**Keywords:** sleep ontogenesis, EEG-monitoring, brain maturation, newborn sleep-wake cycle, childhood sleep disorders

## 1. Introduction

Sleep is a physiological state during which the brain performs different important functions. Moreover, at different age periods, the significance of sleep for the brain and for the body changes; sleep plays a particularly important role for the developing brain. Interest in a detailed study of the ontogenesis of sleep is not accidental, since age-related features of the changing structure of sleep and its functions in different periods of life give necessary information connected with the sleep disorders that appear at these times and their consequences for brain development, as well as it helps to prevent many disorders that subsequently occur in a child's behavior, learning ability, cognitive functions, emotions, memory, immune system, etc.

Healthy mature sleep of an adult is an alternation of Non-Rapid Eye Movement sleep (NREM sleep) and Rapid Eye Movement sleep (REM sleep), each of these states has not only its specific features but also dynamic changes both in duration and in the functions performed and pathognomonic signs on the electroencephalogram (EEG).

However, differentiation into states and stages of sleep in the early period of brain development does not appear immediately. Let us consider the architectonics of sleep, electroencephalographic features, and its functions in their relationship in different age periods of human life.

## 2. Sleep during intrauterine development

Sleep begins to form already during the intrauterine period of the child's development. Between 20 and 22 weeks of gestation is the period when circadian rhythms of the cardiovascular system, general motor activity, respiration, and the level of hormones in the fetal blood can be registered. It is necessary to mention that these fluctuations are synchronized with the alternation of day and night, and it is connected with the changes in the level of melatonin produced by the pineal gland of the pregnant woman and the level of glucocorticoids in her blood [1, 2]. The formation of the suprachiasmatic nucleus of the hypothalamus which is responsible for the establishment of these biorhythms occurs in the fetus by the 20th week of intrauterine development, and its maturation continues after birth. From the 28th to 31st week of gestation, a cyclical pattern of changes in the fetus's state appears with alternating periods of relative activity and rest regulated by the central nervous system (CNS) of the fetus. External stimuli influence these rhythms. The average duration of such episodes at 26–29 weeks of gestation is about 15–17 minutes, and after 34 weeks—28–41 minutes [3].

During the last 10 weeks of pregnancy, the fetal circadian rhythm becomes almost completely synchronized with the mother's circadian rhythm, responding to heart rate, cortisol, and melatonin release, as well as body temperature [4]. In the physiological state of the fetus, the following four variants are distinguished [5–7], which are the predecessors of various phases in the newborn:

- state 1F corresponds to state 1 of the newborn (called "quiet sleep", QS), which may be accompanied by infrequent short-term general movements of the body, most often in the form of jerking. Eye movements are not recorded. The fetal heart rate (HR) is stable, heart rate increases rarely, only during jerks;

- state 2F corresponds to state 2 of the newborn (called "active sleep", AS), during which eye movements, frequent and periodic general movements of the limbs and body of the fetus in the form of stretching and extension of the head are recorded, HR fluctuates, and during the period of movements its increase is registered;

- state 3F conditionally corresponds to quiet wakefulness; there are no general body movements, but fetal eye movements are registered. The HR is stable, tachycardia is absent;

- state 4F conditionally corresponds to active wakefulness; energetic, almost constant movements are observed, including turns of the body; eye movements are also registered. The HR is unstable, heart rhythm increases up to tachycardia [6, 7].

Researchers are cautious about defining 3F and 4F states as true wakefulness as these states are not often recorded in the fetus; in the uterus, there are all the

conditions for continuous sleep: isolation from the outside world, surrounding by amniotic fluid, the effect of maternal hypnogenic progesterone and other biologically active substances that support sleep, such as adenosine, prostaglandin D, neurosteroids, etc. [8]. The fetus is predominantly in the 2F state, which corresponds to active sleep; movements of the body and limbs during this phase affect the formation of interneuronal connections [6], and the fetus reacts maximally to sensory stimuli. In state 1F, endogenous processing of received information occurs, and the fetus maximally does not react to external stimuli [9]. QS (state 1F) can be recorded in the fetus after 26–27 weeks of gestation and until birth; the percentage of state 1F in the overall structure of fetal sleep is relatively small which can be explained by the immaturity of the thalamus (especially the reticular nucleus) and other inhibitory, synchronizing subcortical structures of the fetal brain up to 24–26 weeks of gestation [6].

## 3. Sleep EEG

Fetal electroencephalography (prenatal EEG, fEEG) is not routinely performed in medical practice, it includes any recording of electrical oscillations occurring in the fetal brain. Prenatal EEG can be used to detect and characterize fetal brain activity, such as sleep states, determine the level of reactivity, or assess the risk of epileptic seizures. Taking into account the difficulty of attaching electrodes to the fetus inside the uterus, to minimize the distance between the recording electrode and the neural activity of the fetal brain, the method of attaching electrodes to the mother's abdomen or cervix to record fetal activity in the third trimester can be used [10].

## 4. Sleep in newborns and children during the first year of life

During the first 30 days of life, a newborn does not yet have his/her own circadian rhythm, independent of the mother's rhythm. Already by 5–6 weeks after birth, sleep becomes longer during the night, and wakefulness prevails during the day [11]. By 12–14 weeks of age, a circadian rhythm is established with a longer break for nighttime sleep, shorter episodes of daytime sleep, and usually 1–3 hours of wakefulness preceding nighttime sleep. Consolidation of nighttime sleep occurs gradually as the child grows. Consequently, providing a cycle of darkness and light, for example in neonatal pathology units, may help to establish a circadian rhythm of sleep-wake states [12].

As the difference between the sleep of newborns and sleep in later periods of development is fundamental, specific terminology is used in scientific literature to describe the structure of newborn sleep. The following states are distinguished in the sleep structure: QS, or state 1 (analogous to the NREM phase of slow sleep in adults), and AS, or state 2 (analogous to the REM phase).

QS is defined by the absence of rapid eye movements, fewer body movements (excluding episodic twitching and jerking), reduced variability of respiratory rate and heart rate, higher muscle tone, and the recording of a slow-wave high-voltage EEG [13].

AS is characterized by more manifest restlessness, the presence of twitching, rapid eye movements, irregular breathing with frequent short episodes of respiratory pause (apnea), slow breathing (bradypnea), or, conversely, fast breathing (tachypnea). General atony of skeletal muscles, combined with an extremely pliable chest in newborns, can lead to the formation of paradoxical breathing in the AS phase [14]. Body

movements may be slow, worm-like, or sudden and jerky, and more frequent and longer lasting than those seen in REM sleep in older children or adults. During AS, newborns often grimace, tremor, suck, smile, and vocalize (i.e., cry, whine, etc.) [14].

Intermediate sleep (IS) is registered when it is impossible to refer the sleep stage to QS and AS. This stage is often recorded during the transition from one sleep phase to another (usually from AS to QS) or upon awakening. In preterm children born from 27 to 34 weeks of gestation, IS takes about 1/3 of the total duration of sleep, with a progressive decrease with age. Long-term persistence of IS in a child may be a sign of delay in CNS maturation [15].

Healthy infants typically have sleep cycles lasting an average of 50–60 min (range: 30–70 min). Newborns during the first 8 weeks of life spend up to 90% of the 24-hour day asleep [14]. Up to about 3 months of life, sleep cycles occur polyphasically throughout the day. Every 3–4 hours approximately it interrupts by awakening for feeding and care procedures [16]. Within one sleep cycle, the duration of REM sleep is 10–45 (on average 25) minutes, NREM sleep lasts about 20 minutes, and transition sleep—is about 10 minutes. During the night, the distribution of NREM and REM sleep is usually even [14].

At the age of six months, deep NREM sleep is more represented in the first half of the night, REM sleep—in the second. In newborns 4–12 weeks of age, sleep begins with the REM phase. But from 10 to 12 weeks after birth, the onset of sleep more often starts with the NREM phase.

Full-term babies sleep up to 16–18 hours a day, 50% of this time is in the REM phase [17, 18]. Very premature babies sleep continuously, with their eyes closed. However, they also have alternating episodes of AS and QS. During QS, babies do not move, and their breathing is regular (if it is spontaneous and not supported by artificial ventilation) [19].

During the first 3 months of life after the birth of a full-term baby, the EEG pattern gradually changes from neonatal to infantile. We can observe qualitative changes: the EEG begins to differentiate in accordance with the three stages of the slow sleep phase, and the proportion of AS decreases. By 6 months of life, three main stages specific to the slow sleep phase in adults can be clearly identified in most infants: stage 1 (drowsiness), stage 2 (sleep spindles, SS), and deep delta sleep. And already by 1 year, the proportion of sleep time spent in the REM phase decreases to 30%. The proportion of sleep in the slow sleep phase increases so that deep stage 3 of the slow sleep phase occupies a larger proportion of sleep time than, for instance, the REM sleep phase at the age of 12 months [20].

Sleep at an early age promotes cortical maturation and the formation of new brain connections, optimal neural and cognitive development of the brain [20].

A number of studies have shown that a process known as "synaptic re-reinforcement" occurs during sleep, which causes the consolidation of all skills and memory in the hippocampal region and cerebral cortex through the reactivation of N-Methyl-D-Aspartic Acid (NMDA) receptors and kinase signaling pathways [21].

According to the hypothesis of Roffwarg et al. [22], during the early period of a child's life, when stimulation associated with wakefulness and external environmental factors is very low, REM sleep, during which direct ascending stimulation of the forebrain occurs, promotes brain development. It is believed that the development of the nervous system in the neonatal period occurs as a result of endogenous stimulation, which occurs due to EEG oscillations. During rapid eye movement sleep in very premature infants, frequent (up to tens of thousands per day) myoclonic twitches of individual muscle groups occur. Numerous studies examining these movements

in neonates and in animal models indicate that such twitching of the limbs causes bursts of electrical activity-oscillations, reminiscent of the delta brush pattern, in the corresponding areas of the developing somatosensory cortex due to proprioceptive feedback [23, 24]. Delta brush patterns on EEG bursts of electrical activity with a frequency of 8–25 Hz in the cerebral cortex is specific for preterm infants [25]. In their study, Milh et al., simultaneously recording EEG and EMG of the limbs, showed that sporadic movements of the arms and legs in preterm infants of 29–31 weeks of conceptual age cause the appearance of delta brushes in the corresponding areas of the lateral and medial contralateral central cortex, respectively. Direct stimulation of the upper and lower limbs also provoked delta brushes in similar areas [26]. Blumberg et al. [27] concluded that myoclonic jerks during REM sleep in premature infants lay the foundation for future complex, automatic, and purposeful movements during wakefulness [28]. Movements during sleep and endogenous stimulation are important for ensuring cellular differentiation, neuronal migration, formation of new synapses and dendritic processes, formation of neuronal networks, and apoptosis processes [29].

By 3 to 4 months of life, the baby is increasingly in a state of wakefulness, which allows him/her to interact with others, he/she develop new skills. It is at this age that generalized movements occur less and less in the REM sleep phase. A decrease in the number of night awakenings after 3 months of life, a progressive increase in the continuity of sleep, and its effectiveness are revealed during polysomnographic studies [30].

Sleep consolidation disorder is found in 20–30% of infants up to 3 years of age, which is a common cause of parental complaints.

The immaturity of the circadian system in children during the first months of life sometimes leads to the presence of "free" sleep-wake rhythms in the child with a gradual daily shift in the time of night sleep to later and later hours. In some cases it leads to sleep-wake rhythm inversion. The formation of the circadian sleep-wake rhythm is influenced not only by light-dark alternation but also by such external stimuli as feeding, swaddling, bathing, and other actions accompanied by kinesthetic stimulation during the day [31].

### 4.1 EEG features

During the neonatal period, which is the first four weeks after full-term birth, the EEG reflects the rapid development of the newborn's brain. But the normal EEG of a healthy newborn has many characteristics that would be extremely pathological if recorded in adults, including, for example, diffuse slowing, intermittency, asynchrony, and decreased reactivity, but nevertheless, all the specific characteristics of this period appear sequentially in due time, having their own characteristics in premature and full-term children. Therefore, in EEG analysis the specificity of conceptual (CA), gestational (GA), and chronological age (ChA) of the newborn are taken into account.

Immediately after birth, a pattern called "tracé discontinu" may be registered on the EEG of a premature infant. Tracé discontinu (TD) is the earliest EEG activity that appears in a viable newborn at 22–23 weeks of gestation. These oscillations are described as short bursts consisting of a slow and fast rhythm, alternating with episodes of quiet activity with an amplitude of less than 25 μV [20, 32]. At a very early age of 22–24 weeks GA, the TD duration can vary from 5 sec to 8 min. With increasing age, the duration of interburst intervals (IBI) decreases. According to the literature, the longest acceptable duration of one interburst interval (IBI) is at 26 weeks of CA – 46 sec;

at 27 weeks – 36 sec; at 28 weeks – 27 sec; less than 30 weeks – 35 sec; 31–33 weeks – 15–20 sec; 34–36 weeks – 10 sec; and 37–40 weeks – 6 sec. At 26–27 weeks of conceptual age, it is not yet possible to clearly differentiate active/REM sleep from quiet/NREM sleep on the EEG [20]. A similar problem is also the differentiation of wakefulness and sleep on the EEG pattern. Therefore, the onset of sleep in a premature newborn is often determined by such a behavioral sign as prolonged eye closure. During this period, different sleep phases are also better identified by their behavioral correlates: for example, rapid eye movements and muscle myoclonus during AS, and the absence of eye movements or muscle twitching during periods of QS. TD episodes last about 80 sec at this CA, with an interburst interval of 29–46 sec. By 28–29 weeks of CA, differences between the three behavioral states (wakefulness, REM sleep, and NREM sleep) gradually emerge [32, 33].

The EEG during this period shows bursts of activity lasting up to 160 sec, alternating with periods of inactivity (interburst intervals [IBI], which now last ≤30 sec). Until 28–30 weeks of CA, the newborn's EEG shows little response to tactile and pain stimuli. Children of this age spend most of the 24-hour period in a state of active/REM sleep, and they are awake very little. At 30–31 weeks of CA, the EEG can differentiate wakefulness from active/REM sleep and quiet/NREM sleep. The EEG during active/REM sleep is continuous, while during NREM sleep it remains intermittent with bursts of activity lasting ≥3 sec, alternating with IBIs lasting ≤20 sec.

Thus, TD is the first EEG pattern that occurs during QS, allowing more or less distinct differentiation of wakefulness and sleep in premature newborns at 30–31 weeks CA. In the active sleep phase, the EEG is continuous. A rhythm called "tracé alternant" (TA) is also registered on the EEG of newborns. This EEG variant is an alternating type of EEG, TA replaces TD at 34 weeks of CA and is distinguished by periods of attenuation above 25 μV in amplitude. With TA, bursts of EEG activity of high-voltage and low-voltage waves of low frequency lasting 2–8 sec are recorded, interspersed with episodes of flattened EEG above 25 μV. Starting from 38 weeks of CA and further, TA continues to evolve into slow sleep, including more and more slow waves, eventually evolving into slow-wave sleep between 42 and 46 weeks of CA [20, 32–34].

In a healthy full-term infant, by 3–4 weeks of life, TA disappears, gradually being replaced by high-amplitude slow-wave activity [35, 36]. In visual EEG assessment, three criteria are necessary for differentiation between normal and pathological conditions: determining the duration of intervals between bursts and continuous brain activity, the dynamics of sleep structure, and the morphology of physiological sleep patterns and their evolution [33].

Further, the first significant sign of mature sleep, which is recorded on the EEG during the 12 months after birth, is the SS [37]. SS are present on the EEG during NREM sleep stage 2. Sometimes they appear at 43–44 weeks of CA, in most cases they are registered at 46–48 weeks of CA and must be present by 3 months of life [20, 38–40]. SS is represented by spindle-shaped increasing and decreasing in amplitude rhythmic groups of oscillations in the form of wave runs with a frequency of 11–16 Hz in the central leads with an amplitude of up to 20 μV [41]. SS at the beginning is still rare and short-lived in duration, but by the age of 3 months, they increase in amplitude (up to 30–50 μV) and duration. Up to 5 months of age, SS may not have a spindle-shaped form and manifest themselves as continuous activity lasting up to 10 sec or more. Amplitude SS asymmetry of more than 50% is possible. It is believed that a delay in appearance or an abnormal appearance of SS is an early biomarker

of metabolic disorders or brain pathology. More than 50% of SS are synchronous at 6 and 9 months, and already up to 70% at the age of one year. The appearance of SS depends on the synchronized activity of thalamocortical and thalamic reticular neurons, so changes in the morphology of SS on the EEG probably reflect the process of myelination and growth of dendrites of these neurons, and the process of maturation of the thalamocortical pathways [42]. It is known that sleep spindle anomalies can be found in children with intellectual disabilities [43].

Many researchers have proven that changes in the morphology of SS and/or their frequency and index during sleep are early EEG biomarkers of impaired maturation of thalamocortical connections, which reflects developmental disorders during the first year of life—this can potentially be used for early diagnosis of neurodevelopmental pathology [44].

K-complexes usually begin to be recorded on the EEG at 5–6 months of age, they are characterized by a superficially negative wave of 50–100 μV, lasting 200 msec, followed by a superficially positive wave of 30–50 μV and 300–500 msec, the maximal in the frontal EEG leads. K-complexes can appear spontaneously, in response to external stimuli, and can also be associated with SS [40, 45].

From the age of 5 months, it is possible to differentiate on the EEG the stage I of NREM sleep (drowsiness) characterized by a "sleep rhythm" expressed as a generalized high-amplitude hypersynchronous slow activity with a frequency of 2–6 cycles/sec, amplitude from 100 to 250 μV [45].

In stage N3, the slow-wave sleep phase (SWS) is easily recognized by the appearance of slow, high-voltage delta waves (0.5–2 Hz). Such high-amplitude EEG waves are a manifestation of the synchronization of neuronal activity [40].

EEG in the REM sleep phase the brain is activated and characterized by low voltage and mixed wave frequency (primarily theta and alpha waves), reminiscent of those observed in the waking state. REM sleep can be clearly distinguished with polysomnography (PSG), in particular by recording rapid eye movements [46].

The pattern of hypnagogic hypersynchrony first appears at 3 months of age and consists of paroxysmal bursts or runs of diffuse rhythmic high-amplitude slow waves of 100–350 μV with a frequency of 3–5 Hz, occurring suddenly and lasting several seconds, usually increasing and then decreasing in amplitude, with maximum representation in the central, frontal or frontocentral areas, often having spike components [45]. Their appearance indicates drowsiness and stage 1 of NREM sleep. This pattern usually disappears with deeper stages of NREM sleep but can be seen in stage 2 of NREM sleep. When present in NREM 2, some specialists call it hypersynchronous theta [45]. Hypnagogic hypersynchrony is present in 95% of all healthy infants and children after 6–8 months of age [20].

Thus, during brain maturation, EEG patterns change according to a predetermined scheme. Age-related features of the forms of various waves and patterns of sleep and wakefulness help specialists assess the normal maturation of the EEG, and accordingly of the brain. Most of the changes in the morphological and frequency characteristics of the EEG occur in the neonatal period, when they happen almost weekly from intermittent burst activity to the formation of continuous background activity recorded in older children and adults [47].

By the end of the first year of life, the EEG sleep pattern and PSG of the child approaches that recorded in adults, which allows for a clear differentiation between REM sleep and NREM sleep, as in adults.

## 5. Sleep in young children

Total sleep time gradually diminishes with age. Both the number and duration of daytime sleep decrease, so that 80% of children aged 1.5 years and older do not sleep during the day on some or all days. Typically, by the age of 1.5 years, a child sleeps once during the day and the duration of daytime naps averages 1–2 hours [48]. The average two-year-old child spends 10,000 hours asleep and 7500 hours awake [49]. The greater amount of sleep (especially REM sleep) in infants and young children reflects the crucial role of this physiological state in optimal brain development. The high percentage of REM sleep and its further reduction with age corresponds to critical periods of brain maturation [4, 50].

Thus, REM sleep provides neural activity in the brain that is favorable for its maturation [50, 51]. However, the proportion of the REM phase in the overall sleep structure gradually decreases and reaches adult levels in 5-year-old children—20–25% of the total sleep time. The duration of one sleep cycle is about 50–60 minutes in a 2–3-year-old child and gradually increases to 1.5 hours by the age of five. The average total sleep duration changes from 12.8 hours (one-year-old children) to 11.7 hours (children aged 13–35 months) and 10.4 hours (children aged 3–5 years) [50, 52].

During the first years of life, the process of consolidation of night sleep continues, the child's overall need for sleep decreases, and the need for daytime sleep gradually disappears: the proportion of children sleeping during the day becomes lower, the number of episodes of daytime sleep and its duration reduce. By the age of three, children have only one episode of daytime sleep [53, 54].

The frequency of detected night awakenings in children decreases from 34% during the first year of life to 13.4% at the age of 4–6 years [53].

At this age, there are specific features of the child's awakening. Full awakening (awakening, behavioral awakening, wakefulness) should be distinguished from the awakening reaction (arousal. Arousal is a short-term activation of CNS, manifested either by an increase in the frequency of the EEG rhythm, or by an increase in muscle tone and body movements. There are special criteria that determine arousal in young children [20, 55].

Various sleep problems occur in 21% of young children and persist until the age of three [56].

By the end of the first year of life, healthy cognitively intact children may develop separation anxiety due to the formation of the idea of the permanence of their family, which leads to problems in going to bed explained by the fear of separation from parents. Separation anxiety reaches its maximum by one and a half years and usually persists until two years. The child can be anxious when he/she is forced to part with his parents during sleep [57]. At the age of 2–3 years, the child takes part in family activities, and it influences the resistance to going to bed when his/her parents do not do it. At the age of 3–5 years, problems with going to bed can be connected with fear of the dark, nightmares, etc. [58].

### 5.1 EEG features

At the age of 6–24 months, SS, the typical patterns of the second stage of slow sleep, have a sharp superficial negativity in the central areas. SS in children can occur independently at two different EEG frequencies and are maximal in two different leads: slow, 11–12.75 Hz maximum over the frontal areas, and fast, 12–14.75 Hz over the central-parietal areas. SS at this age continues to decrease in frequency and

gradually increase in duration and amplitude [59] which reflects the maturation of thalamocortical structures [60]. SS is combined with polymorphic bioelectrical activity, sometimes preceded by vertex potentials or K-complexes –bilaterally synchronous, predominantly expressed in the central area, biphasic sharp waves in which the negative sharp potential is accompanied by a slow positive deflection. K-complexes can be induced by presenting a sound stimulus without awakening the person. K-complexes have an amplitude of at least 75 μV. They may not always be distinct in young children, as well as vertex potentials. K-complexes begin to differentiate especially clearly by 1.5 years; the surface-negative component has the greatest amplitude and is most clearly defined at the age of 3–5 years [20].

Vertex potentials are recorded during stages 1 and 2 in the slow sleep phase and are maximal in amplitude in the central EEG leads in the form of a negative peaked wave. Rare wide immature vertex potentials appear in the central leads at 6 months of age. However, vertex potentials resembling those observed in older children and adults first appear later, at 16 months of age. Beginning at about 30 months of age, vertex potentials in young children often occur as repetitive runs. At 3 years of age, vertex waves most often have high-amplitude (>250 μV) and sharp peaks, sometimes misidentified as epileptiform activity. Vertex waves at this age have an initial negative phase (lasting only 1/8 of a second), followed by a subsequent positive wave of about 1/6 of a second, sometimes ending in a slow negative sharp wave [20, 61].

In the state of falling asleep and increased sleepiness in a child, there can be registered EEG phenomena that are normally not detected in adults, such as rhythmic theta activity recorded in the anterior parts of the brain, and hypnagogic hypersynchrony—it is recorded in all children from 6 to 8 months to 2–4 years and after that gradually disappears. The high-amplitude theta rhythm of falling asleep manifests itself steadily throughout the 1st–2nd year of life [20].

## 6. Sleep in school-aged children and adolescents

Between the ages of five and 19, the percentage of REM sleep remains relatively stable at around 25% of total sleep time, while the proportion of slow-wave sleep, stage 2, increases with a concomitant decrease in the deep phase of slow-wave sleep, stage 3. The duration of one sleep cycle gradually increases from 60 min in children under one year, to 85–115 min at ages 8–12, and is stable at around 90 min in adults. This results in fewer sleep cycles occurring over a full night period, but the percentage of time spent in bed during sleep (sleep efficiency) remains constant from early childhood through adolescence [62].

In adolescents, due to significant hormonal influences that occur during this period, the brain undergoes significant morphological changes: the thickness and surface area of the gray matter gradually decrease, while the volume of the white matter of the brain increases, with structural changes occurring actively in the frontal lobe (especially in the area of the anterior cingulate gyrus and orbitofrontal cortex) [63].

By the age of seven, the need for daytime sleep completely disappears. There are no differences in the need for daytime sleep in children related to gender. In schoolchildren, the quantity and quality of sleep are negatively affected by high school workloads, sports, and other additional extracurricular activities. Sleep disorders are frequent at this age. They are especially provoked by addiction to gadgets, psychoactive substances, and caffeine [64, 65]. Sometimes sleep disorders manifest as daytime sleepiness, as well as behavioral and emotional disturbances [66].

At this age, a notable decrease in the representation of the slow-wave component in the overall sleep structure is observed (according to some data, by 40%) [50, 66]. This phenomenon is associated with the programmed reduction of cortical synapses observed in adolescence. This pattern is accompanied by a decrease in the expression of the homeostatic process S, the tendency of the adolescent to a longer period of wakefulness [67]. Falling asleep for a teenager takes more time than for prepubertal children [68, 69] which leads to "evening" chronotype (going to bed later and getting up later) [70, 71].

Disrupted sleep and wake patterns can affect mood and behavior at this age. In children aged 7–13, a higher susceptibility to depression was associated with a later bedtime [72]. There are various hypotheses to explain how circadian rhythm dysfunctions may contribute to the physiopathology of depression. One hypothesis suggests that genetic mutations in certain genes responsible for biorhythms may cause changes in the internal clock [73]. These circadian disruptions can alter the rhythmic activity of neurotransmitter systems, including dopamine and serotonin involved in mood regulation [73].

During adolescence, in puberty, melatonin levels decrease due to activation of the hypothalamic–pituitary–adrenal system leading to the release of luteinizing hormone during sleep and sex hormones that inhibit the release of melatonin. A decrease in melatonin levels leads to a deterioration in the ability of a teenager to fall asleep [74].

Increased social activity, academic and extracurricular loads, stress, abuse of gadgets, emotional instability, and psychoactive substances lead to chronic sleep deprivation. Chronic deprivation leads to behavioral disorders, mood instability, weight gain, metabolic disorders, and problems with academic performance, which in turn worsens sleep disorders [64].

### 6.1 EEG features

Between the ages of 3 and 13, vertex potentials develop into sharp peaks, mostly surface waves, similar to those observed in adults [20].

K-complexes from 3 to 12 years of age occur in series of 3–8 in 1–3 sec, and later in the series may consist mainly of an initial surface-negative component; in adolescence, they typically repeat at every 1–3 sec providing full expression of the biphasic or triphasic waveform [20].

The delta sleep activity index in NREM stage 3 decreases by more than 60% between the ages of 10 and 20 years [70, 75]. The percentage of slow-wave delta activity also declines during repeated periods of NREM sleep within a single night. Longitudinal studies have shown that the EEG delta sleep index begins to decline around 11.5 years, decreasing by 60% nearly 16 years. The decline in delta waves begins earlier in females than in males (consistent with observed age-related changes in gray matter volume on neuroimaging) but then slows, with the rate of decline becoming equal in females and males by 16 years [50, 75].

Hypnagogic synchrony of NREM sleep stages 1–2 is becoming less common, present in 10% of 11-year-olds, and even less common after 12–13 years [20].

## 7. Conclusion

Thus, the most noticeable changes in sleep structure during ontogenesis are: (1) a gradual decrease in total sleep time; (2) a consolidation of sleep periods at night and

an increase in wakefulness during the day; (3) a decrease in the NREM stage 3 slow-wave activity (SWA) index on the EEG; and (4) a steady decrease in the proportion of REM sleep [76]. With regard to the development of brain functions, the following provisions are key during the ontogenesis of sleep: (1) REM sleep (which is predominant in intrauterine life and the neonatal period) is a source of endogenous stimulation of neurons necessary for the development of brain maturation; (2) sleep is a state during which consolidation of experience occurs, which is especially necessary during the developmental period; and (3) the main function of sleep is to reduce the number of useless synapses while maintaining and strengthening a subset of necessary ones [50, 77].

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Chapter 3

# Perspective Chapter: Theory for Nervous System Dysregulation and Sleep Alterations

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## Abstract

Understanding nervous system dysregulation can explain many health conditions based on the alteration of physical and physiological factors that are related to diseases and behaviors that are still understood today. The "sympathetic nervous system" and the "parasympathetic nervous system" are major subdivisions of the nervous system responsible for sensations of danger and safety. The "sympathetic nervous system" prepares the body to face a "fight-or-flight" response to present threats that create stress, responding to how to mobilize the natural body resources to face potential threats. On the other hand, the "parasympathetic nervous system" is the natural body mechanism for relaxation, helping us recuperate and maintain a state of calm that allows us to have a good sleep. In this research paper, the goal is to analyze and define a "theory for nervous system dysregulation and its consequences as reflected in sleep pattern alterations."

**Keywords:** nervous system, emotions, endocrine system, hormones, neurotransmitters

## 1. Introduction

"Sleep alteration" is a condition that results in changes in the way that we sleep as constant interruptions, and "sleep disorder" affects our quality, amount, and timing of sleep, making it difficult to perform regular daytime activities. For most people, it is taken as something that is very common, but the reality is that it is a serious medical condition that impairs natural, normal emotions, affects cognition and physical behavior and causes lower alertness and concentration. When "sleep deprivation" is a continuous, accumulated impairment of functions, it shows a state of "sleepiness," as the desire or need for more sleep creates "anxiety" that increases the longer we stay awake. This condition is reflected in diminishing our quality of life, creating unnecessary confusion when taking even simple decisions and altering how our body's internal functions respond to handle a variety of situations in our daily lives, that is, diminishing our ability to drive safely and increasing our risk of developing health problems. The main goal of this research paper is to analyze and define a "theory for nervous system dysregulation, and its consequences as reflected in sleep pattern alterations."

## 2. Nervous system

The "nervous system," identified as the control center of the body, consists of three main parts: the brain, spinal cord, and nerves, which play an important role in everything that the human body does, such as movement, thinking, and feeling. Another important function of the brain is the regulation of organ functions even without thinking about them, such as digestion regulation, thinking organization, sweating, blinking, and many others. The nervous system keeps track of the inside and outside of our body, deciding how to respond to any situation. "Nervous system" contains the "central nervous system (CNS)," which includes the brain and spinal cord, and the "peripheral nervous system (PNS)," which includes the nerve branch of the spinal cords. All is handled by the "autonomic nervous system (ANS)" which has two major subdivisions to keep track of actions to follow: the "sympathetic nervous system" handles voluntary movements, and the "parasympathetic nervous system" regulates involuntary movements, including all activities without thinking about them, as shown in **Figure 1B**. It is very important to note that the "nervous system" uses "neurotransmitters" as chemical messengers to help nerve cells or neurons communicate with each other.

In general, we can state that "nervous system dysregulation" is a physiological state of imbalances between the "sympathetic and parasympathetic systems" on sensations detected of danger and safety [1].

### 2.1 Nervous system affects all symbiotic system

"Human symbiotic systems" are the close and long-term biological interaction between two different biological entities, systems, or organs. There are many systems in the human body, and the main ones are the "nervous system," "digestive system,"

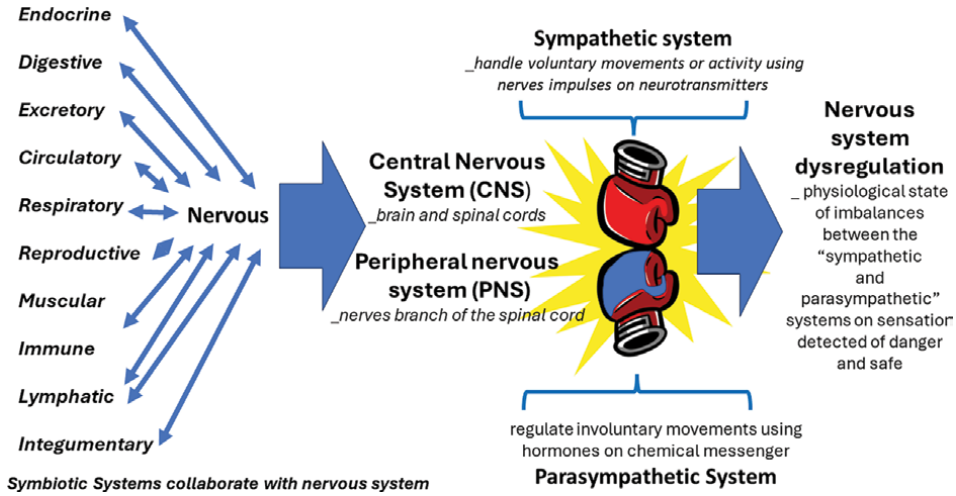


**Figure 1.**
*(A) Symbiotic system interaction with the nervous system. (B) Nervous system dysregulation is a physiological state of imbalances between the "sympathetic and parasympathetic" systems on sensations detected of danger and safety.*

"excretory system," "cardiovascular or circulatory system," "respiratory system," "reproductive system," "muscular system," "immune system," "lymphatic system," "endocrine system," and "integumentary system" [1]. Focusing on the interaction of the "nervous system" with other in the symbiotic systems are shown in **Figure 1A**, and explained as follow:

- "Endocrine system" and "nervous system" works frequently to control and regulate many human body functions that are detected as behaviors. Where the nervous system duration nerves impulses and neurotransmitters that act very fast with short duration, meanwhile the "endocrine system" uses hormones as chemical messengers that act slowly with longer lasting effects alterations. Mainly the timing difference to act between "endocrine and nervous system" trigger anxiety, anguish, panic, and others for more info see [2].

- The "digestive system" is a group of organs working together to convert food into energy and basic nutrients to feed the entire body. It has its own nervous system, identified as the "enteric nervous system" and also known as the "second brain," with over 100 million nerves that control digestion independently without conscious awareness, very closely related to the "gut-brain" that is closely connected to the human brain through a network of nerve bidirectional pathways. This connection explains why stress, anxiety, and altering our digestion raise the possibility of developing a chronic digestive condition such as irritable bowel syndrome or inflammatory bowel diseases [3].

- The "excretory system" is the renal system to eliminate waste from the body, regulate blood and blood pressure, control levels of electrolytes, and regulate blood pH, which refers to acidic or alkaline values. They are the kidneys, ureters, and urinary bladder to remove metabolic wastes from the body as urea from the bloodstream; the kidneys filter toxic substances to avoid accumulation as nitrogenous; and other organs such as the liver, large intestines, and skin excrete specific metabolic waste. The "excretory system" functions with the digestive system" and, by consequence, with the "nervous system," maintains a stable internal "homeostasis." "Excretory system diseases" refers to the array of diseases that cause improper functioning of the excretory system. Urinary diseases encompass both kidney dysfunctions and urinary tract infections.

- "Cardiovascular or circulatory system" is where the heart and blood vessels work together to circulate the blood throughout the body to provide oxygen and nutrients such as amino acids, electrolytes, carbon dioxide, hormones, etc. It is affected by the "nervous system" in different ways, developing symptoms such as impaired metabolism where the normal reactions are disrupted, causing inflammation, raising blood pressure, increasing our risk of cardiovascular diseases, and others. Common circulatory system medical problems include high blood pressure (hypertension), atherosclerosis, coronary artery disease, heart attacks, heart failure, strokes, and others [1].

- "Respiratory system" carries out the exchanges of gases at breath, altering the amount of red blood cells that collect the oxygen from the lungs and carry it to the different parts of the body where it is needed and collect the carbon dioxide

that transports back to the lungs to be expelled from the body. The nervous system and brain steam control breathing, chest movement, the heart's blood circulation, and brain oxygen. "Respiratory system" has complex interactions between the central and peripheral "nervous system," altering the way we breathe, i.e., irregular breathing, disrupting sleep, and in some people, "sleep apnea" that decreases oxygen levels and others [4]. "Reproductive system". It is a set of sex organs within an organism working together for the purpose of sexual reproduction.

- "Reproductive system" and "nervous system" work together to regulate electrical and chemical processes. The nervous system directly controls the reproductive and endocrine systems, creating impulses as orders to secrete hormones to release eggs and sperm. Common alterations are caused by emotional factors such as depression, anxiety, etc. Physical factors such as pain and discomfort, inflammation, hormone desynchronization, etc.

- "Muscular system" permits movement of the body, maintains posture, and circulates blood throughout the body. The muscular system allows for movements by contracting and relaxing; it consists of skeletal, smooth, and cardiac muscles. "Muscular system" and "nervous system" work together as a "neuromuscular system" to move the body as needed. Musculoskeletal disorders are a group of conditions that can affect the muscles, bones, joints, tendons, ligaments, cartilage, and spinal disks, They may cause pain, loss of mobility, swelling, and stiffness. Even people may get paralyzed under stress, anxiety, or fear, and in some cases, this is extreme identified as "anxiety paralysis," where amygdala, as a mayor place processing center for emotions in the brain could shut down movement, making difficult to speak and think to conserve energy [5].

- "Immune system" functions to protect the body against injuries, illnesses, and disease. After people recover from infection with a virus, the "immune system" retains a memory of it. Normally, the immune cells and proteins that circulate in the body can recognize and kill the pathogen if it is encountered again, protecting against disease, and reducing illness severity. "Immune systems" can be weak, underactive, overactive, or even attack your body by mistake. Immune system problems can cause symptoms, allergic reactions, or persistent illnesses. Long-term immune protection involves several components known as "antibodies". "The immune system" acts with the "nervous system," both of which regulate immune responses through the release of neurotransmitters, neuropeptides, and neurohormones [6]. Where:

    - "Neurotransmitters are chemical messengers" carrying chemicals from one neuron to another target cell, such as a nerve cell, muscle cell, or gland.

    - "Neuropeptides" are short chains of amino acids that serve as "neurotransmitters," each amino acid connected by peptide bonds. They are relatively large and composed of 3 to 36 amino acids. They are the most diverse class of signaling molecules in the brain, engaged in many physiological functions.

- "Neurohormones" are groups of substances produced by the "neurosecretory system" and released by neurosecretory cells (neuroendocrine cells) in the "hypothalamus" and "pituitary gland" that act on the nervous system and are secreted into the blood stream as "hormones."

- The "lymphatic system" is a network of tissues and organs that help rid the body of toxins, waste, and other unwanted materials. The primary function of the "lymphatic system" is to transport lymph, as a fluid containing infection-fighting white blood cells, throughout the body. It is in charge of clearing metabolic waste from the gasps between cells in the "central nervous system." There is a brain's dedicated waste clearance system known as the "glymphatic system," which is managed by the brain's glial cells and moves cerebrospinal fluid as a liquid surrounding the brain and spinal cords for removing cell waste. Structural and functional features of central nervous system lymphatic vessels. It is a vital part of your immune system; it protects against infection and destroys old or abnormal cells that the body does not need [7]. Some common issues are infection, inflammation, strep throat, swelling, and others [8].

- "Integumentary system". It regulates body temperature associated with the "sympathetic nervous system." It contains in the skin sensory neurons, where nerves end, for sending messages to the "CNS," where they are processed, including information about sensations such as touch, pressure, temperature changes, pain, and others. Where the "CNS" responds accordingly. The "integumentary system" also has in the skin and its appendages tiny glans that secrete sweat and oil used to regulate the body temperature. "Integumentary system" could present various types of disease, disorders, and injuries. From benign bacterial infections as fungal infections, inflammatory disorders as eczema, seborrheic dermatitis, psoriasis, etc., to severe skin cancer and even severe burns.

The main interaction of the "nervous system" collaborating with others "symbiotic system" are summarized to facilitate consulting on **Table 1**.

Conclusions: The nervous system affects all symbiotic systems.

- It is not surprising that "nervous system dysregulation" also affects to some degree the normal function of other "symbiotic systems" and, as a consequence, our sleep quality.

- "Nervous system dysregulation" can be observed when the nervous system is constantly overwhelmed and has an overactive generation of "neurotransmitters". The body responds with stress and anxiety, and many types of organs in our body that have interdependency with other systems alter their normal function with "sleep alterations," a condition in which constant sleep is disturbed for a long duration of time or "sleep disorders," affecting our quality, amount, and timing of sleep and making it difficult to perform regular daytime activities. Then "nervous system dysregulation" alters the normal function of other symbiotic systems.

| Symbiotic system | Description | Interaction | Nervous system | Alter symptoms |
|---|---|---|---|---|
| Endocrine | Control and regulate many human body functions that are detected as behaviors | "Endocrine system" and "nervous system" works frequently to control and regulate many human body functions that are detected as behaviors | "Endocrine system" Use slow–longer duration hormones as chemical messenger versus "nervous system" use fast-short duration nerves impulses and neurotransmitters | Mainly the timing difference to act between "endocrine and nervous system" trigger anxiety, anguish, panic, and others [2]. |
| Digestive | Group of organs working together convert food into energy and basic nutrients | Digestive nervous systems identified as "enteric nervous system (ENS)" | ENS has million nerves ending control digestion independently without conscious awareness | This connection explains why stress, anxiety and altering our digestion and even the possibility of developing a chronic digestive condition such as irritable bowel syndrome or inflammatory bowel diseases |
| Excretory system | Renal system eliminates wastes from body, regulate blood, blood pH and blood pressure, electrolytes | Work with the "digestive system" and by consequence with the "nervous system" | Maintain a stable internal homeostasis with balance of "digestive and nervous system" | "Excretory system diseases" refers to the array of diseases that cause improper functioning of the excretory system. Urinary diseases encompass both kidney dysfunctions and urinary tract infections |
| Cardiovascular or circulatory | Circulate blood throughout body to provide oxygen and nutrients as amino acids, electrolytes, carbon dioxide, hormones etc. | It is affected by the "nervous system" in different ways developing symptoms such as impaired metabolism | Where normal chemical reactions as disrupted, causing inflammation, raise blood pressure, increasing risk of cardiovascular diseases | Medical problems include high blood pressure, atherosclerosis and coronary artery disease, heart attacks, heart failure, strokes and others |
| Respiratory | Exchanges gases breathe, altering amount of red blood cells that collect oxygen and circulate to expel CO2 | Complex interactions between central and the peripheral "nervous system" altering breath rhythm and length | The nervous system and brain steam control breathing, chest movement, heart's blood circulation and brain oxygen | Irregular breathing, disrupting sleep, and in some people "sleep apnea" that decreases oxygen levels and others |
| Reproductive | Set of sex organs within an organism | "Nervous system" works together to | Nervous system controls directly | Inflammation, hormones |

| Symbiotic system | Description | Interaction | Nervous system | Alter symptoms |
|---|---|---|---|---|
| | working together for the purpose of sexual reproduction | regulate electrical and chemical processes. | reproductive and endocrine systems, creating impulses to secrete hormones for release eggs and sperm. | desynchronization, sexual dysfunction, others |
| Muscular | Permits movement of the body, maintains posture, and circulates blood throughout the body. The muscular system allows for movements by contracting and relaxation | Muscular and nervous system works together as a "neuromuscular system" to move the body as needed | Musculoskeletal disorders are group of conditions that can affect the muscles, bones, joints, tendons, ligaments, cartilage, and spinal disks. | It may cause pain, mobility, swelling, and stiffness. It is possibly get paralyzed under stress, anxiety or fear, even "anxiety paralysis" |
| Immune | Protect the body against injuries, illnesses and disease. After recovering from infection with a virus, the "immune system" retains a memory of it. | Acts with the "nervous system", for regulates immune responses releasing neurotransmitters, neuropeptides and neurohormones | "Neurohormones" are groups of substances produced by specialized neurosecretory cell (neuroendocrine cells) and secretes into the blood circulation as "hormones" | "Immune system" can be weak, underactive, overactive, or even attack your body by mistake |
| Lymphatic | It is a network of tissues and organs that help rid the toxins of the body, waste, and other unwanted materials. | Clearing metabolic waste from the gasps between cells in the "central nervous system" and is a vital part of your immune system, lymphatic system protects from infection and destroys old or abnormal cells | Glymphatic system is a brain's dedicated waste clearance system that managed by the brain's glial cells and moves cerebrospinal fluid as a liquid surrounding the brain and spinal cords for removing cells waste | Some common issues are infection, inflammation, strep throat, swelling, and others |
| Integumentary | It regulates body temperature associated by the "sympathetic nervous system". | It contains in the skin sensory neurons where nerve end, for sending messages to the "CNS", | Nervous system processed sensory information including sensations as touch, pressure, temperature changes, pain, and others | From benign bacterial as fungal infection, inflammatory disorders as eczema, seborrheic dermatitis, psoriasis, etc., to severe as skin cancer and even severe burns |

**Table 1.**
*Summary of the interaction of the "nervous system" collaborating with others "symbiotic system".*

## 3. Brain process emotions

There are regions in the brain where "emotions" are processed, the majority of them are found in the "limbic system." It is a group structure in the brain involved in the formation of long-term memory, and the handling of emotions, motivation, behaviors, and the sense of smell. "Limbic system" has complex interconnections [9, 10], but its primary components are "thalamus," "hypothalamus," "basal ganglia," "cingulate gyrus," "hippocampus," and "amygdala," as shown in **Figure 2A**.

### 3.1 Limbic system

The limbic system's main structures and functions are explained as follows:

- "Thalamus" is a pair structure at the center of the "limbic system," where there are many neural pathways from and to the cerebral cortex, and it is the main place to organize sensory signals sent to higher brain functions and handle motor signals. The "thalamus" maintains alertness and directs attention to sensory events. "Thalamus" malfunctions or damage are detected as motor impairments, attention problems, insomnia, memory loss, vision loss, and even motor system disorders

- "Hypothalamus" has the main basic function of maintaining a steady interstate, known as "homeostasis." It works with the "endocrine system," as explained in the section on the nervous system, which affects all symbiotic systems and regulates sexual activity. It also controls emotions and states such as hunger, thirst, body temperature, blood pressure, and heart rate, helping to control "stress." "Hypothalamus" malfunctions or damage are detected as acute stress, aggression, fatigue, weight changes, sex drive, and others.

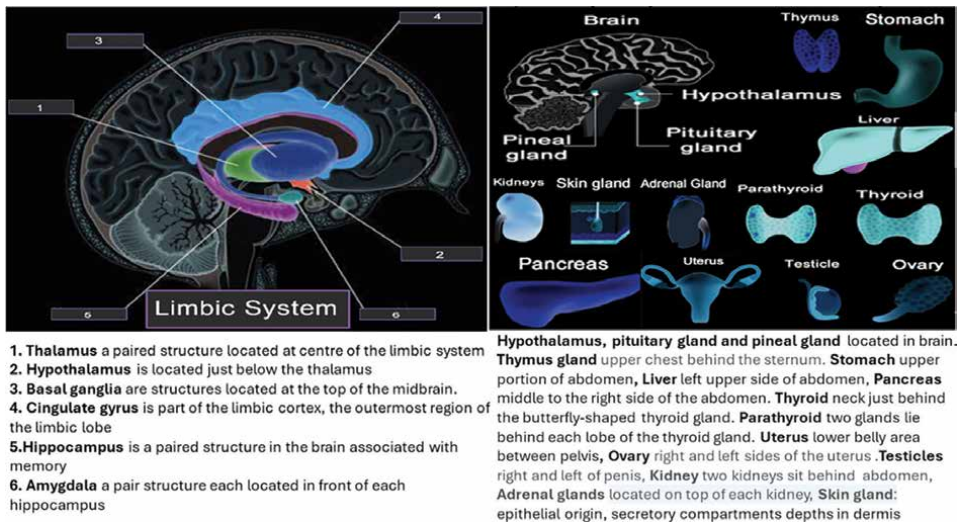


**Figure 2.**
*(A) Primary components in limbic system brain structures for handling emotions, motivation, sense of smell and behaviors. (B) Primary components in the endocrine system.*

- "Basal ganglia" has the main function of regulating voluntary body movements, balance, and posture. It helps with cognitive and emotional behaviors. "Basal ganglia" malfunctions or damage are detected as tremors, involuntary body movements, and abnormal postures, all related to the symptoms of Parkinson and Huntington disease.

- "Cingulate gyrus" helps with the emotion's regulation, some behaviors, such as aggression, pain, and controls autonomic motor functions. It is related to anxiety disorders, addiction, depression, and bipolar disorder. Schizophrenia, Alzheimer disease, and others.

- "Hippocampus" is associated with storage for long-term memories, spatial processing, and navigation. It is the place for neurogenesis, the process of creating new nerve stem cells. Malfunctioning and damage lead to memory impairment, amnesia, and detected cell loss in the hippocampus in Alzheimer's disease.

- "Amygdala" has the function of mediating emotional learning and behaviors. It helps in the modulation of memory storage, focusing on the ones associated with strong emotions. It prepares the body for emotional situations by recognizing threats and preparing the "fight-or-flight reactions," increasing heart rate and breathing rate. Malfunctioning and/or damage led to excessive aggression, irritability, poor emotional control, an inability to recognize emotions as fear, and others taking risky decisions.

The main functions, characteristics, and symptoms of each main structure of the limbic system are summarized for easy consultation in **Table 2**.

### 3.2 Where emotions are processed on the limbic system

"Emotions" are complex physiological processes that can manifest as physical behaviors and physiological activities. "Emotions" processing has an extraordinary complexity, and many of them are combinations of others' emotions. Finding where emotions are processed on the limbic system in the brain, some methods for measuring brain electric or metabolic activity are known as "brain activity detection." Five of the most frequently used techniques are:

- Functional Magnetic Resonance Imaging (fMRI) allows us to measure the brain's blood flow, reflecting its neural activity.

- Electroencephalography (EEG) allows measuring brain electric activity for the detection of seizures or epilepsy.

- Electrocorticography (ECoG) allows measuring brain electric activity using electrodes implanted on the surface of the cortex.

- Somatosensory Evoked Potentials (SSEP) allows measuring how electricity flows through the brain and body in response to sensory stimulations.

- Angiography uses contrast dye and X-rays to visualize brain blood vessels.

| Limbic system | Main function | Characteristics | Symptoms of malfunctioning |
|---|---|---|---|
| Thalamus | Organize sensory for signal send to higher brain functions for motor signaling | Maintains alertness and directs attention to sensory events | Motor impairments, attention problems, insomnia, memory loss, vision loss, and motor system disorders |
| Hypothalamus | Maintaining a steady interstate known as "homeostasis" | Works with the "endocrine system". controls emotions and states for helping to control stress | Acute stress, aggression, fatigue, weight changes, sex drive and others |
| Basal ganglia | Regulating voluntary body movements, balance, and posture | Helps with cognitive and emotional behaviors | Tremors, involuntary body movements, abnormal postures, related with symptoms for Parkinson and Huntington disease. |
| Cingulate gyrus | Help on the emotion's regulation, some behaviors | Handle emotions as aggression, pain, and control autonomic motor functions | Anxiety disorders, addiction, depression bipolar disorder. Schizophrenia, Alzheimer disease |
| Hippocampus | Associated with storage for long-term memories, spatial processing and navigation | It is the place for neurogenesis, the process for creating new nerve stem cells. | Memory impairment, amnesia and detected cell loss in the hippocampus in Alzheimer disease. |
| Amygdala | Mediating emotional learning and behaviors | Memory storage, focusing on the ones associated with strong emotions. Prepares the "fight-or-flight reactions" | Excessive aggression, irritability, poor emotional control and inability to recognize emotions as fear taking risky decisions. |

**Table 2.**
*Limbic system main component indicating symptoms and emotions.*

Applying electroencephalography-based recognition for emotions in virtual reality environments [11], it is possible to detect brain activity for the six basic emotions identified as "anger," "happiness," "sadness," "fear," "surprise," and "disgust." The basic emotions are defined as:

- "Anger" is a strong emotion of displeasure or hostility and is sometimes extremely hard to control. It is associated with activity on the right hippocampus, the amygdala, and both sides of the prefrontal cortex and the insular. Other emotions derived from anger are mad, irritated, disgusted, furious, raging, and others.

- "Happiness" is an emotion for feeling pleasure or contentment. It is especially important to keep in balance with other emotions in life. It is associated with activity within brain areas such as the right frontal cortex, precuneus (located on the medial surface of each cerebral hemisphere), left amygdala, and left insula, located deep within the lateral sulcus of the brain in both hemispheres. Other emotions derived from happiness are joyful, pleasing, optimistic, delighted, and others.

- "Sadness" is an emotion of unhappiness showing extreme despair and anguish. It is hard to control and could evolve into depression. It is associated with activity in the right occipital lobe, left insula, left thalamus, amygdala, and hippocampus, where specific memories could bring sadness recursively and evolve into depression. Other emotions derived from sadness are upset, crushed, weepy, depressed, desperate, and others.

- "Fear" is an emotion as a response to a threat or harm, which could be physical, emotional, physiological, real, or imaginary. It is a normal natural emotion as a protective response during the "fight-or flight" decision, but when the reaction is out of proportion, it is a problem, as seen in mental conditions such as panic disorder, anxiety disorder, phobias, and others. It is associated with activity in the bilateral amygdala, hypothalamus, and left frontal cortex area. Other emotions derived from fear are frightened, panicked, scared, terrified, and others.

- "Surprise" is an emotion with extreme opposite responses, feeling good or bad. It is associated with activity in the in the bilateral inferior frontal gyrus and the bilateral hippocampus. Other emotions derived from surprise are amazement, astoundment, confusion, and others.

- "Disgust" is an emotion as a response to something unpleasant or offensive. It is associated with activity in the left amygdala, left inferior frontal cortex, and insular cortex. Other emotions derived from disgust are avoidance, repulsion, revolt, sickness, and others.

The six basic emotions describing their specific brain activity location, and some of their emotions derived are summarized for easy consultation on **Table 3**.

Conclusions for brain-processed emotions

- It is the brain-limbic system where emotions are processed.
- There are six basic emotions, and it is possible to detect their specific brain activity locations.
- All other emotions are derived from the basic six ones.

## 4. Sleep alterations

"Sleep" changes patterns could be by internal or external factors. The internal factors could be anxiety, stress, inflammation, injury, pain, aging, and others. The external factors could be by AI algorithms inspired by behaviorist psychology, smart devices screen and their blue light, side effects of medicines, and many others. "Sleep" plays a key role in "nervous system regulation." "This is a stable state involving necessary changes to keep physical, internal chemical, and social conditions

| Basic emotions | Description | Brain activity | Emotions derived |
|---|---|---|---|
| Anger | Displeasure or hostility and sometimes is extremely hard to control | Right hippocampus and the amygdala, and both sides of prefrontal cortex and insular | Mad, irritated, disgusted, furious, raging, others |
| Happiness | Feeling pleasure or contentment | Right frontal cortex, precuneus, left amygdala, and left insula | Joyful, pleasing, optimistic, delighted, others |
| Sadness | Unhappiness showing extreme despair and anguish | Right occipital lobe, left insula, left thalamus, amygdala, and hippocampus | Crushed, weepy, depressed, desperate, others. |
| Fear | Response to a threat or harm, could be physical, emotional, physiological, real, or imaginary | Bilateral amygdala, hypothalamus, and left frontal cortex area | Frightened, panicked, scared, terrified, others. |
| Surprise | Extreme opposite responses feeling good or bad | Bilateral inferior frontal gyrus a bilateral hippocampus | Amaze, astound, confuse, others. |
| Disgust | Response to something unpleasant or offensive | Left amygdala, left inferior frontal cortex and insular cortex. | Avoidance, repulsion, revolt, sicken, others. |

**Table 3.**
*The 6 basic emotions descriptions, brain activity location in the limbic system, and their emotions derived.*

balanced." If the "nervous system" is overwhelmed with emotions, including stressful events, then "nervous system dysregulation" is generated, and this is reflected in bad quality sleep identified as "sleep altered or sleep dysregulation."

We can deduce that accumulated "emotional events" processed in the brain limbic system during our wake or walking time affect the quality and timing of sleep. Both are key elements to generate "sleep alterations," which evolved into "nervous system dysregulation," which affects "all symbiotic systems," as shown in **Figure 1A**, and, by consequence, our overall health [2].

### 4.1 Emotions regulated by endocrine system

The "endocrine system" has a collection of glands as shown in **Figure 2B**, they are responsible for "emotion regulation" generated by the "nervous system." The "endocrine system" releases "hormones" identified as "regulatory chemical messengers" segregated into the circulatory system to be carried to distant target organs to maintain the tendency toward a relatively stable equilibrium, between interdependent elements in physiological processes (homeostasis).

Conclusions:

- Accumulated "emotional events" processed in the brain limbic system during our wake or walking time affect the quality and timing of sleep.
- "Sleep" plays a key role in "nervous system regulation."

- The "endocrine system" and "nervous system" work frequently to control and regulate many human body functions that are detected as behaviors, which are the responses to the balance of emotions helping in important body decisions, known as the "fight-or-flight response."

- The "stress" response is driven by the "sympathetic nervous system" to stay and fight and regulated by hormones from the "endocrine system" to take the decision for a dangerous event to stay and fight, or run to safety, helping us to survive excessive stress and life-threatening situations [2].

## 5. The theory of nervous system dysregulation and sleep alterations

For easy understanding of the "theory for nervous system dysregulation and sleep alteration," we divide the theory into two parts, one is normal, named "nervous system regulated allows normal sleep," and the other is when the nervous system is overwhelmed, named "nervous system dysregulated generates sleep alteration." Where each is shown is in **Figure 3**, and explained with details as follows:

A. "Nervous system regulated allows normal sleep*"

As explained in Section 2, the "autonomic nervous system" uses signals based on "neurotransmitters" to communicate neurons with other cell nerves. "neurotransmitters" are nerve signals that are compared to electric pulses, because they are very fast and have a short duration. When our brain detects through the many body senses different situations i.e., too hot, or any danger, they compared with previous experiences, and begin the process on the "limbic system" (see Section 3.1) for different kind of emotions (see Section 3.2), requesting "regulation" for the situation to the "endocrine system" (see Section 4.1), where endocrine glands secrete into the bloodstream the necessary "hormones" to balance the situation. The "hormones" travel relatively slow, and act slowly with longer lasting effects alterations in their specific target cell until reach the balanced systems identify as "homeostasis", a condition needed for a normal sleep (see Section 4).

Note: *The main steps for a "nervous system regulated allowing normal sleep" are shown in **Figure 3A**.

B. "Nervous systems dysregulated generate sleep alteration".

When there are repetitive requests to the "nervous system" with almost continuous generation of electric pulses on the "neurotransmitter," we achieve an "overactive nervous system." Its symptoms include a wide range of physical, behavioral, cognitive, and emotional problems. Usually vary from person to person depending on his "stress threshold." The normal process for emotions is converted to "exaggerated emotions," allowing momentary emotions to become too strong, flooding the brain with intense emotions. The behavior of receiving too many requests from the "endocrine system", results in an "unbalanced process," creating "emotional dysregulation." This is a mental health emotion involving trouble controlling them, and how to act on those feelings. These are reflected in the sleep quality, with continuous alterations or interruptions during the normal sleep period.

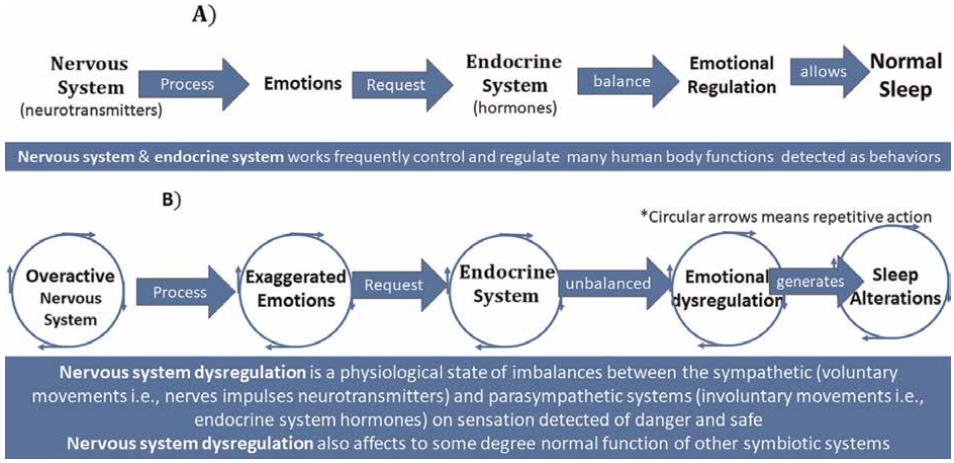


**Figure 3.**
*The theory for nervous system dysregulation and sleep alterations: (A) how nervous system regulated allows normal sleep, and (B) how* nervous system *dysregulation generates sleep alterations.*

Note: *The main steps for a "nervous system dysregulated to generate sleep alteration" are shown in **Figure 3B**.

In summary, the "theory for nervous system dysregulation and sleep alterations" is based on the "sympathetic nervous system" and the "parasympathetic nervous system" as major subdivisions of the nervous system, responsible for sensations of danger and safety. The "sympathetic nervous system" prepares the body to face a "fight-or-flight" response to the present threat that creates stress, mobilizing the natural body resources to face potential threats. On the other hand, the "parasympathetic nervous system" is the natural body mechanism for relaxation, helping us recuperate and maintain a state of calm that allows us to have a good sleep.

## 6. Conclusions

The "nervous system" could be altered at any time by "nervous triggers," which we can avoid and find ways to measure. We need to be aware of common symptoms of "nervous system dysregulation," such as "extreme reactions," "crying spells", "irritable mood", "dissociation", "trouble focusing on small tasks", and "physical changes", and others.

- "Extreme reactions" are frequently identified with overexaggerated reactions, i.e., very anger, rage, excessive criticism, shut down, and others.
- "Crying spells" generate tears without any reason, or "uncontrollable laughs" are due to "emotional dysregulations" by an "overreactive nervous system."
- "Mood swings" are passive moods that suddenly evolved, even to irritability and sometimes aggressive behaviors.

- "Dissociation" is the experience of feelings like daydreaming with intense focus, being disconnected from reality, and losing the natural integration of consciousness, identity, memory, and perception [12].

- "Trouble focusing on small tasks" and unable to follow instructions.

- "Physical changes" as elevated heart rate, blood pressure increased, veins constrict, muscle tense up, speaking fasted, loud voice, fast/hard movements

- Others

The "theory of nervous system dysregulation and sleep alterations" is very useful to understand how to develop an unregulated nervous system, detect it, and analyze how it can be evaluated.

Physical symptoms that can be measured for "nervous system dysregulation" include "polysomnography," a test during a sleep study that records heart rate, breathing, and oxygen levels in the blood, brain waves, eyes, and leg movements [13].

In my opinion, more research is needed with a focus on "the human body's circular chains of symptoms, disorders, and diseases". Some of them are documented and on previous publications as:

- "Unregulated nerve system" can evolve to "stress", o vice- versa stress can evolve to "nervous system dysregulation" and each way "sleep alterations" are present as explain in this research "theory for nervous system dysregulation and sleep alterations".

- "Stress" can also evolve to "depression" involving "sleep alterations" as explained on "Theory for Anxiety Disorder" [2]

- "Chronic stress and/or depression" with "sleep alterations" are linked to a risk to develop neurologic diseases as Parkinson's and Alzheimer's. Documented on my previous research: "The Progressive Connection Between Stress, Anxiety, Sleep and Neurological Disorders" [14].

- Many more are coming soon.

Please sleep well, if you could not find the cause of your "nervous triggers" for "sleep alterations", do not be afraid to require professional help before using any kinds of any type of sleep pills to treat only the symptom.

**Notices**

Knowledge and best practices in this field are constantly changing as new research and experience broadens our understanding, changes in research methods, professional practices, or medical treatment may be necessary. To the fullest extent of the law, neither the publisher nor the authors, contributors or publishers assume any liability for any injury and/or damage to persons or property as a matter of product liability, negligence or otherwise, or for any use or operation of any method, product, instruction or idea contained herein.

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Section 2

# Sleep Changes during the Lifespan

Chapter 4

# Insomnia in Childhood and Adolescence

*Mohamed Binali*

## Abstract

Sleep disturbance in childhood and adolescence is crucial for their health and growth. It impacts up to 60% of the health status among children all over the world. Various factors, such as genetic, prenatal, postnatal, environmental, psychosocial, and others, contribute to a child's sleep insufficiency. Research indicates that untreated childhood insomnia can persist in adolescence and adulthood, potentially leading to medical conditions. Early diagnosis and therapy are crucial because bad sleeping habits become harder to manage as the patient ages. Pharmacological measures are used in association with non-pharmacological measures. Drug treatment alone should not be used for insomnia. Childhood insomnia must be diagnosed and guided by the primary care pediatrician, who will initiate the most appropriate treatment in each case.

**Keywords:** sleep disorder, mental illness, childhood insomnia, adolescent insomnia, cognitive-behavioral therapy (CBT) for insomnia

## 1. Introduction

Sleep, as a physiological process that during the period of growth, constitutes approximately 40% of a child's daily routine from early infancy to adolescence [1]. It plays a vital role in promoting health and overall well-being of children. Insufficient sleep is an escalating public health concern, affecting a significant proportion of children globally, ranging from 20–60% [2]. Insomnia frequently goes undiagnosed and undertreated. In the initial year of life, parents typically observe that newborns encounter difficulties initiating sleep and/or experience frequent awakenings throughout the night [3].

A multitude of factors, including genetic, prenatal, postnatal, environmental, psychological, and other variables, collectively contribute to the inadequacy of sleep in children. Extensive evidence-based research has documented the adverse impact of insufficient sleep on various aspects of human functioning, including physical health, behavior, emotional well-being, cognition, psychopathology, and familial relationships [4].

Research also indicates that untreated childhood insomnia can persist in adolescence and adulthood. In 2015, the recommendations were derived from an expert panel (**Table 1**).

| Age range | Ideal hours of sleep | Acceptable hours of sleep (maximum and minimum) |
|---|---|---|
| Newborns (0–3 months) | 14–17 | 19 and 11 |
| Infants (4–12 months) | 12–15 | 18 and 11 |
| Toddlers (1–2 years) | 11–14 | 16 and 10 |
| Preschoolers (3–5 years) | 10–13 | 14 and 8 |
| School-aged children (6–13 years) | 9–11 | 12 and 7 |
| Adolescents (14–17 years) | 8–10 | 11 and 7 |
| Young adults (18–25 years) | 7–9 | 11 and 6 |
| Adults (26–64 years) | 7–9 | 10 and 6 |
| Elderly (>65 years) | 7–8 | 9 and 5 |

**Table 1.**
*Sleep duration and habits in children (the National Sleep Foundation 2015) [5].*

Insomnia, as defined by the American Academy of Sleep Medicine (AASM) in its third edition, refers to a chronic challenge in initiating, maintaining, or enhancing the quality of sleep. This difficulty persists even when individuals have sufficient opportunities and conditions to sleep, and it results in a disruption in daytime functioning. The inability to initiate or sustain high-quality sleep can be observed through a sleep delay exceeding 30 minutes and/or awakenings lasting longer than 20 minutes, leading to a no stable decline in several areas of functioning [2]. Past expectations and upbringing play a significant role in this transmission. Moreover, the repercussions of this transmission have an impact on both the child and the entire family [6].

The AASM 3rd edition classifies insomnia into three categories:

1. *Chronic insomnia disorder (CID)*. Chronic initiating sleep and/or poor sleep maintenance are associated with deterioration and impairment during the day. This term is reserved for individuals whose sleep difficulties exceed the minimum thresholds for frequency and duration (at least three times a week and persist for at least 3 months).

2. *Short-term insomnia disorder*. It is characterized by sleep/wake difficulties, which do not meet the criteria in terms of frequency and duration of CID. It is associated with clinically significant sleep dissatisfaction or impaired wakefulness. The criteria can be seen in **Table 2** below.

3. *Other insomnia disorders*. They are assigned to rare cases who do not meet the criteria for short-term insomnia and who have sufficient symptoms of insomnia to require medical attention. The AASM [9] recently released revised criteria for certain sleep disorders (ICSD-3-TR) in June 2023. Specifically, criterion F for chronic insomnia disorder states that sleep disturbance and related daytime symptoms cannot be solely attributed to another existing sleep disorder, medical condition, mental disorder, or medication or substance use. Insomnia as a sleep disorder may have various medical causes, including gastric reflux, respiratory issues, or chronic pain syndrome. If a medical disease is the sole cause of sleep-

| Sleep deficiency | Definition and manifestation |
|---|---|
| Sleep duration | The National Sleep Foundation recommends newborns (0–3 months) and infants (4–11 months) to spend 14–17 hrs. and 12–15 hrs. a day asleep, respectively.<br>The suggested duration subsequently decreases with age: 11–14 hrs. For toddlers, 10–13 hrs. For preschoolers, 9–11 hrs. For school-age children, and 8–10 hrs. For adolescents. |
| Sleep quality | Sleep quality is usually defined based on sleep continuity, sleepiness, sleep architecture and daytime behaviors.<br>A global approach for indexing sleep quality often involves self-rating indices that reflect an individual's satisfaction with sleep.<br>Objectively, the National Sleep Foundation identifies various factors that indicate overall sleep quality, including spending at least 85% of the time in bed asleep, falling asleep within 30 min, waking at most once per night, and being awake for 20 min or less after falling [7]. |
| Sleep disorders | Insomnia is characterized by challenges in beginning and sustaining sleep or awakening prematurely, resulting in daytime dysfunction despite sufficient opportunity for sleep.<br>A common feature of childhood insomnia is a persistent problem of getting to sleep or staying asleep, even when no external factors are causing it [8]. |

**Table 2.**
*Definitions and manifestations of common childhood sleep deficiency problems.*

lessness, it is not appropriate to diagnose insomnia independently. Having said that, sleep disruptions in cases of acute insomnia can arise from various etiologies, including the earliest manifestation of autoimmune encephalitis or psychiatric conditions [10].

The frequently seen factor contributing is the utilization of pharmaceutical substances, including decongestants, selective leukotriene receptor antagonists (montelukast), beta-blockers, antidepressants, stimulants, corticosteroids, and others. It is most beneficial to focus on the following categories when assessing and implementing targeted behavioral interventions in clinical settings: behavioral insomnia, psychophysiological insomnia, and transient sleep disturbances.

## 2. Prevalence of insomnia in children

A significant number of children and adolescents exhibit insomnia symptoms, with heightened frequency among those with psychiatric or neurodevelopmental disorders. Insomnia affects 20–30% of the juvenile and adolescent population at different life stages [11]. The current increase in incidence is linked to familial social activities and the prevalence varies by age: it peaks at almost 30% in the first 2 years of life, stabilizes at about 15% after the third year, and thereafter increases during puberty [12]. Children with mental and neurodevelopmental impairments, such as autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD), and blindness, are at an increased risk of sleeplessness. According to a study conducted in the Valencian Community [13], 27% of children aged 5–12 demonstrate resistance to sleep onset; 11% experience extended sleep latency; 6% awaken frequently; and 17% struggle to rise in the morning. Among adolescents, 38.5% report poor subjective sleep quality, and 23.1% have sleep latency exceeding 30 minutes [14].

## 2.1 Pathogenesis

Childhood insomnia is the consequence of an imbalance of various component that intervene in the maturation of childhood sleep, in addition to predisposing, precipitating and perpetuating factors [8]. The concept of "sleeping through the night" in an infant does not mean sleeping without interruption, but rather it is a progressive maturation process based on three skills: 1. A continuous period of sleeping. 2. Nighttime sleep schedule that matches the rest of the family. 3. Ability to fall asleep autonomously again, after physiological awakenings.

Childhood insomnia has five components that intervene in the maturation of childhood:

1. *Circadian component*: the ignorance of physiology and the evolution of sleep favors a lack of coordination between the time selected by the parents for the child to fall asleep and the child's personal biological rhythm. This biological rhythm is established after 5–6 months of life, with an individualized circadian time for each baby [15].

2. *Homeostatic component*: the sleep regulatory mechanism establishes that the more hours of wakefulness prior to sleep, the greater the sleep pressure and, therefore, the less difficulty in initiating it.

3. *Environmental component*: the presence or absence of light during the day and the night. The concentration of melatonin increases during the night (the darkness), and an adequate concentration at the time of going to bed is prevented in the presences of light from different sources.

4. *Educational component*: sleep is part of the habits of a healthy life. Health education is basic, since establishing sleep routines is associated with better quality of sleep [16].

5. *Neuroendocrine component*: the establishment of the circadian rhythm of cortisol and the baby's acquisition of the ability to sleep through the night are closely related. So, the establishment of the circadian rhythm of cortisol occurs coinciding with the establishment of the circadian wake-sleep rhythm.

As mentioned above, we will address different factors that may lead to childhood insomnia:

i. *Predisposing factors*: factors that may contribute to the development of insomnia. Those include age, sex, genetic predisposition, maternal behavior and stress during pregnancy, type of delivery and care during it, nutrition after birth (with melatonin concentration in breast milk being minimal at the beginning of the day and increasing in the evening feedings), developmental status, temperament or personality, psychological state, or anxiety level, and underlying medical or psychiatric conditions.

ii. *Precipitating factors*: those factors may trigger insomnia such as acute events, stress, post-traumatic events, parental psychopathology and poor interaction between parents and children.

| Age | Causes |
|---|---|
| Infants | Food allergies<br>Gastroesophageal reflux<br>Colic<br>Excessive intake of fluid at night<br>Acute otitis media |
| 2–3 years | Fears<br>Parental separation anxiety<br>Napping in inappropriate hours<br>Acute diseases |
| Preschool & school | Fears<br>Nightmares<br>Sleep hygiene problem<br>Acute diseases |
| Teenagers | Sleep hygiene problem<br>Anxiety, depression, ADHD<br>Phase delay<br>Sleep-disordered breathing Movement disorders<br>Family and school pressures cute infections |

**Table 3.**
*Different triggers of insomnia depending on age.*

iii. *Perpetuating factors*: those factors maintain insomnia such as inadequate sleep hygiene, schoolwork or peer pressure, unrealistic parental expectations about the child's sleep, negative parenting styles and lack of constant discipline.

iv. *Other factors* (adolescents), that cause inadequate sleep hygiene practices are bedtime screen use, caffeine consumption, and inappropriate naps [17].

**Table 3** below showed the different causes of insomnia through depending on age.

## 2.2 Manifestations

Insomnia produces serious clinical manifestations such as psychological, emotional, cognitive, physical, and social, affecting the quality of life of the child and their family. They are divided into:

### *2.2.1 Chronic insomnia disorder*

While CID is more prevalent among adults and it has the potential to appear at any stage of childhood. The onset might be either gradual or sudden and is contingent upon the underlying reason. Sleep deprivation may lead to several complications, such as irritation, tiredness, cognitive impairment (including attention and memory), compromised academic performance, and alterations in mood [18].

Insomnia also exhibits natural progression, commencing during childhood, characterized by behavioral changes, diminished social aptitude, irritability, and impulsivity. Subsequently, it manifests as impaired concentration, hindering academic performance, and various other domains of life. Prolonged chronic insomnia can have

detrimental impacts on physical well-being, manifesting in cardiovascular, immunological, and metabolic changes. These abnormalities encompass glucose metabolism, leading to the development of diabetes, as well as endocrine function, resulting in overweight, obesity, and delayed growth.

**Table 2** shows and provides a graphic representation of the symptoms. It can occur at any age, in isolation, or in conjunction with a mental, physical, or substance use disease. Occasionally, the manifestation of this phenomenon is sporadic, coinciding with stressors, while in other cases, the root reason remains undetermined. Symptoms resembling those of chronic insomnia disorder (CID) may be observed during periods of wakefulness, such as fatigue, challenges in maintaining attention and concentration, compromised memory function, irritability, and anxiety stemming from insufficient sleep. When an individual encounters stressful circumstances, they may manifest symptoms including worry, sadness, and depression.

*2.2.2 Short-term insomnia disorder*

Also, the short occurrence of insomnia is also referred to as behavioral insomnia. Resistance to bedtime leads to a delay in the commencement of sleep and/or prolonged intervals of awakening during the night. The highest incidence is observed in children between the ages of 1 and 5 years, and its presence can persist beyond this age range. The manifestation of sleep resistance or insomnia in children is commonly observed, but it is temporary in duration. To meet the criteria for classification as a disorder, the symptoms must manifest a minimum of three times per week, endure for a duration of at least 3 months, and exert a substantial influence on the functioning of both the kid and their family. There has been recent speculation indicating that a significant proportion of childhood insomnia cases, which were formerly ascribed to behavioral factors, may potentially have a circadian basis [8]. This leads to the fact that most cases of idiopathic childhood insomnia will have mixed components such as circadian-behavioral. The other forms of insomnia in children are:

*2.2.2.1 Insomnia due to lack of appropriate limits*

*Insomnia due to lack of appropriate limits,* resulting from incorrect associations during the initiation of sleep [19]. This form of insomnia manifests in newborns, toddlers, and preschool-aged children, who are unable to independently settle their minds or acquire the ability to sleep without specific associations or circumstances.

Individuals may experience challenges in initiating or maintaining sleep, or both, because of unfavorable associations with the onset of sleep-in children experiencing worries, separation anxiety, and anxiety related to solitary sleeping. Also, certain forms of stimulation (such as rocking, receiving petting, feeding or traveling in a car), objects (such as bottles), or the presence of parents in the room or near them are often associated with better sleep habits.

*2.2.2.2 Insomnia related to excessive time in bed, psychophysiological insomnia*

Parents may impose a schedule that exceeds the child's demands, leading to the child's struggle to go to sleep, overnight awakenings, early morning awakenings, or a combination of these factors. It becomes evident during the period of upper childhood and adolescence that they will encounter restlessness, unease, increased

alertness and exhibit repetitive cognitive patterns during sleep. So consistently they are monitoring the passage of time while retaining negative beliefs about their future performance.

Instances of awakenings and learned connections that impede the sleep process have significantly increased. Children often have enhanced sleep quality during periods of vacation, when they are exposed to unfamiliar surroundings, or when they are not actively pursuing sleep. This manifestation of insomnia is distinguished by a confluence of diverse etiological elements, encompassing genetic and psychological predispositions, stress-inducing stimuli, and suboptimal sleep practices.

*2.2.2.3 Temporary sleep disturbances*

Children who have previously exhibited consistent sleep patterns commonly exhibit this phenomenon. On-going stress can trigger a series of sudden nighttime awakenings that resolve spontaneously or travel-induced sleep disruptions can lead to jet lag. A range of diseases causes temporary disturbances in sleep patterns, which endure over a period if parents display inaccurate reactions that repeat nighttime awakenings or adopt inappropriate sleep routines.

*2.2.2.4 Children with neurodevelopmental disorders*

Sleep disturbances are commonly observed in children with ADHD, ASD, eating disorders, intellectual impairment (ID), Smith-Magennis syndrome, Angelman syndrome, Rett syndrome, Williams syndrome, and Down syndrome. The occurrence of insomnia has a chronic course, exhibiting more pronounced symptoms and a greater frequency of manifestation. Sleep difficulties among children diagnosed with ADHD, ASD [20], and ID will range from 30–86%, depending on the specific study series [21].

## 2.3 Diagnosis

The diagnosis of insomnia is fundamentally clinical and is made with a structured clinical history, a complete physical examination, and a sleep diary. It includes the following items:

*2.3.1 General history and structured sleep history*

It includes information's about child sleep habits and routines including one parent may consider something normal that is not normal for another. It should be done in a friendly way, without blaming, using open, indirect questions. It is necessary to include different issues such as:

- Detailed nighttime and daytime sleep schedules: including start and wake times, whether there are naps, total sleep time difference at normal school days and holidays. Whether pre-bedtime routines are performed and whether transitional objects or electronic devices are used. Child nighttime exposure to light, noise, presence of electronic devices (such as TV, computer and cell phone). Child's behaviors during the night, the frequency and the duration of awakenings. The child exhibits limb movements during sleep, snores or has trouble breathing while sleeping.

- The child's behavior during the day: the rest period, the school performance with signs of hyperactivity or daytime sleepiness. Physical exercise practice and morning natural light exposure and the use of screens in the late afternoon. The Strategies or medications and the response obtained. The impact of the problem on the child, family life, parents and at school.

- Personal background: the type of attachment, bond, family educational patterns and maternal stress during pregnancy including breastfeeding and Psychomotor development during childhood. Parental sleep expectations and cultural aspects included.

- Assess emotional and psychiatric (anxiety, depression and phobias) or medical problems and their treatments. The presence of other primary sleep disorders or drug use.

- Family history of insomnia.

*2.3.2 Complete physical examination*

Complete physical examinations include that may underline pathology. The evaluation of weight stature and psychomotor development, assessment of the ENT issues (snoring, adenoid hypertrophy, and nose malformations), gastrointestinal reflux, neurological or behavioral alteration and dermatological alterations (atopy) may lead to clinical evidence of sleep disturbance in children.

*2.3.3 Sleep diary or agenda*

It is an essential tool for diagnosis since it provides an objective view of the child's sleep patterns. It is a daily record of the child's sleep schedules, including the time of going to bed and waking up at night and daytime naps, usually between 2nd and 4th weeks. For the diagnosis of insomnia, it is preferable that the diary be with a free sleep schedule [21]; that is, the child goes to bed when he is sleepy and wakes up on his own, without interference from school schedules.

*2.3.3.1 Complementary tests*

They are reserved for diagnostic doubts of cases comorbid with neurological or psychiatric conditions, or the association of insomnia with other sleep disorders is suspected (obstructive sleep apnea syndrome (OSA), periodic leg movements, parasomnias, and nocturnal epilepsy), since comorbidity in sleep disorders is important to report. Those tests include:

a. *Actigraphy*: it is recording the patient's body movements during the night by using a device like a wristwatch [22]. Being simple and comfortable method for collecting data over a period of 5 to 14 days, an important advantage over polysomnography. Also, it provides information about sleep and wake cycle, more objectively than the sleep diary. It is used in research by sleep experts nowadays.

b. *Polysomnography (PSG)*: it is a sleep recording throughout the night to characterize sleep architecture and its pathology. Numerous physiological parameters are

measured, such as EEG, ECG, eye movements, EMG, limb movements, thoracic movements, and respiratory flow, as well as audio and video recording. It is performed in a sleep laboratory and must be interpreted by a sleep specialist.

c. *Night video recording*: If patient history indicates events or actions happening during the night or nocturnal snoring associated with OSA.

### *2.3.4 Screening tools*

The prevalence of insomnia and other sleep disorders is high in the children and adolescent population, and its consequences are important [23]. The pediatrician must know and use the screening tools that exist in the periodic health check-ups of children and adolescents. They are useful as general screening [21] such as the BISQ test (Brief Infant Sleep Questionnaire), for children under 2 years of age; and BEARS test (Bedtime problems, Excessive daytime sleepiness, Awakenings during the night, Regularity and duration of Sleep, Sleep-disordered breathing) for those over 2 years of age, is used. For further assessment, using the Sleep Disturbance Scale for Children (SDSC) may be useful in evaluating sleep in the last 6 months. **Figure 1** below shows multiple Risk factors associated with childhood sleep deficiency.

We will discuss the following factors:

### *2.3.5 Biological factors*

Children may exhibit specific sleep disorders because of hereditary factors. In recent years, twin studies have provided evidence that heredity has a significant role in many sleep-related diseases, including variations in daytime and nighttime sleep duration and the occurrence of overnight awakenings.

The impact of genetics on sleep length was significant in children who continuously had short sleep duration throughout the test period. Several genes (BMAL1/Mop3 and ABCC9) have been identified as potential biological processes. Evidence-based research conducted on smaller monozygotic and dizygotic twin

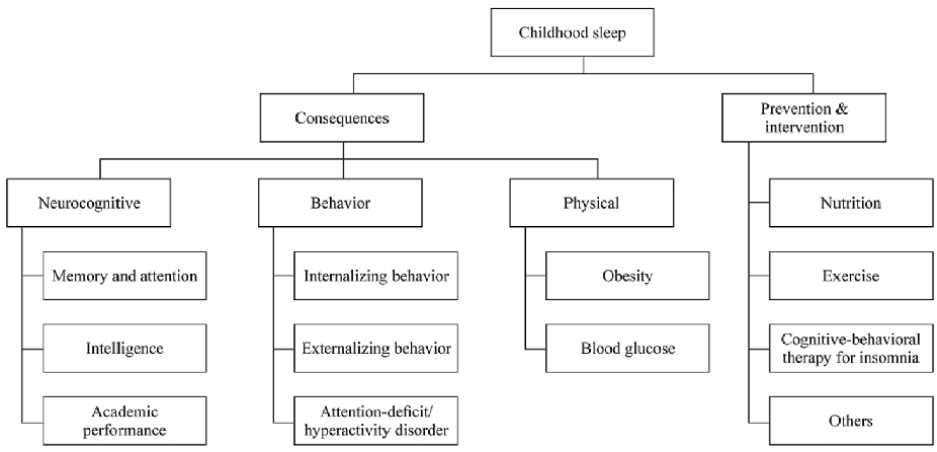


**Figure 1.**
*Childhood sleep disturbances and associated factors [8].*

cases demonstrated additive genetic factors with a moderate effect on the length of infant sleep during both nighttime and daytime periods; shared environmental factors have a considerably greater influence, nearly twice as much as genetic factors. Nevertheless, the current state of research in this area is limited to the dynamics process between genetic and environmental factors in changing the physiological attributes of sleep during the developmental process.

Females frequently achieve superior sleep quality in comparison to males, since studies have demonstrated that males exhibit lower sleep efficiency (the ratio of total sleep duration to time spent in bed), allocate less time to bed, are more susceptible to sleep disturbances, and engage in greater physical activity when sleeping [24]. Also, it was found that females within the age range of 11 to 12 had an increase in the incidence of insomnia. In contrast, a multitude of research suggests that there are no significant discrepancies observed between genders with regards to sleep commencement, sleep duration, or other objective measures of sleep (**Figure 2**).

The role of age and the start of puberty is of particular significance. Between childhood and adolescence, children see a significant rise in both the timing and duration of their sleep [26]. This change is primarily driven by biological, psychological, and lifestyle factors that undergo modifications as they mature. Up to 68.9% of teenagers suffer from insufficient nighttime sleep duration and impaired sleep quality, which is influenced by age-specific social and behavioral factors [27]. Adolescents' sleep problems adversely affect their daytime performance. Chronic sleep deprivation in adolescents has been found to be associated with elevated levels of sadness tiredness, moodiness, irritability, lack of rest, and increased stress in comparison to their counterparts who maintain appropriate sleep patterns.

### *2.3.6 Nutrition, dietary intake, and weight*

The current research has primarily focused on the possible association between sleep deprivation, subsequent dietary consumption, and metabolic results. Growing evidence suggests sleep health can be influenced by both macronutrients and micronutrients, as well as the frequency and timing of meals [28].

#### *2.3.6.1 Macronutrients role*

In the brain, micronutrients function as antagonists of excitatory neurotransmitters, specifically the N-methyl-D-aspartate receptor and dopaminergic neurons. Additionally, they function as agonists of inhibitory neurotransmitters and GABA receptors, which facilitate the process of sleep. The metabolism of monosaccharides, such as carbs and amino acids like tryptophan, has the capacity to influence neurotransmitters involved in sleep promotion, such as serotonin.

Children between the ages of 0 and 6 years demonstrate decreased consumption of tryptophan following breakfast and experience prolonged sleep latency, difficulty in beginning sleep during the night, and challenges in waking up in the morning [29]. Children who received a dinner with high carbohydrate content in the evening had higher arousal and lower sleep quality. Insufficient amounts of micronutrients, such as iron and zinc, pose potential risk factors for sleep deprivation. Infants with iron deficiency anemia have an increased frequency of nocturnal awakenings and reduced overall sleep duration. Also, they exhibit alterations in nonrapid eye movement sleep

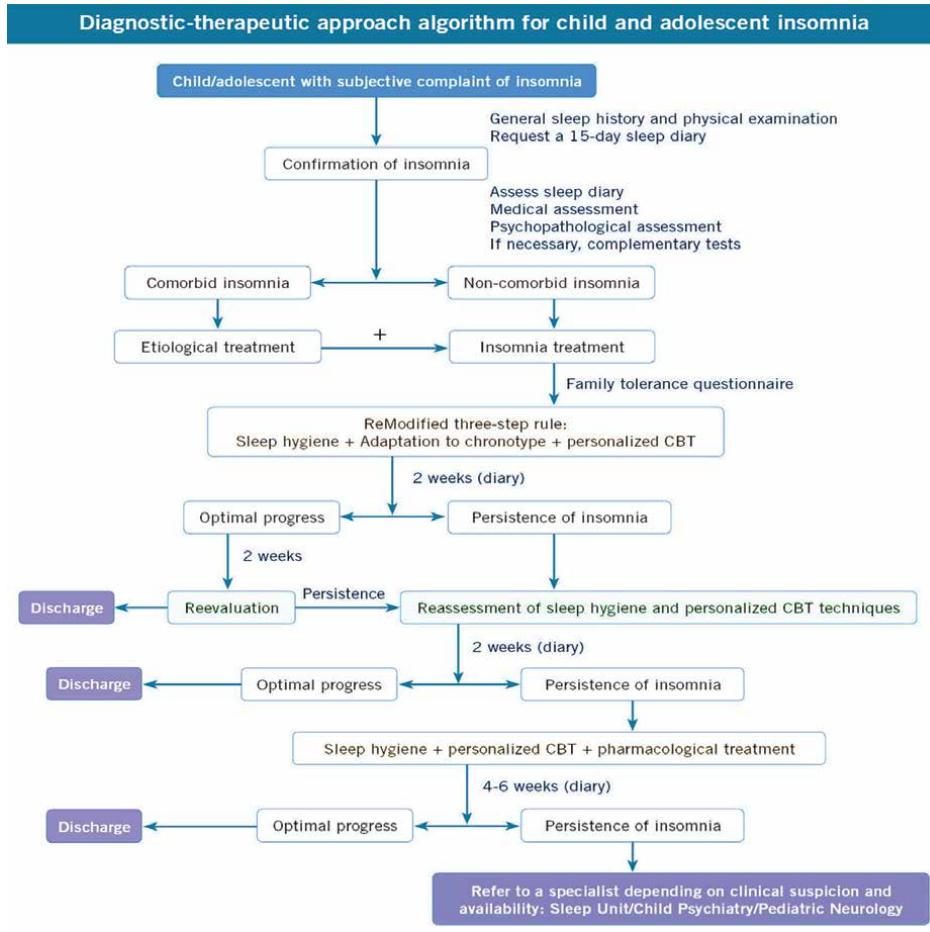


**Figure 2.**
*CBT: cognitive behavioral therapy. Modified from: [25].*

(NREM) stage 2 and slow wave sleep in infancy, including decreased density, frequency, and extended intervals.

Moreover, infants who are undernourished exhibit a distribution of nonrapid eye movement (NREM) and rapid eye movement (REM) sleep, in contrast to infants who are more well-fed. Also, some research has shown a correlation between decreased zinc levels in the circulation throughout the ages of 3 to 5 and 11 to 14 and insufficient sleep duration, poor sleep efficiency, sleep quality, and increased sleep disturbances [30].

*2.3.6.1.1 Omega-3 fatty acids*

Omega-3 long-chain polyunsaturated fatty acids (LC-PUFAs) have the potential to enhance sleep quality in children experiencing clinical sleep insufficiency, according to a recent meta-analysis. Animal models have observed the potential impact of omega-3 insufficiency on melatonin production and neuronal membrane function,

influencing the initiation and maintenance of sleep. Further investigation is required and needed [31].

*2.3.6.2 The role of obesity*

In the field of obesity, the last research has examined the potential association between sleep deprivation and obesity given the rising incidence of childhood obesity. However, it has been reported that adolescents who are obese tend to have significantly worse sleep outcomes compared to their counterparts who have a normal weight. These outcomes include variations in sleep length, quality, and daytime somnolence [32].

*2.3.6.3 Physical environmental exposures*

The association between environmental exposures and sleep health; recent studies are starting to demonstrate a connection between the two [8]. Exposure to lead during early childhood is linked to sleep deprivation in adolescents. Being exposed to light at night can lead to reduced sleep duration and other symptoms of sleep deficit in girls at the age of 7, as well as later bedtimes in adolescents. Research has indicated that exposure to artificial light before sleep has the potential to inhibit the release of melatonin, resulting in a delay in the onset of sleep, a decrease in sleep duration, and a decline in alertness the following morning. A new, comprehensive analysis of the effects of air pollution exposure on sleep health showed both indoor and outdoor air pollution were factors in the development of respiratory-related sleep problems, such as snoring and wheezing, in children. Additionally, studies have demonstrated that children's immature immune and neurological systems, as well as their respiratory anatomy, make them more susceptible to the effects of air pollution [33].

*2.3.6.4 The family role*

Orfeu Marcello Buxton et al. [34] found that sleeping or sharing a bed with parents are one family-related element that affects children's sleep. Shorter sleep duration, aversion to going to bed, anxiety about falling asleep, parasomnia, noisy night awakenings, and behavioral issues are all more common in those who do not sleep. Conversely, kids and teens whose parents strictly enforced regulations around things like caffeine consumption and bedtime rituals reported higher overall sleep health.

*2.3.6.5 Violence and abuse*

Exposure to domestic violence, as well as physical and sexual abuse, has been linked to sleep deficiency during childhood. Domestic violence correlates with inadequate sleep patterns in infants and nocturnal enuresis in children. Research indicates that addressing sleep issues may enhance the relationship between domestic violence among household members and subsequent depression [35].

Experiencing domestic violence can lead to enduring sleep deficiency, which may continue even after the cessation of abuse. Research surveys and polysomnography showed abused victims exhibit extended sleep latency, reduced sleep efficiency, heightened nighttime activity and wakefulness, and diminished sleep duration [8].

Children who experience physical abuse exhibit lower sleep efficiency compared to those who experience sexual abuse. Furthermore, children who have experienced

sexual abuse exhibit diminished overall sleep quality, indicated by sleep difficulties and increased daytime sleepiness. Victims of sexual abuse exhibit greater disturbances during the night compared to controls, characterized by increased nocturnal activity, heightened parasomnia, and frequent awakenings [36].

Additionally, girls who have experienced sexual abuse report a higher incidence of sleep disturbances compared to boys, and there exists a correlation between these sleep disturbances in sexually abused girls and the likelihood of revictimization.

*2.3.6.6 Screen media use*

Recent literature indicates that sleeping with a screen device, particularly a mobile phone, in the bedroom is adversely correlated with sleep length. Increased utilization of screen media adversely affects sleep results [23]. A cross-sectional study indicated that heightened screen media usage correlated with prolonged sleep start, reduced sleep duration, and elevated daytime drowsiness in infants and toddlers [8].

Numerous research indicated that sleep duration in newborns diminished markedly with each extra hour of screen exposure, while in toddlers and young children, both heightened screen media usage at night and the consumption of violent content during the day correlated with exacerbated sleep deficit problems.

In school-aged children, increased screen media usage is predominantly linked to reduced sleep duration and postponed bedtimes [37]. Extended screen time in children and teenagers correlates with increased reports of sleep deficit, with sleep disruptions mediating the association between extended phone usage and adolescent depression. Possible modes of action encompass heightened physiological arousal and diminished melatonin synthesis, leading to a delay in circadian rhythm. These pathways may lead to suboptimal sleep outcomes by causing delayed bedtimes, prolonged sleep onset, reduced sleep duration, and modified sleep architecture.

*2.3.6.7 Physical injury*

Actigraphy tests, parent reports, and self-reports all show an increase in sleep insufficiency in children with traumatic brain injury (TBI). Additionally, kids who have traumatic brain injuries often experience a range of sleep-wake disturbances, including trouble falling asleep or staying asleep, excessive daytime drowsiness, and frequent nightmares. In teenagers, minor head traumas correlate with prolonged sleep disruptions [38]. When compared to control adolescents, those with sleep apnea report much more frequent and longer night awakenings, worse sleep efficiency, and severe subjective sleep complaints. It is critical to comprehend the connection between sleep disruptions in childhood and brain damage since regular brain function controls sleep behavior.

*2.3.6.8 Socioeconomic status*

A child's sleep may be impacted by factors outside their immediate family environment, such as their neighborhood and other socioeconomic status indicators. Questions about the neighborhood's housing stock, security, cleanliness, vandalism, walkways, and proximity to parks and other public areas are all fair games. Poor sleep efficiency, shorter sleep duration, and severe sleep deprivation are more common in children from low-income and otherwise unfavorable situations. Children from low-income families are more likely to suffer from obstructive sleep apnea (OSA), and these community

factors explain the condition better than indications at the individual level. Various psychosocial and environmental factors, such as parental stress, feelings of insecurity, nighttime noise or interruptions, and others, could account for this correlation. To fully comprehend the complex interplay between children's physical sleep environment and their larger social context, additional studies are required in this field.

*2.3.6.9 School factors*

According to Shameka R. Phillips et al. [39], one of the most influential factors in a child's sleep length and quality is the time when school starts. Few studies have looked at how academic stress could affect sleep in children and teenagers, even though sleep deprivation is common among students and has been shown to have a major impact on students' academic performance. Research has demonstrated that when students are under higher academic pressure, they may spend more time studying, worry more, and spend less time sleeping [40].

## 3. Treatment

The treatment of insomnia should be addressed after an adequate diagnostic process that manifests symptoms of insomnia. Therefore, the treatment must be personalized and appropriate to the characteristics of the child and the family. Therapeutic options include non-pharmacological measures and pharmacological treatment.

### 3.1 Non-pharmacological treatment of insomnia

These are interventions that help to achieve better sleep quality. The recommendations are to start treatment in each child following the "3-step rule": sleep hygiene measures, adaptation to the patient's circadian rhythm and cognitive-behavioral therapy.

1. *Sleep hygiene* (**Tables 4** and **5**): it promotes routines and habits to improve sleep quality and current evidence cautions against using sleep hygiene alone as the sole treatment technique. It should always be present in the management of any sleep problem or disorder and could be adapted to different ages, delivered in writing and explained to the patient and their parents.

When the patient tries to follow a sleep schedule that does not fit their own circadian rhythm (in the case of children and adolescents, marked by what their parents consider appropriate), a scheduling discrepancy can occur, with harmful effects on sleep quantity and quality. This will lead to increased sleep latency, decrease sleep efficiency and increase nocturnal awakenings.

1. *Adaptation to the circadian rhythm*: there are numerous environmental chron-regulators that are interesting to know when treating a patient with insomnia [41]:

    a. *Influence of ambient light*: It is important that the child is exposed to bright morning light, while nighttime sleep should be in the dark. If, due to childhood fears, the child requires light in the room, this should be orange light and as dim as possible since night light has proven effects, altering the circadian rhythm.

- Establish a pleasant "presleep" routine
- Acquire habits that highlight the contrast between day and night, using exposure to light during the day.
- Use the bed only to sleep. Do not punish the child by sending him to bed.
- Find a transitional object (stuffed animal, blanket) to be the child's companion in the crib
- The environment in the bedroom should be quiet and dark
- Avoid using screens before the age of 2 and never use them in the hours before going to bed.
- The daily wake-up time and bedtime should be approximately the same every day
- The child can learn to fall asleep alone, without help. If he has tantrums, you must be firm and always act in the same way, establishing clear limits with affection and calmness. Parents must convey the message that this is not a punishment or a dispute between parents and children.
- Until the age of 5, it is normal for the child to need to take a nap. Avoid very long or late naps.
- Do not lose your temper when sending your child to sleep. The message is: "you are capable of enjoying sleeping alone". If the parents get angry, the child will become even more agitated.

**Table 4.**
*Lists recommendations for parents to help infants and young children sleep well.*

- Maintain a stable sleep routine, with stable schedules, and a maximum of 1 hour difference between getting up every day and on weekends.
- Perform relaxing activities before going to bed.
- Avoid hunger and heavy dinners.
- Avoid exciting substances, such as caffeine and chocolate.
- Spend daily time outdoors.
- Perform moderate physical exercise daily, avoiding late exercise.
- Maintain a dark and silent night environment, with a comfortable temperature.
- Avoid using the bed for activities other than sleeping.
- Avoid using the bedroom as punishment.
- Avoid screens at least an hour before bed. Keep screens out of the bedroom during nighttime sleep.
- Avoid naps, especially if they are long or late or interfere with nighttime sleep.

**Table 5.**
*Sleep hygiene recommendations for older children and adolescents.*

b. *Exposure to screens*: Both due to the exciting effects of exposure to electronic devices, as well as the suppressive effect of melatonin that has been shown to be caused by the blue light of said devices. Prolonged exposure to screens should be avoided and Exposure especially before going to bed, improve sleep.

c. *Physical exercise*: It is a beneficial chrono regulator, and there is evidence that regular physical activity improves sleep quality in general. But intense physical activity in the late afternoon hours should be avoided, since, if it is too late, exercise can delay the secretion of melatonin and make it difficult to fall asleep [42].

d. *Food: composition and schedules*. There is increasing evidence of the influence of the type and schedule of feeding on the chronological regulation of the individual. Regular feeding schedules should be recommended, with breakfasts rich in tryptophan.

### 3.2 Cognitive behavioral therapy for insomnia

Cognitive-behavioral therapy is currently the first-line treatment in the treatment of insomnia in adults of any age, emerging in the same way in childhood and adolescent insomnia, together with education and sleep hygiene measures. Its objectives are to eliminate routines that are harmful to sleep, regulate the patient's sleep-wake rhythms, and modify thoughts or worries that contribute to or perpetuate insomnia. This therapy is based on the idea that thoughts (cognitions) influence emotions and experiences, generating various behaviors (actions) that will be reinforced or limited depending on the achievement of certain consequences. Cognitive-behavioral therapy has been shown to be effective, well accepted by patients, and has lasting effects, with studies showing benefits even after 2 years. It has no side effects and some of the techniques that have proven to be effective in the intervention of patients with insomnia are presented. They must be adapted to the individual needs of the child.

The components of CBT for insomnia are:

1. *Stimulus control technique*: Stimulus control describes the situation in which there is a high probability that a particular response will occur in the presence of a previous n stimulus. In the field of insomnia, this strategy focuses on modifying the associations between behaviors that take place in the bedroom and the bed, with the aim of creating a stronger association between bed and sleep, avoiding activities that could associate the bed with wakefulness or activity. Therefore, the bedroom and bed should be reserved exclusively for sleep, avoiding stimulating activities there, such as using electronic devices, watching television, or reading exciting books.

2. *Extinguishing techniques*: They are used to intervene and modify conflictive sleep patterns when there is reinforcement toward an unwanted behavior (e.g., the child shows disruptive behaviors instead of sleeping and the father goes to his room and lies in bed with the child). The aim is to eliminate the expected reinforcement after the emission of a behavior that had previously been reinforced and achieve a consistent decrease in unwanted behavior. It can be applied in the form of "pure extinction", in which the parent is asked to leave the child sleepy but awake in his or her bed and not respond to his/her complaints, ensuring the child's safety.

   Also, there is "gradual extinction", when the father can respond to the child's demands, but in a progressively more spaced manner. Additionally, there are "paternal fading", when the father decreases his interaction with the child during the onset of sleep (initially, he can be in child bed, but without touching, then sitting on the edge of the bed, after that, he is sitting in a chair outside the bed, and lastly, he is standing in the room, next to the door).

3. *Sleep restriction technique*. It involves restricting time in bed to the amount of time that is estimated for the sleeping patient. The process begins with an assessment of how much time the patient sleeps during the night, and a more restrictive sleep schedule is designed where, initially, time in bed is reduced. This way, the patient will spend less time awake in bed. This approach generates a kind of "interest in rest", since, by spending less time in bed, you tend to fall asleep more quickly and experience deeper sleep. As the quality of sleep increases and

nighttime awakenings are reduced, the time in bed is gradually increased, so that when a sleep efficiency (time sleeping/time in bed) of 5% is achieved, a child can gradually increase the time he/she is allowed to stay in bed [43].

The aim is to find a balance between time in bed and efficient rest. For example, if a person spends 9 hours in bed but only sleeps 6 hours, sleep restriction allows the patient to spend only 6 hours in bed initially and, as sleep improves, that time is increasing gradually. By delimiting time in bed and reinforcing the association between bed and sleep, patients may perceive a substantial improvement in sleep quality. Variants of this technique include "delaying bedtime", a technique used, above all, in cases where prolonged sleep latency is observed. Parents are instructed to put their child to bed later than usual, at the actual time the child usually falls asleep. The goal and basis of this technique are like sleep restriction.

4. *Relaxation techniques*: Relaxation techniques, in the context of cognitive-behavioral therapy (CBT) for insomnia, aim to reduce psychophysiological arousal and relieve tension and stress that can interfere with the ability to fall asleep and stay asleep. Stress is a biological response to situations perceived as threatening and in which the body feels that it does not have sufficient resources to cope. If this response is repeated very frequently or is disproportionate to the situations that trigger it, it can affect the neurophysiological, neuroendocrine and neuroimmune systems. Relaxation helps to calm the mind and body before going to bed, as a "deactivation", promoting a favorable environment for sleep.

   There is various relaxation techniques used in CBT for insomnia:

   - Progressive muscle relaxation: will involve consciously tensing and relaxing the different muscle groups in the body, which will promote the release of accumulated tension.

   - Meditation: will focus on mindfulness and mental relaxation and deep breathing techniques will focus on breathing slowly and deeply to calm the nervous system.

   - Deep breathing techniques: contribute to relaxation and stress control.

5. *Cognitive restructuring techniques*: Cognitive restructuring techniques can only be used in older children, with the threshold at the age of 7 years, and subject to the child's maturation. Techniques aimed at identifying inappropriate thoughts (cognitions) of the patient, which are affecting their emotions and producing inappropriate behaviors, with the aim of modifying them or replacing them with more suitable ones. In the context of CBT for insomnia, cognitive restructuring will focus on identifying and changing negative or anxious thought patterns related to sleep. Professionals will help patients address erroneous beliefs about sleep and develop more positive and realistic thoughts related to rest. This technique involves changing dysfunctional thought patterns to reduce anxiety and worry related to insomnia.

   Cognitive restructuring involves several steps:

- *Recognition of dysfunctional thoughts*: The first step is to identify and record the negative and anxious thoughts that arise in relation to sleep. This may include statements such as: "I will never be able to sleep" or "I will fail the exam if I can't sleep".

- *Evaluation of thoughts*: once dysfunctional thoughts have been identified, it will be assessed whether they are realistic and whether there is solid evidence to support these beliefs. In numerous situations, it is discovered that these thoughts are unrealistic ("Have you ever failed a test because of not sleeping?").

- *Alternative thought formulation*: replace negative thoughts with more balanced and realistic thoughts.

- *Train new thoughts*: patients practice and consolidate new alternative thoughts. This can be done through repetition and self-affirmation.

## 3.3 Pharmacotherapy

It should never be the initial treatment for a child or adolescent's sleep problem, but it may be necessary when cognitive-behavioral treatment is not sufficient. Drug treatment alone should not be used for insomnia. If the doctor considers using medication, it should always be after an adequate evaluation and risk-benefit assessment.

The use of drugs will be considered only in the event of failure of other measures, except in some very selected cases in which, due to their severe involvement. The use of medications for insomnia will be for the shortest periods of time possible (most guidelines propose 4 weeks) and at the lowest effective dose.

### *3.3.1 Melatonin*

The principal pharmacological treatment for pediatric insomnia, although the presence of many hypnotic medications. Melatonin is a neurohormone chiefly responsible for the regulation of the sleep-wake cycle. It is produced in the pineal gland, stimulated by the absence of light perceived by the suprachiasmatic nucleus, with synthesis increased in darkness and suppressed in illuminated conditions. Its secretion is a biological process regulated by a circadian rhythm. It functions through MT1 and/or MT2 receptors.

#### *3.3.1.1 Exogenous melatonin fulfills two functions*

It promotes sleep *via* its hypnotic properties and modulates circadian rhythms through its chrono regulatory influence. Each of these actions is executed through specific administration protocols and differing quantities. The greatest effectiveness is observed in decreasing sleep latency, early insomnia, and phase delay syndrome. Melatonin is employed in the management of insomnia in both adults and children.

During childhood, it was the favored product owing to its safety. Melatonin has demonstrated efficacy in children and adolescents with phase delay and onset insomnia, especially in individuals with ASD and ADHD [44, 45].

Melatonin is the first-choice medication for childhood insomnia, although there are multiple drugs with hypnotic effects. Most insomnia drugs have been approved for short treatments, up to 4 weeks. The notable prevalence of sleep disorders in childhood, along with the broad market availability of diverse melatonin formulations and the confidence expressed by parents and professionals regarding its safety relative to conventional hypnotics, are the primary explanations for the considerable increase in melatonin usage among children in the Western world.

Moreover, serotonin contamination was observed in up to 26% of supplements. Melatonin formulations are categorized into two basic types: immediate-release and extended-release [46, 47]:

- *Rapid-acting melatonin*: an onset of action occurs in approximately 30 minutes. It serves as both a sleep inducer and a chrono regulator, employing varying dosages for each purpose.

- *Prolonged-release melatonin*: including a coating that enables the progressive release of melatonin over a prolonged period.

The European Medicines Agency has approved its use in children and adolescents with autism spectrum disorder and Smith-Magennis syndrome. It may be employed in the treatment of insomnia, substantiated by evidence of its effectiveness and safety, increasing overall sleep duration and reducing nighttime awakenings. The melatonin dosage depends on the intended effect and the particular sleep condition. For early insomnia, the hypnotic dosage should be titrated, starting with minimal amounts: 1–2 mg for preschoolers, 2–3 mg for schools, and up to 5 mg for teenagers, administered 30–60 minutes before bedtime.

In children with ASD, it is provided at increased dosages, reaching up to 10 mg. As a chronoregulator, during phase delay, it should be administered at a diminished dosage (0.3–0.5 mg) in accordance with the DLMO (Dim Light Melatonin Onset). This stimulates endogenous melatonin synthesis and improves the circadian rhythm, mitigating phase delay. The assessment of DLMO should preferably be performed using the measurement of salivary melatonin. It should be administered roughly 3–6 hours before the actual sleep onset or about 2 hours before the desired sleep onset.

### *3.3.2 Side effects of melatonin*

The side effects described in general include daytime drowsiness, fatigue, episodes of nocturnal confusion, rebound effect, tolerance, and dependence. Relative contraindications have been established for starting pharmacological treatment in childhood and adolescent insomnia: acute insomnia due to specific events, alcohol or drug abuse in adolescents and the impossibility of adequate follow-up.

Various studies have confirmed the safety of melatonin at the recommended doses and guidelines, with follow-ups of up to 4 years. No effects on growth or puberty, nor a rebound effect, have been described. Morning drowsiness and drunken sleep have been described in adolescents. It is used together with certain drugs that act on CYP1A2 (cytochrome P450 1A2): tricyclic antidepressants, fluvoxamine, cimetidine, ciprofloxacin, oral contraceptives, carbamazepine, omeprazole, or alcohol, can modify the metabolism of melatonin and decrease or increase its concentration.

Accidental ingestions of melatonin in children have increased in recent years, accounting for 5% of all accidental pediatric drug ingestions recorded in the US. Most of insomnia drugs are authorized for short-term use, restricted to a maximum period of 4 weeks. The negative effects differ by medicine but typically include daytime drowsiness, fatigue, nighttime confusion, rebound effects, tolerance, and dependence. Relative contraindications for pharmacological intervention in pediatric and teenage insomnia encompass acute insomnia due to specific events, drug dependence in adolescents, and the incapacity to ensure adequate follow-up care.

Other medications for insomnia (Alternative pharmacological interventions for insomnia).

### 3.4 Antihistamines

Antihistamines have been widely employed to improve sleep in children because of the reassurance they offer to parents and clinicians, their substantial treatment efficacy for numerous pediatric illnesses, excellent tolerability, availability of pediatric formulations, and cost-effectiveness. Their sedative properties are ascribed to their anti-H1 activity, especially in first-generation drugs like diphenhydramine, hydroxyzine, chlorpheniramine, and doxylamine. The second and third generations demonstrate a diminished sedative effect. They demonstrate a rapid initiation of activity. They implement minor alterations to the structure of sleep. Their effectiveness in addressing childhood insomnia is disputed, with some research

| | |
|---|---|
| Melatonin receptor agonists<br>• Ramelteon | MT1 and MT2 receptor agonist. Its use in children is not approved, being anecdotal |
| **Alpha-agonists**<br>• Clonidine | They inhibit the release of norepinephrine. Indicated for insomnia in children with Tourette syndrome and attention deficit hyperactivity disorder |
| • Guanfacine | Side effects: dizziness and hypotension |
| **Antidepressants**<br>• Tricyclics: amitriptyline, doxepin<br>• Atypical: mirtazapine, trazodone<br>• SSRI: fluvoxamine, citalopram | Some antidepressants with histamine H1 receptor antagonist action have been used in insomnia due to their sedative effect<br>Its use in children has not been established. They can be considered in children with psychiatric comorbidity such as mood disorders, or in the case of amitriptyline, as prophylaxis in children with chronic migraine |
| | Anticholinergic side effects: dry mouth, urinary retention. If they are from the tricyclic group, risk of cardiac arrhythmias and poisoning |
| **Benzodiazepines** | Hypnotic and anxiolytic effect. GABA receptor agonists |
| | They are not indicated in childhood insomnia, although due to their anxiolytic effect they may influence some patients with psychiatric comorbidity |
| **Non-benzodiazepine GABA agonists** | Indication for adult insomnia |
| • Zolpidem<br>• Zopiclone | Two clinical trials in children with zolpidem and zopiclone do not show improvement in sleep in children |
| **Plants with sedative effects**<br>Lavender, passionflower, lemon balm and valerian oil | Questionable effectiveness. Anxiolytic and sleep facilitating effect |

**Table 6.**
*Off-label hypnotic drugs in pediatrics.*

demonstrating a decrease in sleep latency and nighttime awakenings, contrary to the results of others.

They are not delineated in the insomnia guidelines for adults. Its use may be considered in specific situations, particularly in pediatric children with atopic dermatitis; nevertheless, extended treatment is not recommended. A primary concern in clinical management is the swift onset of tolerance associated with extended usage. Although typically well accepted, they may cause side effects including xerostomia, urinary retention, constipation, cognitive impairment, and visual abnormalities.

### 3.5 Other hypnotic drugs

Various pharmacological drugs exhibit hypnotic characteristics, primarily with restricted use in pediatric populations. Their use in treating insomnia in children and adolescents within Primary Care is inadvisable (**Table 6**).

## 4. Summary

Sleep, the main brain function during growth, makes up approximately 40% of a child's day from childhood through adolescence and is crucial for children's health and well-being. Sleep deficiency is an escalating public health concern, affecting up to 60% of children globally. Insomnia is frequently underdiagnosed, and its symptoms frequently prompt consultations with physicians in Primary Care settings and sleep specialists. As children get older, they may experience insomnia, parasomnia and respiratory issues during sleep. Starting in preschool, issues are commonly linked to poor sleep habits. Multiple factors, including genetic, prenatal, postnatal, environmental, psychological, and others, contribute to a child's sleep deprivation. Many factors lead to poor sleep quality and quantity during childhood and adolescence. A sleep deficit has been proven to negatively affect physical health, behavior, emotional well-being, cognition, psychopathology, and familial connections. Early diagnosis and therapy are crucial because bad sleeping habits become harder to manage as the patient ages. Childhood sleeplessness may require further diagnosis and management by child sleep specialists who will implement the most suitable treatment for each individual case.

## Conflict of interest

There are no conflicts of interest.

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Chapter 5

# Sleep in Elderly

*Ling Xu and Wantao Ding*

## Abstract

Sleep is one of the important physiological needs of human beings. One-third of people's life is spent in sleep. Enough sleep helps to maintain physical health and a good mental state. It is commonly believed that "the older you get, the less sleep you get" and that sleep deprivation is simply a phenomenon of old age. Many people will suffer from insomnia after entering old age. Long-term insomnia is harmful to the human body: it can lead to decreased immunity, weakened resistance to various diseases, cause memory loss and headache, and seriously affect the quality of life. Excessive sleep and even "hypersomnia" in older people are also sleep disorders. There may also be organic diseases or psychological problems behind the sleep problems in the elderly. What is prone to sleep disorders? How can we improve the sleep quality of middle-aged and elderly people? Let us talk about that.

**Keywords:** sleep, the elderly, insomnia, diseases, disorder

## 1. Introduction

"Sleep disturbance is a very common phenomenon in the elderly, and studies have shown that the incidence of elderly people is as high as 60% [1]." Sleep disorder refers to the rhythm disorder of sleep and awakening caused by various reasons, such as abnormal sleep quality, abnormal behavior during sleep, and other clinical syndromes. It is a large class of sleep-related diseases, including dozens of diseases, among which the most common sleep disorders are insomnia and sleep breathing disorders. Sleep needs vary from person to person and are affected by many factors such as age, gender, physical health status, and lifestyle. According to a joint consensus statement from the American Academy of Sleep Medicine and the Sleep Research Society, adults should get between 7 and 9 hours of sleep per day, while older adults are recommended between 7 and 8 hours [2]. However, many older adults experience shorter sleep duration as they age. This may be related to physiological factors, such as decreased thermoregulation ability and changes in sleep structure in the elderly [2]. Therefore, sleep needs in older adults should be based on individual differences and need to be adjusted according to individual circumstances. According to the International Guidelines for Sleep Disorders, the diagnostic criteria for chronic insomnia is difficulty falling asleep (longer than 30 minutes), sleep maintenance disorder and easy to wake up (number of awakenings ≥2 times throughout the night), wake up early, decreased sleep quality and total sleep time, with daytime dysfunction

and lack of sleep, and at least three times per week for 3 months [3]. Sleep disorders are harmful. For normal people, if there is not enough sleep at night, and there is a lot of mental pressure to work, study, and live during the day, it can easy to lead to mental weakness, anxiety, depression, and other psychological problems will occur in the long run. For people who are disturbed by sleep for a long time, it often induces cardiovascular and cerebrovascular diseases, such as hypertension, angina pectoris, stroke, etc., which seriously affects health.

## 2. Main text

### 2.1 Epidemiology

According to the World Health Organization, the global prevalence of sleep disorders is as high as 27%. In 2007, the World Health Organization surveyed 25,916 primary care patients in 14 countries and 15 regions and found that 27% of them had sleep problems. Among them, the incidence of insomnia is as high as 32–50% in the United States, 10–14% in the United Kingdom, 20% in Japan, 30% in France, and more than 30% in China [4]. The prevalence of insomnia was 43.90–53.89%, and the prevalence of chronic insomnia was 21.84%. A survey showed that the prevalence of persistent insomnia in elderly patients (75–89 years old) was as high as 33.33%. According to the 2022 white paper on Healthy Sleep of the Chinese People, 42% of the elderly take more than half an hour to fall asleep, the rate of insomnia is as high as 21%, and 46% of the elderly do not sleep well for health reasons. Insomnia will not only increase the risk of cardiovascular and cerebrovascular diseases [5], diabetes [6], and neurodegenerative diseases [7–9] but also damage mental health, easy to anxiety, depression, and other adverse emotions [10], which seriously reduces the quality of life of the elderly.

### 2.2 Etiology and triggers of insomnia

#### *2.2.1 Altered circadian clock*

Sleep architecture is altered in older adults, with decreased duration of deep and rapid eye movement (REM) sleep and an increased risk of wakefulness and insomnia [8, 11]. With the increase of age, the secretion of growth hormone in the body decreases and the secretion of melatonin in the body decreases [12], and people's sleep patterns will also be changed. Most of the elderly's biological clock will be advanced, and many of them will feel sleepy at 6 or 7 in the evening and will wake up at 3 or 4 in the morning, resulting in sleep disorders and other diseases.

#### *2.2.2 Lifestyle factors*

The lifestyle of the elderly may also affect sleep quality, such as lack of exercise [13], poor diet [14], alcohol consumption [15], and smoking habits [16]. Since the elderly are basically retired, they do not need to do any physical work, and when the body's energy consumption is not large, they will not feel tired, and they will not easy to feel sleepy, especially the elderly who have a nap, they are more likely to fall asleep at night.

*2.2.3 Side effects from illness or medication*

The body organs of the elderly gradually degenerate and are prone to the attack of various diseases, such as cardiovascular and cerebrovascular diseases, migraine, and other physical discomfort, which will lead to sleep disorders in the elderly. In addition, long-term use of some drugs, such as glucocorticoids, thyroid hormones, chlorpromazine, and other drugs, can lead to insomnia [17].

*2.2.4 Environmental factors*

The elderly may face a variety of environmental factors, such as noise, light, temperature, etc. When the surrounding sound is too noisy, the room is too bright, so that the elderly are in a poor sleep environment, which may interfere with sleep [2].

*2.2.5 Psychological factors*

With the increase of age, excessive worry, excessive missing of children, and excessive pressure to help children with children, elderly people may suffer from mood fluctuations, anxiety, depression [18–20], and other problems, which may affect sleep.

**2.3 Types of insomnia in the elderly**

*2.3.1 Difficulty falling asleep*

Difficulty falling asleep refers to lying in bed when it is time to fall asleep. Generally, lying in bed at most 30 minutes can cause sleep; if after 30 minutes, you still cannot fall asleep, then it can be called sleep difficulties. Difficulty falling asleep is the most common form of insomnia. Patients lie in bed tossing and turning and are unable to sleep, when sleep difficulties are often accompanied by anxiety and irritability. The more you cannot sleep, the more irritable you are, and the more irritable you are, the more you sleep, forming a vicious circle.

*2.3.2 Wake up early*

It means that people generally wake up in advance at 3–4 o'clock. After waking up, there is a feeling of lack of sleep, but it is difficult to fall asleep again.

*2.3.3 Day and night reversal*

In this type, daytime sleepiness is very strong, and it is easy to fall asleep; if you cannot sleep, then feel listless and yawn. At night, I could not sleep. This has a lot to do with the living habits of the elderly.

*2.3.4 Hypersomnia*

It includes excessive daytime or nighttime sleep that is not due to sleep deprivation or the presence of other neuropsychiatric disorders such as narcolepsy. Sleepiness is often associated with psychological factors. The main manifestations of salivation were longer sleep than usual, difficulty in waking up, or a brief state of confusion after waking up. During sleep, the brain waves are the same as normal sleep brain waves.

*2.3.5 Easy to wake up*

It is mainly manifested as multiple awakenings during sleep; even slight stimulation of the external environment can wake him up from sleep.

## 2.4 Harms of insomnia in the elderly

*2.4.1 Causes of decreased immunity*

Insufficient sleep in the elderly is associated with depression and poor appetite, which significantly compromises their immune function. For instance, insomnia leads to frequent awakenings and heightened sensitivity to cold temperatures, making them more susceptible to catching colds and experiencing recurrent episodes. This can be attributed to a decline in both the immune system's efficacy and the body's resistance.

*2.4.2 Increases the risk of heart disease*

Sleep deprivation also elevates the likelihood of developing heart disease by two to three times [21]. Heart disease poses a significant threat to elderly individuals' health as it disrupts autonomic nervous system regulation due to lack of sleep, leading to increased sympathetic nerve excitability and excessive release of catecholamines that accelerate heart rate. Consequently, this may result in ventricular tachycardia, ventricular fibrillation, or even sudden cardiac death.

*2.4.3 Raises the risk of diabetes*

Reduced sleep duration among older adults increases their probability of developing diabetes compared to the general population [22]. Inadequate sleep contributes to insulin resistance because severe insomnia activates the body's stress system, causing an increase in the secretion of "blood glucose-raising hormones" while exacerbating insulin resistance. As a result, glucose metabolism disorders occur and induce diabetes.

*2.4.4 Contributes to gastrointestinal diseases*

Prolonged sleep deficiency interferes with normal secretion rhythms within the gastrointestinal tract by reducing gastric juice and intestinal juice production during sleep processes, consequently greatly increasing susceptibility to gastrointestinal ulcers [23].

*2.4.5 Disorders associated with depression and anxiety*

Among individuals with chronic sleep disorders, the prevalence of depression is higher compared to those without such disorders [24]. Moreover, patients who experience remission from depression are more likely to relapse if they also suffer from long-term sleep disorders [25]. Long-standing insomnia can lead to emotional instability, irritability, and conflicts within the family unit. In severe cases, it may result in a lack of emotional support and symptoms indicative of anxiety and depression.

## 2.5 Evaluation and examination

### *2.5.1 Assessment of sleep disorder*

Subjective sleep assessment can be performed by Insomnia Severity Index (ISI), Pittsburgh sleep quality index (PSQI), and Athens Insomnia Scale (AIS). Spiegel scale, self-rating sleep scale (SRSS), fatigue severity scale (FSS), Epworth sleepiness scale (ESS), and morning and evening questionnaire (MEQ) can also be used.

### *2.5.2 Sleep diary*

Sleep diary is an internationally recognized auxiliary examination method for sleep disorders. Sleep diary can reflect sleep quality and help analyze sleep condition. Moreover, keeping a daily sleep diary is a behavioral therapy for some elderly patients with insomnia. Because most people's sleep is related to psychological and mental factors, through the sleep diary, doctors can have a comprehensive and objective understanding of the patient's sleep, so as to help them eliminate or reduce the worry, anxiety, and fear of insomnia, and help to correct the patient's wrong cognition of sleep, develop good sleep hygiene habits.

### *2.5.3 Polysomnography*

Polysomnography(PSG) showed prolonged sleep latency, increased number and duration of awakenings, decreased sleep efficiency, and decreased total sleep time.

### *2.5.4 Physical disease-related examinations*

Various imaging examinations, neuroendocrine (transmitter, hormone, etc.) determination, other organ function, and biochemical tests can show or exclude the etiological and pathological relationship related to insomnia.

## 2.6 Prevention and treatment

### *2.6.1 General treatment*

It includes the development of good sleep hygiene habits, removal of interfering factors, sleep exercise, withdrawal of drugs that may cause sleep disorders, treatment of medical and psychiatric disorders (such as heart failure, emphysema, endocrine diseases, depression, nocturnal muscle cramps, etc.), and sleep disorders. Muscle relaxants are effective in relieving muscle spasms at night.

Specific sleep hygiene habits include:

#### *2.6.1.1 Sleep duration*

Keep a regular sleep schedule and try to keep the same wake-up time and bedtime every day, including weekends.

#### *2.6.1.2 Sleep environment*

Ensure a quiet, comfortable, dark, and cool sleep environment. Avoid noise, light, and interference from too high or too low temperatures.

*2.6.1.3 Bed comfort*

Choose appropriate mattresses, pillows, and bedding to ensure adequate support and comfort.

*2.6.1.4 Avoid irritants*

Avoid irritating foods and beverages, such as caffeine, nicotine, and alcohol, right before bed. These substances may interfere with sleep quality.

*2.6.1.5 Bedtime relaxation*

Do some relaxation activities before bed, such as deep breathing, meditation, a warm bath, or reading, to reduce physical and mental stress and promote sleep.

*2.6.1.6 Avoid long naps*

Limit the time and duration of daytime naps to avoid long naps that can lead to difficulty falling asleep at night.

*2.6.1.7 Exercise regularly*

Moderate physical activity and exercise can improve sleep quality. However, avoid intense exercise before bed so as not to interfere with sleep.

*2.6.1.8 Use electricity before bed*

Avoid using electronic devices like cell phones, computers, and televisions right before bed, as the blue light from these devices can inhibit melatonin production and interfere with sleep.

*2.6.1.9 Deal with stress*

Learn to deal effectively with everyday stress and anxiety and avoid bringing these problems into sleep time.

*2.6.1.10 Respect your personal needs*

Different people have different sleep needs. Some people need more sleep, while others need less. Know your sleep needs and give yourself enough time to meet them.

*2.6.2 Sleep hygiene education and psychotherapy*

Psychological and behavioral interventions are the preferred approach for treating insomnia, with cognitive-behavioral therapy for insomnia (CBTI) being the most commonly used method. In the long term, CBTI has been found to be more effective than pharmacotherapy alone. The aim is to modify maladaptive cognitive and behavioral factors in individuals with insomnia and enhance their self-efficacy in managing sleep difficulties. Treatment modalities include addressing sleep hygiene practices, implementing cognitive restructuring techniques, employing sleep restriction

strategies, utilizing stimulus control methods, incorporating relaxation therapy, exploring ambivalence intentions toward sleep improvement, adopting multimodal approaches, considering music therapy as an adjunctive treatment option, and exploring the potential benefits of hypnotherapy.

Specific methods include:

1. Stimulus control training: This is a program to help people with insomnia reduce sleep-unrelated behaviors and establish regular sleep-wake patterns, including going to bed only when they are sleepy and using the bed and bedroom only for sleep rather than reading, watching television, or working in bed; If you cannot fall asleep in 15 to 20 minutes after going to bed, you should get up. Do not doze off during the day, and get up on time in the morning.

2. Sleep restriction: the insomniac should be instructed to reduce the time of non-sleep in bed. When the sleep efficiency is over 90%, the time in bed should be increased by 15–20 minutes, and when the sleep efficiency is less than 80%, the time in bed should be reduced by 15–20 minutes. When the sleep efficiency was 80–90%, the time in bed was kept constant.

3. Relaxation training: treating insomnia by relaxing to reduce mental and physical tension. Relaxation methods include muscle relaxation training, biofeedback, meditation, Qigong, Tai chi, etc.

4. Paradoxical intention training: persuade insomnia to engage in their most afraid of sleep behavior, which is not sleeping; if insomnia tries not to sleep, anxiety will be reduced, and it is naturally easy to fall asleep.

5. Phototherapy: light of a certain intensity (7000–12,00Lμx) and appropriate time can change the sleep-wake rhythm, which is especially effective for the treatment of sleep-wake rhythm disorders (such as delayed sleep phase syndrome or premature sleep syndrome).

6. Time therapy: it is suitable for patients with delayed sleep phase syndrome. Patients are instructed to advance their sleep time for 3 hours every day until the sleep-wake cycle conforms to the general social habits.

*2.6.3 Medication*

Target of drug therapy: The objectives of pharmacotherapy are to alleviate symptoms, enhance sleep quality and/or extend the duration of effective sleep, reduce sleep onset latency, decrease the frequency of awakenings after falling asleep, achieve a balance between efficacy and potential adverse drug reactions, improve patients' subjective satisfaction with both the quality and quantity of their sleep, restore social functioning, and enhance patients' overall quality of life.

Principles of drug treatment: In addition to etiological treatment, cognitive-behavioral therapy for insomnia (CBTI), and education on sleep health, hypnotics should be administered as appropriate using a minimal effective dosage. Intermittent administration (two to four times per week) is recommended, along with short-term medication (no longer than 3 to 4 weeks on a regular basis). Gradual reduction and gradual withdrawal (25% reduction in dosage per day) should also be implemented.

There are several classes of medications currently used to treat insomnia:

*2.6.3.1 Benzodiazepines*

Benzodiazepines are the most commonly used sedative drugs (about 70%). This kind of drugs can be divided into three kinds of short-acting, medium-acting, and long-acting preparations, and their representatives are triazolam (half-life 3.5 hours), estazolam (sulazepam) and alprazolam, diazepam (diazepam), and nitrazepam (nitrodiazepam). Benzodiazepines have a good effect on patients with anxiety and insomnia. It can increase the total sleep time, shorten the sleep onset latency, and reduce the frequency of night awakening, but it can significantly reduce slow-wave sleep, resulting in a decreased sense of recovery after sleep. The most common adverse effects were dizziness, dry mouth, loss of appetite, constipation, delirium, amnesia, falls, potential dependence, residual sedation the next day, worsening symptoms of chronic obstructive pulmonary disease and obstructive sleep apnea syndrome, and withdrawal syndrome due to abrupt drug discontinuation.

*2.6.3.2 Non-benzodiazepines*

Non-benzodiazepines are currently new oral hypnotics, including zolpidem tartrate, zaleplon, zopiclone, and dexzopiclone. The onset of action is relatively fast, the half-life is relatively short, the time of action is relatively short, there is no hangover-like feeling on the second day, and there is no inhibition of the second day's awakening, so it can be recommended to use.

*2.6.3.3 Antidepressants*

Antidepressant drugs with sedative effect: especially suitable for the treatment of depression and/or anxiety associated with insomnia, the treatment dose of insomnia is lower than the dose required for antidepressant effect, such drugs include:

1. Trazodone (guidelines): Compared with tricyclic antidepressants, they have no or little anticholinergic activity and are suitable for patients with depression, severe sleep apnea syndrome, and a history of drug dependence.

2. Mirtazapine (clinical recommendation): improving sleep by blocking the 5-HT2A receptor and histamine H1 receptor can increase sleep continuity and slow-wave sleep, shorten sleep onset latency, increase total sleep time, improve sleep efficiency, especially for depression patients with insomnia, can improve objective sleep parameters.

3. Fluvoxamine (clinical recommendation): it can improve sleep by delaying the metabolism of melatonin in the body, increasing the concentration of endogenous melatonin, shortening the REM sleep time without increasing the number of wakefulness, prolonging the REM sleep latency of depression patients, and improving the sleep of depression and anxiety patients.

4. Doxepin (standard): it is the only antidepressant approved by the FDA for the treatment of insomnia because it can selectively and strongly block the histamine H1 receptor, which allows doxepin to exert sedative and hypnotic effects only at

low doses. It is mainly suitable for patients with difficulty in maintaining sleep and short-term sleep disorders.

*2.6.3.4 Barbiturates*

Barbiturates, such as phenobarbital (phenobarbital), are rarely used as sleeping pills.

*2.6.3.5 Antipsychotic drugs and others*

Antipsychotic drugs and others, such as gabapentin (standard), quetiapine (guideline), and olanzapine (guideline), are also commonly used in the treatment of insomnia in the elderly.

*2.6.3.6 Sleep-promoting substance slow-wave sleep peptide (DSIP)*

Sleep-promoting substance slow-wave sleep peptide (DSIP), sleep factor, prostaglandin D2, and other related sleep substances: under study.

*2.6.4 Physical therapy*

Physical therapy serves as a complementary technique in the treatment of insomnia, exhibiting minimal adverse reactions and high clinical acceptability. It encompasses various therapies such as light therapy, repetitive transcranial magnetic stimulation, biofeedback therapy, electric therapy, and other modalities (including ultrasonic therapy, music therapy, and electromagnetic therapy).

## 3. Discussion

Nowadays, insomnia has emerged as a significant determinant impacting the well-being of the elderly population. Difficulties in initiating sleep, maintaining sleep, and early morning awakenings are three pivotal challenges that afflict numerous older individuals. Prolonged insufficient sleep can give rise to various health complications including obesity, diabetes, cardiovascular diseases, and stroke, among others. The etiology of sleep problems in the elderly is multifaceted due to diverse factors contributing to their occurrence. Insomnia in older adults not only encompasses difficulties falling asleep and frequent nocturnal awakenings but also entails alterations in circadian rhythms. Furthermore, excessive use of medications for physical ailments represents a common yet often overlooked cause of sleep disturbances among this demographic group. Addressing the root causes of insomnia necessitates meeting the specific sleep requirements of older adults while comprehending its underlying triggers. We cannot prevent aging, but we can assist older individuals in achieving better sleep by creating a comfortable sleeping environment, cultivating healthy sleep habits, alleviating psychological stressors unique to the elderly population, and selecting appropriate physical activities. Consequently, managing sleep issues in this population should adopt a comprehensive approach targeting all aforementioned aspects rather than solely relying on prescribing sedative-hypnotic drugs or escalating dosages thereof. Establishing an accurate understanding followed by implementing appropriate measures constitutes the fundamental basis for resolving these concerns

effectively. Sleep assessment serves as an efficacious tool aiding older individuals in developing an accurate perception regarding their own sleeping patterns and the quality thereof. Cognitive-behavioral therapy for insomnia (CBT-I), which modifies maladaptive behaviors and promotes healthy sleep habits, currently stands as internationally recognized as the optimal non-pharmacological treatment modality for insomnia disorder, offering valuable insights into sustaining adequate levels of restorative slumber among seniors. Sleep not only facilitates the body's repair and restoration of energy but also enhances cognitive function and fortifies the immune system. The elderly should prioritize their physical well-being, promptly address any physical discomfort symptoms, and ensure restful sleep. Regardless of age, it is imperative for everyone to obtain an adequate amount of quality sleep.

## 4. Conclusions

The elderly frequently exhibit symptoms of insomnia, with some cases being attributed to physiological factors while others are caused by pathological conditions. Drug-induced effects, physiological and somatic diseases, as well as mental disorders like anxiety and depression, along with environmental health conditions, constitute the primary causes of insomnia in older adults. The detrimental impact of insomnia on both physical and mental well-being should not be underestimated, as it can lead to reduced work efficiency, physical ailments, and significantly affect life expectancy. Therefore, obtaining a restful night's sleep is crucial. It is advisable to cultivate healthy sleep habits, establish an optimal sleep environment, engage in relaxation techniques for the body and mind, avoid stimulating substances or activities before bedtime, incorporate appropriate exercise routines into daily life, and consider pharmacological interventions for improving insomnia.

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## Conflict of interest

The authors declare no conflict of interest.

## Acronyms and abbreviations

| | |
|---|---|
| REM | rapid eye movement |
| ISI | Insomnia Severity Index |
| PSQI | Pittsburgh Sleep Quality Index |
| AIS | Athens Insomnia Scale |

| | |
|---|---|
| SRSS | self-rating sleep scale |
| FSS | fatigue severity scale |
| ESS | Epworth sleepiness scale |
| MEQ | morning and evening questionnaire |
| PSG | polysomnography |
| CBTI | cognitive-behavioral therapy for insomnia |

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Section 3

# Sleep in Pathologic Conditions

Chapter 6

# Perspective Chapter: Sleep-Related Breathing Disorders – Comprehensive Approach to Obstructive Sleep Apnea

*Dianelys Perla Sierra Martinez*

## Abstract

This chapter offers a detailed examination of obstructive sleep apnea (OSA), exploring its connection to respiratory physiology and the spectrum of sleep-disordered breathing types. It delves into the pathophysiology of OSA, alongside its epidemiology, risk factors, and clinical manifestations. The chapter outlines diagnostic criteria and severity classification, emphasizing the importance of polysomnography (PSG) and home sleep apnea testing (HSAT). It also addresses the various comorbidities linked with OSA, including cardiovascular, metabolic, and neurological conditions. A key focus is on patient education and the need for a multidisciplinary management approach, highlighting the effectiveness of positive airway pressure (PAP) therapy and alternative treatment options. Overall, this chapter provides healthcare professionals with a thorough understanding of OSA and its comprehensive management.

**Keywords:** sleep-related breathing disorders (SRBD), obstructive sleep apnea (OSA), apnea-hypopnea index (AHI), polysomnography (PSG), positive airway pressure (PAP)

## 1. Introduction

During sleep in healthy individuals, we can observe a progressive decrease through the different stages of sleep in tidal volume compared to the waking state and consequently, minute ventilation decreases. The rise in gamma-aminobutyric acid-secreting neuron activity impacts the respiratory center, leading to a slight elevation in carbon dioxide, partial pressure, and a minor decline in oxygen partial pressure. The response to hypercapnia and hypoxemia is reduced due to decreased sensitivity of chemoreceptors. Muscle tone is decreased, and the resistance of the upper respiratory tract increases due to the loss of muscle tone of the nasopharynx, the activity of the intercostal muscles is also affected, especially in the rapid eye movement phase, and the diaphragm maintains ventilation. During sleep, a certain degree of

bronchoconstriction can also be observed, which produces a slight increase in the resistance of the lower airways [1].

In healthy individuals, these alterations typically do not yield any clinical manifestations, though oxygen saturation during sleep tends to be lower compared to wakefulness. However, these shifts are often magnified those with chronic respiratory conditions.

Sleep comprises separate phases that cycle between non-rapid eye movement (NREM) sleep consists of three stages: N1, N2, and N3. In contrast, rapid eye movement (REM) sleep is marked by vivid dreaming and muscle atonia [1, 2].

### 1.1 Breathing during NREM sleep

*N1 (Transition from wakefulness to Sleep)*: during N1, the body transitions from wakefulness to sleep. Respiratory drive decreases slightly, and tidal volume may fluctuate. The upper airway remains patent, but subtle changes in muscle tone can predispose to snoring.

*N2 (Light Sleep)*: here, respiratory patterns stabilize. The ventilation remains adequate, but inspiratory effort decreases. The pharyngeal muscles maintain tone, preventing airway collapse. However, partial upper airway obstruction may occur, leading to brief arousals.

*N3 (Deep Sleep)*: respiratory drive diminishes further, resulting in hypoventilation. The diaphragm contracts rhythmically, but overall ventilation decreases. OSA events are more common during N3 due to muscle relaxation and narrowed airways.

### 1.2 Breathing during REM sleep

REM sleep is paradoxical; the brain is active but skeletal muscles experience atonia. The diaphragm and intercostal muscles exhibit irregular contractions, resembling rapid shallow breathing. This paradoxical pattern, coupled with decreased upper airway tone, predisposes to OSA exacerbations.

### 1.3 Sleep-related breathing disorder

Sleep-related breathing disorder refers to a spectrum of breathing anomalies and can be classified into diverse types, including [2]:

- OSA
- Central sleep apnea (CSA).
- Other SRBD, this category encompasses syndromes involving hypoventilation and hypoxemia during sleep.

The frequency in the adult population of SRBD ranges from 2 to 4%. OSA is a prevalent condition, potentially affecting up to 30% of adults, with a higher incidence in men than in women. However, it is considered that OSA is often underdiagnosed. Elderly individuals also show higher incidences of sleep-disordered breathing, with prevalence rates ranging from 28 to 67% for men and 20 to 54% for women. Among those with severe OSA, men exhibit an eight-fold higher frequency. Moreover, prevalence estimates for children are approximately 5–6%. These findings underscore the significant impact of breathing-related sleep disorders across different age groups [3–6].

Sleep-related breathing disorder events are divided into [4]:

- Apnea: a cessation of airflow that is complete or nearly complete, lasting at least 10 seconds.
- Hypopnea: a decrease in airflow by 30–90% often associated with Electroencephalogram (EEG) arousals and/or a 3–4% drop in oxygen saturation, lasting at least 10 seconds.
- Respiratory event-related arousals (RERA): breathing reductions in RERAs are milder than with apneas or hypopneas. RERAs involve 10 or more seconds of decreased nasal breathing immediately followed by an arousal from sleep.

Comprehending these event types is essential for accurately diagnosing and effectively managing SRBD. Respiratory effort is a key factor in categorizing apneas into three distinct types [3, 4]:

- Obstructive apnea: throughout the event, there is consistent respiratory effort, suggesting an obstruction in the upper airway.
- Central apnea: respiratory effort is entirely absent during the event, indicating a malfunction this refers to the control center for breathing located in the ponto-medullary region of the central nervous system.
- Mixed apnea: initially, there is no respiratory effort, followed by a gradual increase in effort during the latter part of the event.

### 1.4 Central sleep apnea

CSA is characterized by the temporary cessation or reduction of the respiratory rhythm generator located in the pontomedullary region of the central nervous system. This condition typically manifests cyclically during sleep, alternating between episodes of apnea or hypopnea, where there is no respiratory effort, and periods of hyperpnea. It is more prevalent in males, middle-aged, and elderly individuals. Central apnea typically occurs during NREM stages 1 and 2, with rare occurrences during REM sleep. These events disturb the normal sleep pattern and can lead to nocturnal awakenings, daytime drowsiness, or insomnia [2, 4].

Various comorbidities can contribute to the onset of central breathing disorders during sleep, leading to CSA. Health conditions such as heart failure (HF), whether characterized by preserved or reduced ejection fraction (EF), as well as atrial fibrillation (AF), cerebrovascular disease, renal failure, spinal cord injury, and chronic opioid use, contribute to the development of CSA. These conditions often lead to temporary reductions in ventilatory output, promoting the occurrence of CSA. This disorder is notably prevalent in various cardiovascular ailments and represents an independent risk factor linked to unfavorable health outcomes (3). In some cases, the cause cannot be identified, leading to the term idiopathic or primary CSA [7].

### 1.5 Hypoventilation syndrome and hypoxemia during sleep

The International Classification of Sleep Disorders-3rd edition (ICSD-3) distinguishes between sleep-related breathing disorders characterized by hypoventilation

| Disorder | Key characteristics |
|---|---|
| Obstructive Sleep Apnea (OSA) | Snoring, episodes of apnea, and hypopnea with respiratory effort due to upper airway obstruction |
| Central Sleep Apnea (CSA) | Apnea and hypopnea with absence of respiratory effort due to failure in brain signaling |
| Hypoventilation Syndrome | Hypercapnia, nocturnal hypoxia, common in obesity and COPD |
| Sleep-related breathing hypoxemia disorder | The desaturation is not fully explained by hypoventilation, obstructive sleep apnea, or other sleep-related breathing disorder |

**Table 1.**
*Types of sleep-related breathing disorders.*

and those characterized by hypoxemia. There are six subtypes of hypoventilation syndrome: obesity hypoventilation syndrome (OHS), congenital central alveolar hypoventilation syndrome (CCHS), late-onset central hypoventilation with hypothalamic dysfunction, idiopathic central alveolar hypoventilation, sleep-related hypoventilation due to medication or substance, and sleep-related hypoventilation due to medical disorder. In contrast, sleep-related hypoxemia is not further subdivided in the classification [7, 8].

The ICSD-3 defines sleep-related hypoxemia as oxygen saturation dropping to ≤88% for ≥5 minutes, without concurrent sleep-related hypoventilation. Sleep-related hypoxemia is typically caused by an underlying medical or neurological condition, though a co-existing sleep-related breathing disorder may also be present (**Table 1**), [8].

## 2. Obstructive sleep apnea

OSA is the predominant form of sleep-related breathing disorder (SRBD), characterized by recurring episodes of obstructive apneas, hypopneas, and/or respiratory effort-related arousals (RERAs). These events stem from repeated collapse of the upper airway during sleep. While it primarily affects older males, females, and children can also be impacted. Following menopause, the incidence of women rises, with subsequent rates similar between genders [3].

### 2.1 Epidemiology and risk factors

Obesity stands out as a primary risk factor for OSA. Numerous cross-sectional studies consistently demonstrate a link between higher body weight and increased susceptibility to OSA. Approximately 40% of individuals with obesity experience significant sleep apnea, and about 70% of OSA patients are classified as obese [9]. The prevalence of OSA varies across racial groups, African Americans under 35 years old exhibit higher rates of OSA compared to White Americans of the same age, regardless of body weight. In Asia, the OSA prevalence mirrors that of the United States despite lower obesity rates [3, 4].

Risk factors for OSA encompass four major categories: age, sex, obesity, craniofacial and upper airway abnormalities [3, 4, 9, 10].

- Age: OSA prevalence escalates with age, peaking typically in the sixth to seventh decade of life.

- Sex: OSA occurs more frequently in males than females, typically two to, three times more, although after menopause, the risk may become similar between genders.

- Obesity: obesity and hypoventilation syndrome are associated with OSA in approximately 90 percent of cases.

- Craniofacial and upper airway abnormalities: These abnormalities raise the likelihood of developing OSA. Examples include abnormalities such as a diminished size of the maxilla or mandible, a broad craniofacial base, and hypertrophy of the tonsils and adenoids, which is particularly prevalent among children [3].

There are other factors that are less directly related but nonetheless crucial to consider [3, 4]. Factors contributing to worsened OSA include smoking, a family history of snoring or OSA, nasal congestion, and the use of substances and medications such as alcohol, benzodiazepines, narcotics, and gabapentin.

Various medical conditions also exacerbate or contribute to OSA. These include systemic hypertension, especially resistant hypertension, atrial fibrillation, heart failure, pulmonary hypertension, advanced kidney disease, asthma, chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis, cerebrovascular disease, transient ischemic attacks, pregnancy, acromegaly, hypothyroidism, diabetes mellitus, polycystic ovary syndrome, Parkinson's disease, floppy eyelid syndrome, fibromyalgia, Barrett's esophagus, gastroesophageal reflux disease (GERD), secondary polycythemia, Down syndrome, multiple sclerosis, and post-traumatic stress disorder (PTSD). These conditions can worsen the severity of OSA or contribute to its development [3, 4].

### 2.2 Pathophysiology

OSA occurs when there is partial or complete obstruction of the nasopharynx, oropharynx, or both during sleep. This obstruction leads to repetitive episodes of apnea or hypopnea due to fluctuating airway patency. Consequently, patients experience multiple interruptions in breathing, resulting in episodes of hypoxia and hypercapnia. These disruptions alter normal sleep patterns, causing frequent arousals from both NREM and REM sleep. The effort to breathe against a closed upper airway creates fluctuations in intrathoracic pressure, which can impact cardiac function. Additionally, OSA may contribute to endothelial and neurotransmitter dysfunction [3, 4].

### 2.3 Clinical presentation

The clinical presentation of OSA is characterized by excessive daytime sleepiness (EDS), and fatigue which are commonly reported as the primary complaint. Partners may also mention loud snoring, choking, gasping, snorting, or interruptions in breathing during sleep. These symptoms are often discovered coincidentally during consultations for other reasons. Patients typically report feeling drowsy or nodding off in dull, passive, or uneventful circumstances. Morning headaches, typically frontal and squeezing, are common and lack associated symptoms such as nausea, sensitivity to light, or sensitivity to sound [3].

Insomnia is reported by around one-third of OSA patients instead of daytime sleepiness, with a higher prevalence among females. Nocturia, the need to urinate frequently at night, is also reported by OSA patients. It occurs due to negative

intrathoracic pressure caused by inspiratory efforts against a closed airway. The body's response involves a natriuretic reaction triggered by the secretion of atrial natriuretic peptide, induced by cardiac distention from the vacuum-like pressure. This hormone increases sodium and water excretion while suppressing other hormonal systems responsible for fluid volume regulation, such as vasopressin and the renin-angiotensin-aldosterone system. Managing sleep apnea and addressing airway impairment has shown effectiveness in reducing or eliminating nocturia [3, 4, 9, 10].

Obesity is the most prevalent clinical feature in OSA patients, although individuals may vary in weight status. Various craniofacial deformities and a crowded oropharyngeal airway can reduce upper airway space, contributing to OSA. Examples include retrognathia, micrognathia, lateral narrowing near the peritonsillar area, macroglossia, tonsillar enlargement, elongated or enlarged uvula, a high or narrow palate, deviation of the nasal septum, and nasal polyps. The modified Mallampati classification is commonly used to assess airway constriction, with grades 3 and 4 indicating significant narrowing. Both the Mallampati classification and Friedman tongue position correlate with OSA severity [3, 4, 9, 10].

An increased neck circumference, especially above 17 inches in males and 16 inches in females, is closely associated with OSA. Comorbidities and complications in OSA patients often manifest as signs of associated illnesses, with systemic hypertension and HF being frequently observed, and pulmonary hypertension less commonly encountered [3, 4].

To accurately differentiate OSA from other conditions, it is crucial to consider its key symptoms:

- Excessive Daytime Sleepiness (EDS): various conditions have EDS as a symptom, but clinical history and polysomnography (PSG) can help distinguish them from OSA. Home Sleep Apnea Test (HSAT) might not adequately evaluate complex sleep disorders causing daytime sleepiness, such as periodic limb movement disorder, restless leg syndrome, narcolepsy, CSA, and sleep-disordered breathing conditions not related to OSA [3, 4].

- Abrupt Awakenings or Abnormal Sleep Sensations: conditions like gastroesophageal reflux, Asthma, "swallowing issues, nighttime seizures, and psychological conditions like panic attacks may lead to sudden awakenings or unusual sensations while asleep. PSG is essential for differentiating these issues from OSA [3, 4, 9–11].

- Primary Snoring: is more prevalent than OSA. The sole dependable method to differentiate between snoring linked to OSA and primary snoring is through sleep apnea testing [3, 4].

- Headaches occurring in the early morning: can also be associated with insomnia and bruxism, or the presence of a brain mass. Therefore, a thorough interrogation, physical examination, and appropriate tests such as PSG and brain imaging when warranted are essential for accurate diagnosis and management [3].

### 2.4 Diagnosis

Considering that OSA cannot be clinically diagnosed, patients demonstrating frequent EDS alongside a minimum of two of the subsequent clinical signs should

undergo testing, Frequent loud snoring, witnessed episodes of apnea, gasping, or choking during sleep, and a medical history of systemic hypertension [3, 4, 11].

When these criteria are not present, diagnostic testing may also be necessary for individuals exhibiting only EDS or showing additional clinical signs of OSA such as tiredness, abnormalities in the upper airway, or snoring, as well as those with related conditions or complications like resistant hypertension, atrial fibrillation, nighttime chest pain or irregular heart rhythms, heart failure, stroke, and temporary interruptions in blood flow to the brain. Additionally, diagnostic testing may be required for patients in scenarios where OSA needs confirmation or exclusion as a potential cause or contributing factor to their symptoms, such as unexplained pulmonary hypertension or polycythemia, or following a car accident due to falling asleep at the wheel [3, 4].

Polysomnography (PSG) conducted in a laboratory setting is regarded as the primary diagnostic test for OSA. This test can be performed as either a complete overnight study or a split-night study. If OSA is diagnosed during a complete overnight study patient may need to return for a separate study to titrate the appropriate pressure to administer (PAP) therapy). In a split-night study, the diagnostic portion is performed solely during the early part of the night. Patients identified with OSA during this phase can undergo PAP therapy adjustment in the latter part of the night [3].

If clinical suspicion for OSA remains high despite a negative in-laboratory PSG result, repeat testing is recommended due to considerable variability in PSG outcomes from one night to another. For individuals with a high probability of having moderate to severe uncomplicated OSA and no indication of nonrespiratory sleep issues, a Home Sleep Apnea Test (HSAT) using suitable equipment can serve as a substitute for PSG, assuming the patient is not engaged in mission-critical work [3, 4, 8, 9].

The diagnostic criteria and indices utilized for reporting differ between PSG and home sleep, apnea testing HSAT [3, 11–13].

PSG:

- At least five episodes of primarily obstructive respiratory events (like obstructive or mixed apneas, hypopneas, or RERAs) per hour of sleep in patients who exhibit symptoms such as sleepiness, nonrestorative sleep, fatigue, insomnia, waking up with breath-holding, gasping, or choking, habitual snoring noted by a bed partner, or have associated conditions such as hypertension, mood disorders, cognitive impairment, coronary artery disease, stroke, heart failure, atrial fibrillation, or type 2 diabetes mellitus.

- Fifteen or more predominantly obstructive respiratory events (including apneas, hypopneas, or RERAs) occur each hour during sleep, regardless of the presence of symptoms or other medical conditions.

PSG data provide two indices that quantify obstructive events occurring during sleep per hour [3, 4]:

- The apnea-hypopnea index (AHI), which is calculated as the total number of apneas and hypopneas divided by the total sleep time in hours.

- The respiratory disturbance index (RDI), which is calculated as the total number of apneas, hypopneas, and RERAs divided by the total sleep time in hours.

There is ongoing debate regarding whether the AHI or RDI should be considered the primary index for diagnosing OSA. The RDI offers additional insights into sleep fragmentation and enhances sensitivity in OSA diagnosis by incorporating RERAs alongside apneas and hypopneas. In contrast, relying solely on the AHI may not fully predict symptoms and complications [3].

Regarding HSAT, most devices do not include an electroencephalogram, which complicates the reliable identification of RERAs and arousals associated with hypopneas. Instead, the Respiratory Event Index (REI) is utilized, measuring the count of respiratory events per hour of recording time rather than total sleep time. The cutoff values for diagnosing OSA using REI are like those used in-laboratory sleep testing. Patients with a negative study, inconclusive results, or technically insufficient outcomes should undergo further evaluation in a laboratory setting [3, 11, 12].

### 2.5 Classification of severity

Patients are generally categorized as follows based on their: [3, 4, 11].

- Mild: patients diagnosed with mild OSA generally show an AHI/RDI/REI from 5 to 14 respiratory events per hour of sleep, often accompanied by symptoms.
- Moderate: individuals with moderate OSA typically exhibit an AHI/RDI/REI of 15–30 respiratory events per hour of sleep.
- Severe: those with severe OSA usually present with an AHI/RDI/REI exceeding 30 respiratory events per hour of sleep.

### 2.6 Complications

Patients diagnosed with OSA are at increased risk of several adverse clinical outcomes, including motor vehicle accidents occurring at rates two to three times higher than those without the condition. Cognitive deficits, such as memory impairment and reduced executive function, further contribute to the risk of errors and accidents. Neuropsychiatric symptoms such as irritability, depression, psychosis, and sexual dysfunction may also manifest in individuals with OSA. Untreated OSA significantly raises the likelihood of developing systemic hypertension, coronary artery disease, cardiac arrhythmias, heart failure, and stroke [3, 4, 12–14].

OSA is associated with group 3 pulmonary hypertension, particularly in cases involving OHS or other causes of daytime hypoxemia, such as chronic lung disease. Severe hypoxemia can also lead to secondary polycythemia. Additionally, patients with OSA have a higher prevalence of insulin resistance, type 2 diabetes, and related complications. Moreover, severe cases of OSA are linked with a two- to threefold increased prevalence of nonalcoholic fatty liver disease (NAFLD) [3, 4].

### 2.7 Screening for OSA

The American Academy of Sleep Medicine (AASM) advises against the routine use of screening tools, such as questionnaires, in asymptomatic individuals. However, several assessment tools are commonly utilized, including the STOP-Bang questionnaire, the Epworth Sleepiness Scale (ESS), the Berlin score, and the sleep

apnea clinical score. These tools are valuable for identifying patients with a high probability of moderate to severe OSA. It is essential to recognize that while these questionnaires aid in screening for OSA, they are not substitutes for a formal sleep apnea test [15, 16].

### 2.8 Management

OSA should be managed as a chronic condition requiring long-term, multidisciplinary care. Effective treatment of OSA can yield numerous benefits, including clinical improvement such as reduced daytime sleepiness, decreased healthcare utilization and costs, and potentially lowered cardiovascular morbidity and mortality.

Patient education is crucial, encompassing comprehensive information about the disease, its risk factors, progression, and potential outcomes. It is essential to highlight the increased risk of motor vehicle accidents associated with untreated OSA and caution patients about the dangers of driving or operating machinery while experiencing drowsiness. Patients should be advised to avoid activities requiring vigilance and alertness if they feel sleepy. Additionally, patients must understand the importance of disclosing their sleep apnea status to healthcare providers, particularly before undergoing any surgical procedures or starting opioid medications [3, 12, 17].

The lifestyle modification in OSA management varies depending on individual patient characteristics. Overweight or obese patients should be encouraged to pursue weight loss as a key strategy. Weight management strategies, including dietary changes and exercise, should be emphasized, with possible referral to a nutritionist for tailored advice. Exercise can offer modest improvements in OSA, independent of significant weight loss. For those with positional OSA, adjusting sleep positions can be beneficial, though this may pose practical challenges [3].

Patients should be informed about the impact of alcohol and certain medications, such as opioids, on worsening OSA symptoms [3, 12, 17]. Prescribing clinicians should be aware of the patient's OSA status when considering medications, as certain drugs with central nervous system depressant properties should be avoided if feasible. This includes benzodiazepines, barbiturates, antiepileptics, sedative antidepressants, antihistamines, and opioids. Concerns arise with antidepressants linked to weight gain, such as mirtazapine, while others may worsen sleep disturbances by triggering restless legs syndrome or periodic limb movements [3, 4, 12, 17].

PAP therapy is the primary treatment for adults diagnosed with OSA, functioning by maintaining a positive pharyngeal transmural pressure to prevent upper airway collapse during sleep. This mechanism supports end-expiratory lung volume and stabilizes the upper airway, thereby reducing respiratory events like apneas and hypopneas. PAP therapy effectively decreases the occurrence of these events, improves daytime alertness, lowers systemic blood pressure, reduces accident risk, and addresses issues such as erectile dysfunction, enhancing the overall quality of life across varying disease severities. However, its impact on mortality remains uncertain [3, 4].

Indications for PAP therapy includes [3]:

- Patients with an AHI >5 events per hour of sleep, coupled with one or more symptoms associated with OSA.

- Patients with an AHI ≥15 events per hour of sleep, regardless of symptom severity.

- Individuals in safety-sensitive professions (e.g., pilots, air traffic controllers, engineers, drivers) with an AHI between 5 and 15 events per hour, even without clinical symptoms.

- Patients with a significant number of RERAs (e.g., ≥10 per hour) and excessive daytime sleepiness, even if the AHI is ≤5 events per hour.

PAP therapy encompasses several modalities such as CPAP, bi-level PAP (BPAP), and auto-titrating PAP (APAP). However, treatment can fail due to various factors, including nonadherence or poor adherence to therapy, inappropriate positive pressure settings, or the presence of concurrent sleep disorders like narcolepsy that may require different treatment strategies. It is crucial to evaluate the patient's medication regimen, as certain medications can induce sleepiness. Additionally, inadequate sleep duration can reduce the effectiveness of OSA treatment [3, 4].

Comorbidities such as diabetes, hypertension, heart, failure, and ischemic heart disease, need close monitoring because potentially affected by OSA therapy is crucial posttreatment initiation. Adjustments to therapy for these comorbidities may be necessary once OSA-specific treatment is underway [3, 11, 16].

Alternative therapeutic approaches for treating OSA include advancement devices, tongue-retaining devices, oral appliances, surgical interventions, and pharmacological options. These alternatives are typically considered for patients with mild to moderate OSA who either cannot tolerate or prefer not to use PAP therapy. However, oral appliances may not be as effective for those with severe OSA or significant sleep-related hypoxemia [3, 12, 17].

Surgical treatments, such as upper airway, maxillofacial, or bariatric surgery, may be recommended if PAP therapy or oral appliances are declined or prove ineffective after a trial period of at least 3 months. Another surgical option involves hypoglossal nerve stimulation, which uses an implantable neurostimulator device and is suitable for certain individuals with moderate to severe OSA who do not respond well to PAP therapy and meet specific criteria [3, 4, 11].

Pharmacological treatments have been investigated in clinical trials but have generally not shown sufficient effectiveness to replace standard therapies. These include ventilatory stimulants like medroxyprogesterone, which have shown limited success. Clinical trials with modafinil, a wakefulness-promoting agent, demonstrated mild efficacy in reducing daytime sleepiness in OSA patients who continue to experience symptoms despite treatment [6].

The identification of different phenotypes in patients with OSA emerges to achieve personalized treatment and identify patients with a higher risk of comorbidities. Different clinical phenotypes such as sleep disturbance, minimal symptoms, excessive daytime sleepiness, and upper respiratory symptoms... have been described in the medical literature. More research is needed to understand the relationship between different phenotypes and the risk of adverse outcomes and to predict responses to specific treatment [18].

## 3. Conclusion

Sleep-related breathing disorders encompass a spectrum of conditions that cause breathing difficulties during sleep, ranging from mild to severe. OSA is characterized by recurrent episodes of partial or complete upper airway obstruction during sleep.

Other disorders include central sleep apnea, where the brain fails to signal the muscles controlling breathing, sleep-related hypoventilation involving inadequate ventilation, and hypoxemia disorders. These disorders can significantly impact well-being, leading to symptoms such as excessive daytime sleepiness, fatigue, and snoring.

Healthcare professionals should be vigilant as these disorders are often diagnosed incidentally during consultations for other complaints or comorbidities. Management typically involves lifestyle modifications, weight loss, positional therapy, and the use of interventions like PAP devices and oral appliances to maintain open airways during sleep. In some cases, surgical treatment may be necessary. Early recognition and management of sleep-related breathing disorders are essential for improving sleep quality and reducing associated health risks.

In conclusion, SRBD are an important health problem that can affect the quality of life of the individuals, family and society. OSA is the most common SRBD, and it has seen significant global growth, becoming a major public health issue in industrialized and non-industrialized nations due to its association with key global health priorities like obesity, arterial hypertension, diabetes mellitus, and depression [3]. Consequently, it incurs high healthcare costs. It is important for healthcare professionals to be able to identify and diagnose these disorders, as they can lead to serious health consequences if they are not treated. With the properly approach, patients with sleep breathing disorders can experience improvements in their overall health and well-being. Continued investigation in this area is vital for advancing our understanding and knowledge of these disorders.

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Chapter 7

# Obstructive Sleep Apnea Syndrome (OSAS) and Menopause

*Esra Dugral*

## Abstract

Obstructive Sleep Apnea Syndrome (OSAS) is a sleep disorder in which intermittent hypoxia and systemic inflammation mechanisms are prominent, leading to many serious health problems. Cardiovascular and metabolic diseases are among the leading clinical problems caused by OSAS. When left untreated, its reflection on society is increased morbidity and mortality rates. For this reason, many clinical studies have focused on the reasons that increase the risk of OSAS. Menopause has taken its place in research as one of these reasons. The fluctuation in the secretion of female reproductive hormones manifests itself in a wide range of problems in the field of sleep, ranging from insomnia to OSAS. Hormonal changes and body fat distribution are thought to play an important role in the pathology leading to OSAS. The aim of this article is to provide a better understanding of the bridges between OSAS and menopause and to show that sleep-related problems of women close to menopause age who come to health examinations may indicate OSAS even if they do not have obvious complaints.

**Keywords:** Obstructive Sleep Apnea Syndrome (OSAS), intermittent hypoxia, menopause, sex hormones, body fat distribution

## 1. Introduction

Obstructive Sleep Apnea Syndrome (OSAS) is a sleep disorder characterized by intermittent hypoxia, sleep interruptions and excessive daytime sleepiness due to obstruction in the upper airway during sleep. As studies on sleep have increased over the years, it has been realized that it is a subject that is sometimes overlooked among clinicians and that it actually affects many more people than expected. The suspicion that the hypoxic and inflammatory environment caused by OSAS in the body may form the basis of many chronic diseases is gradually giving way to reality. One of the conditions in which the prevalence of OSAS increases is menopause. Menopause is a physiological period that roughly corresponds to one-third of a woman's life, in which hormonal changes are at the forefront. Since the woman cannot ovulate during this period, she has lost her reproductive abilities. In addition, she has to get used to a different life due to the absence of the hormonal cycle that has accompanied her for years. One of the most common problems in early menopause is sleep problems. Among these, OSAS emerges as a disease that requires special attention due to the clinical comorbidity it causes.

The hormonal changes that begin in women in the premenopausal period bring with them a number of health-related conditions that require attention. Among these conditions, OSA is important because of the chronic consequences of intermittent hypoxia and systemic inflammation, but it is often overlooked because it presents itself as subtle symptoms in women. The aim of this article is not to overlook the sleep-related symptoms that should be questioned in the health examinations of older women and to contribute to facilitating the postmenopausal life of women.

## 2. Obstructive Sleep Apnea Syndrome (OSAS)

### 2.1 OSAS definition

Obstructive Sleep Apnea Syndrome (OSAS), which is ranked first in the title of sleep-related respiratory disorders in the latest update (International Classification of Sleep Disorders-3; ICSD-3) [1] by the American Academy of Sleep Medicine (AASM), is a sleep disorder characterized by complete (apnea) or near-complete (hypopnea) interruption of airflow measured through the mouth and nose due to narrowing of the upper airway during sleep [2]. The narrowing of the upper airway as a result of decreased dilator muscle activity during sleep causes a decrease in oxygen saturation, leading to awakenings. Arousal is mostly detected as a bioelectric wakefulness reaction (arousal) in EEG recordings used during polysomnography (PSG). With arousal, the person experiences a conscious awakening or an unconscious awakening with a transition to a lighter stage in the sleep stages. The mechanisms of upper airway narrowing and pharyngeal obstruction during sleep are still unknown and multifactorial effects play a role in the pathogenesis [3]. Studies suggest that the effect of decreased respiratory drive on muscle tone during sleep and the contribution of upper airway anatomical and neuromuscular structures to the event play an important role in this narrowing [4]. Recurrent obstructions cause oxygen saturation to decrease, initiating respiratory effort and bioelectric wakefulness reaction (arousal) occurs. With the formation of arousal, respiration begins to return to normal and deoxygenation improves [5, 6]. Frequent deoxygenation/reoxygenation cycles during sleep cause intermittent hypoxia and an increase in oxygen radicals, leading to systemic inflammation. Increased respiratory effort causes fluctuations in intrathoracic pressure, leading to sympathetic system activation [7]. The fragmented sleep caused by arousal manifests itself as excessive daytime sleepiness, fatigue, reluctance and lack of attention and concentration in people with OSAS. This leads to an increase in work and traffic accidents, impairment in social communication and quality of life [8].

### 2.2 OSAS risk factors

Factors that cause upper airway narrowing in support of pathophysiology constitute risk factors for OSAS. The most important risk group is obese patients, especially those with increased adipose tissue around the neck and tongue [9, 10]. Studies have shown that fat accumulation in the upper airway reduces airway diameter and facilitates the formation of OSAS by increasing the susceptibility to collapse [11]. Increased abdominal pressure during sleep in central obese patients with prominent abdominal adiposity causes loss of end-expiratory volume and subsequently facilitates airway collapse [12]. In support of all these data, 22% of obese OSAS patients improved in the non-supine position as a result of weight loss [13].

OSAS can be seen at any age, but it is known that the frequency of apnea increases in advanced age and plateaus after the age of 65 [14, 15]. Interestingly, studies have also found that the prevalence of OSAS increases with age but its severity decreases [16]. Although the effect of age is not known exactly, the increase in co-morbid diseases supporting the development of OSAS with advancing age is one of the plausible reasons. When analyzed in terms of anatomical and neuromuscular changes, it has been found that advanced age causes changes in body fat distribution, loss of lung elastic recoil, decrease in airway dilator muscle activity, and slowing of respiratory control. These factors are thought to facilitate the development of OSA [16, 17].

Gender is another parameter investigated in OSAS prevalence. Male gender stands out as an important risk factor especially in the presence of obesity [18]. Studies show that the estimated male/female prevalence is 1.5:1 [19]. Although the reasons for the disparity are not fully known, some issues come to the forefront of studies. From an anatomical point of view, it has been suggested that men have a longer airway regardless of their body size and this may predispose them to collapse [20]. In another study, it was mentioned that men are more prone to central obesity and obstruction is more common due to excess fat accumulation in the abdominal and neck region [21].

Certain facial phenotypes due to craniofacial differences that may increase upper airway obstruction have also been associated with OSAS. Studies have shown that there is a correlation between sleep apnea and anatomical pathologies such as soft tissue disorders such as tongue, tonsillar and adenoid hypertrophies or abnormalities in the size and location of the maxilla and mandible [22–24]. The prevalence of OSAS varies according to race and ethnicity. Studies have found a higher prevalence and severity of OSAS in African-Americans compared to Caucasians and in Asians compared to Europeans [25, 26].

Smoking and alcohol consumption seem to have effects on the prevalence of OSAS. Active smoking has been found to facilitate obstruction by increasing upper airway inflammation and to be effective on arousal [27]. Although alcohol and sedative use is not clear, it is thought to be effective in the upper airway musculature by decreasing neuronal stimulation activity and facilitating collapsibility during sleep [28].

### 2.3 OSAS epidemiology

OSAS is a common sleep-related respiratory disorder and can be detected in all age groups. According to a 1993 study conducted in the United States of America (USA), when the presence of an apnea-hypopnea index (AHI) ≥ 5 events/hour was taken as a criterion, the prevalence of OSAS was found to be 2% in women and 4% in men [14]. In another study led by the same author and conducted in the USA in 2009, the prevalence of OSAS was found to be 9% in women and 24% in men when AHI ≥ 5 events/hour was taken as a criterion. When AHI ≥ 15 events/hour was taken as a criterion it found 4% in women and 9% in men [29]. In another study with a large participation (n: 2121) of people of white European origin, the prevalence of OSAS was reported as 23.4% in women and 49.7% in men according to the AHI ≥ 15 events/hour criterion [30]. In a 2017 review, it was found that the general population prevalence ranged between 9% and 38% when AHI ≥ 5 events/h, and between 6% and 17% when AHI ≥ 15 events/h. In addition, in this study, it was stated that the prevalence of OSAS increased up to 90% in men and 78% in women in some populations with increasing age and obesity [31]. A recent study reported approximately 1 billion affected people worldwide [32].

### 2.4 OSAS and clinical outcomes

Today, the elderly population is increasing rapidly with the prolongation of the average human life expectancy in societies. In younger populations, obesity is emerging as a public health problem. The effects of both conditions on the prevalence of sleep apnea have been mentioned above. The problem is not only the increased prevalence of sleep apnea but also the comorbidities caused by this disease. Intermittent hypoxia, intrathoracic pressure fluctuations and sleep interruptions occur due to transient airway collapse during sleep [33]. While intermittent hypoxia and sleep fragmentations cause sympathetic system activations, the repetitive hypoxia-reoxygenation cycle induces oxidative stress, increases the production of free oxygen radicals and causes inflammation, leading to vascular endothelial dysfunction [34]. This chain reaction in the body has the most effect on the cardiovascular system [35]. Studies have shown that OSAS is closely associated with hypertension, arrhythmias, coronary artery disease and stroke [36, 37]. In addition, metabolic consequences such as type 2 diabetes mellitus, chronic liver failure and mood disorders, especially depression, are also clinical consequences of OSAS [38–40]. For these reasons, the treatment of sleep apnea is becoming increasingly important because almost every organ is affected by its chronic effects. The return of untreated sleep apnea to society may be increased mortality and morbidity rates and unpredictable health expenditures.

### 2.5 OSAS and females

The most important point of the OSAS mechanism is the recurrent stenosis of the upper airway. In studies on these stenoses, it has been determined that the amount of soft tissue surrounding the upper airway is higher in men and the mechanical effect of this situation may facilitate collapse [21]. In addition, in the following years, it has been determined that the upper airway distance of men is longer than that of women regardless of height. Because of this length, it was thought that obstruction would occur more easily [20]. In studies on the passive pharyngeal airway collapse pressure that would cause collapse of the upper airway, it was found to be higher in men when body mass index (BMI), age and AHI grade were controlled [41]. In another study, it was found that the waist-to-hip ratio (Waist-to-hip ratio) was more effective in predicting the severity of the disease in men than in women, although it was not sufficient alone to indicate the severity of OSA [42]. The fact that men have more central obesity according to fat distribution causes a decrease in lung volumes during sleep and facilitates the occurrence of sleep apnea. In addition, women's lower respiratory need and higher minute ventilation responses to breathing difficulties also have a protective effect [43]. All these and similar studies have led to the replacement of male gender among OSAS risk factors.

In men, the symptoms of OSAS are more often manifested as snoring and witnessed apnea, which can be easily detected during clinical examination by self-report or by a bedmate, making it easier to reach a diagnosis. In women, OSAS symptoms are more subtle and often present as morning headache, attention deficit, memory difficulties, fatigue and mood disorders. These symptoms can easily be confused with other illnesses such as depression, making diagnosis difficult. In addition, men are more likely to report symptoms, while women are less likely to complain. It is stated that insomnia problems such as difficulty in initiating and maintaining sleep and early morning awakening are more prominent in women [44–46].

When PSG data were analyzed, it was found that women had lower sleep apnea severity, higher hypopnea and oxygen saturation levels and longer stage 3 sleep duration. While there was no difference between genders in terms of REM (Rapid Eye Movement) sleep, women were found to have lower AHI values during non-REM sleep. Even in women with higher age and BMI, lower AHI values were found in the non-REM sleep phase [43, 47]. When male and female patients of the same age were analyzed, it was found that women had worse sleep quality and sleep efficiency than men, but sleep apnea severity was less [46]. In addition, AHI values of women in supine positions were found to be lower than men [48].

## 3. Menopause

### 3.1 Definition

The World Health Organization (WHO) defines menopause as "the loss of ovarian activity and the permanent cessation of menstruation". Although menopause is a physiological period in women's lives, it can also occur as surgical menopause after bilateral oophorectomy or iatrogenic menopause after chemotherapy and radiotherapy. If a woman who experiences menstrual irregularities after hormonal changes does not have menstrual bleeding for 1 year, she is considered to have entered the menopause period from the last bleeding [49]. The age of menopause varies according to geographical characteristics and race, ranging from 50 to 51 years in North America, 50–53 years in Europe and 42–49 years in Asia [50].

Perimenopause is characterized by irregular menstrual cycles and hormonal fluctuations and begins approximately 4 years before the last menstrual period. From perimenopause onwards, there is a decrease in estrogen levels due to the depletion of ovarian follicular reserves and a corresponding increase in follicle stimulating hormone (FSH) and luteinizing hormone (LH) levels. Although this period in the female life cycle is considered physiological, its early and late effects on women's health cannot be ignored. In the early period, symptoms such as hot flashes, sleep disturbances, mood changes, skin and breast changes and vaginal dryness are observed. In the late period, many problems such as cardiovascular changes, osteoporosis and musculoskeletal problems are added to the picture [51, 52].

### 3.2 Menopause and sleep disorders

Insomnia, decreased sleep efficiency and quality are frequently encountered in women due to hormonal changes brought about by advancing age. Since increased complaints mostly coincide with the perimenopausal-menopausal period, most studies have examined women in this age group. In studies conducted on women of reproductive age, the effects of menstrual cycle on sleep were examined, but it was found that stress caused by physical/mental health and responsibilities undertaken were more effective on sleep [53]. Changes in estrogens and progesterone levels during pregnancy affect sleep physiology and disrupt sleep architecture. As pregnancy progresses, sleep duration decreases and restless leg syndrome increases [54].

Menopause is a period of sharp hormonal changes that covers approximately one-third of a woman's life. Sleep disorders are a common problem starting in the early stages of menopause. It has been documented that low estrogen levels and high follicle stimulating hormone (FSH) levels detected in the perimenopausal period are

associated with frequent sleep problems [55]. Studies have found that 38% of older women experience sleep difficulties. When adjusted for age, this rate increases to 45.4% in late perimenopause and 47.6% in surgical menopause [56]. The reason for higher sleep complaints in surgical menopause was found to be related to the rapid disappearance of sex hormones [57]. In addition, vasomotor symptoms and fibromyalgia caused by hormonal changes that begin with menopause are thought to be related to sleep disorders [58, 59].

In addition to sleep difficulties and OSA, other sleep disorders such as parasomnias, night terrors, bruxism, periodic leg movement disorder (PLMD), restless leg syndrome(RLS) and REM-related sleep disorder are less common in menopause [60, 61]. Studies suggest that the increase in the prevalence of RLS and PLMD after menopause may be related to aging rather than hormonal changes [62].

### 3.3 Menopause and OSAS

Among the studies investigating the relationship between menopause and sleep apnea, the Wisconsin Sleep Cohort Study stands out. When factors such as age, BMI and smoking were controlled, it was observed that mild sleep-disordered breathing (AHI $\geq$ 5) increased 2.6-fold and more severe sleep-disordered breathing (AHI $\geq$ 15) increased 3.5-fold in postmenopausal women [63]. Menopause itself is thought to be an independent risk factor for sleep-disordered breathing. In a large study conducted by Bixler et al., in which more than twelve thousand women were contacted by telephone and then PSG was performed on 1000 selected women, the prevalence of moderate and severe OSAS in postmenopausal women who did not use hormone replacement therapy was found to be 9.7% and 2.7%, respectively. This rate was found to be 3.2% and 0.6%, in premenopausal women [64]. In addition to the loss of the protective effect of progesterone, one of the female reproductive hormones, in the increase in the incidence of OSAS after menopause [64], it is thought that changes in fat distribution due to the absence of estrogen after menopause [65].

#### *3.3.1 Hormonal changes*

In women, menopause begins with the loss of ovarian activity and permanent termination of the menstrual cycle or surgical removal of the ovaries. The absence of previously regularly secreted estrogen and progesterone causes postmenopausal symptoms. In menstruating women, reproductive hormones have a protective effect on women in terms of OSA. The stimulatory effect of progesterone on upper airway dilation and ventilation drive is recognized as a protective feature of women from apnea [66]. Progesterone also promotes sleep by acting as an anxiolytic. The relationship between the decrease in progesterone before menstrual bleeding and sleep irregularity is therefore important [60]. Estrogen improves sleep by increasing REM sleep and total sleep time. When postmenopausal women of similar age groups were analyzed, women with severe OSAS (AHI $\geq$ 30) were found to have lower estrogen levels than others [67].

Testosterone, the other sex steroid hormone, is secreted in both sexes. Studies have shown that OSAS symptoms occur or worsen in hypogonadal men receiving testosterone replacement therapy [68, 69]. One reason for the increase in the incidence of OSAS in postmenopausal women may be thought to be the increase in testosterone levels. In a very recent study published in 2023, it was reported that ovarian androgen production during the menopausal transition did not change significantly due

to menopause. In the same study, it was mentioned that decreasing estrogen levels caused a decrease in sex hormone-binding globulin (SHBG) levels and an increase in the free circulating amount of androgen that cannot bind to this protein. It has been suggested that this leads to a relative predominance of androgen hormones during the menopausal transition and may be used to explain the facial hair growth or hair loss seen in some postmenopausal women [70]. The most common cause of absolute androgen excess in postmenopausal women is polycystic ovary syndrome. It has been found that the risk of OSAS development in women with polycystic ovary syndrome, in whom testosterone levels are high, is higher than in the healthy control group [71].

*3.3.2 Changes in body fat distribution*

Weight gain in women is thought to be caused primarily by age-related changes. Animal experiments on this subject have shown that peri/postmenopausal hormonal changes alter body composition and that estrogen reduction contributes to the increase in abdominal fat. It was also found that the findings improved with the therapeutic administration of the deficient estrogen hormone [72]. Studies using radiologic methods in humans have similarly found that intra-abdominal adiposity increases in menopause [73]. The waist-to-hip ratio is a measure of intra-abdominal adiposity. It is known that an increase in waist circumference is closely associated with visceral organ adiposity, which is associated with cardiovascular disease risk. Abdominal fat is also responsible for the release of adipokines and inflammatory markers that promote chronic inflammatory diseases such as type 2 diabetes and metabolic syndrome [74]. Studies show that abdominal adiposity, rather than weight gain with age, is strongly associated with menopause. In a study of 3426 data from 543 perimenopausal or postmenopausal women followed for 6 years, an increase in fat mass and waist circumference and a decrease in skeletal muscle mass were found in the third follow-up year compared to baseline [75]. In another interesting study, significant increases in total fat mass and percentage of abdominal fat mass were found in non-obese perimenopausal women who were followed for several years [76].

## 4. Conclusion

In summary, clinical studies suggest that menopause, which takes place in the physiological life cycle of women, may increase the risk of non-physiological and even pathological health problems. Hormone replacement therapy recommended by some clinicians during menopause cannot be used in all women due to its side effects. However, studies have shown that estrogen alone or estrogen-progesterone therapy provides a decrease in overall fat mass, improvement in AHI levels, improvement in insulin sensitivity and a decrease in the rate of development of type 2 diabetes [72, 77]. Therefore, there is a need for large-scale studies that better demonstrate the profit-loss relationship to be used in selected cases.

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Chapter 8

# Thirty-Year Trends in Sleep Disorders and Cardiovascular Disease Risk

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**Abstract**

The aim of the study was to examine the prevalence and trends of sleep disorders and to assess the impact of sleep disorders on the risk of cardiovascular disease in the population aged 25–64 years. Surveys of representative samples of the population aged 25–64 in Novosibirsk were conducted in 1988–2018.2650 men and 3113 women were studied. The risk of developing arterial hypertension (AH) during the first 5 years of follow-up was 5.4 times higher in men and 4.35 times higher in women with sleep disorders than in those without. Men with sleep disorders had a 2.4 times higher risk of MI than those without. The risk of stroke was 3 times greater in men and 1.9 times greater in women with sleep disorders than without. Sleep disorders are a risk factor for MI only in men; for AH and stroke - in both men and women.

**Keywords:** sleep disorders, sleep duration, arterial hypertension, myocardial infarction, stroke

## 1. Introduction

The growing interest in sleep disorders is due to several reasons. Insomnia is the most common sleep disorder, affecting an estimated 30% of the world's adult population on a regular basis; 10% of people suffer from chronic insomnia [1–3]. Sleep disorders can lead to accidents and human error [1]. They can double the risk of fatal accidents [2–4]. The rapid emergence of "24/7" communities, i.e., 24 hours a day, 7 days a week, with attendance at round-the-clock events and increased use of television, Internet, and cell phones at night, means that adequate, uninterrupted nighttime sleep is becoming a rarity. Sleep problems are only getting worse every year. The research findings suggest that nighttime sleep duration has decreased over the past 30 years [5]. Complaints about sleep problems have increased significantly over the same period, and short sleep (<6 hours/night) has become increasingly common among full-time workers [6]. There is likely to be an increase in the proportion of workers with circadian rhythm disorders who are in demand to serve the "24/7"

communities. Similarly, as the proportion of the world's population that is elderly and the prevalence of obesity increase, sleep disorders will become more prevalent in the population and will increase in both low- and high-income countries [7]. Sleep plays an important role in maintaining good health. Studies conducted over the past decade have confirmed that sleep disorders have a powerful effect on the risk of infectious diseases, the onset and progression of a number of major medical conditions, including cardiovascular disease and cancer, and the incidence of depression [8, 9]. For optimal health and well-being, it is recommended that adults between the ages of 18 and 60 get at least 7 hours of sleep each night [10]. Sleep of <7 hours per day is associated with an increased risk of obesity, diabetes mellitus, hypertension, coronary heart disease, stroke, frequent mental disorders, and mortality from all causes [10–13]. According to the results of a national survey, 25% of adults in the United States self-report that they do not get the recommended amount of sleep. There is also evidence that in many modern societies, there has been a decrease in the amount of sleep per night [14]. It is now known that the amount of sleep Americans get is on the decline, and the percentage of men and women who have slept less than 6 hours has increased significantly over the past 2 decades. *In 1942*, Americans slept an average of *7.9 hours* per day, compared to *6.8 hours in 2013*, which is *13%* less [15]. Insufficient sleep impairs cognitive performance, which can increase the likelihood of road and other transportation accidents, occupational injuries, medical errors, and productivity losses that can affect society as a whole [16]. The relationship between sleep duration and adverse health outcomes is often described as a U-shaped curve, with minimal health risk associated with sleep duration of 7–8 hours, but the role of prolonged sleep >9 hours and its impact on health is less clear [10, 17]. The American Academy of Sleep Medicine (AASM) and the Sleep Research Society (SRS) concluded that "it is unclear whether sleeping more than 9 hours per day is associated with health risks" [18].

In Russia, about 45% of adults suffer from sleep disorders. Nearly 20% need serious sleep treatment [19]. In both physiological and pathological conditions, sleep is the most important modulator of the cardiovascular system. Sleep has a significant effect on the autonomic nervous system, hemodynamics, cardiovascular function, endothelial function, and the coagulation system. Epidemiologic and pathophysiologic studies have shown that sleep problems can be a contributor to cardiovascular disease (CVD) [20]. Robillard R. and co-authors found that sleep deprivation contributes to an increase in both SBP (systolic blood pressure) and DBP (diastolic blood pressure) in normotensive older people aged 60–69 years. The authors concluded that sleep deprivation leads to a change in blood pressure regulation mechanisms and may increase the risk of hypertension in healthy normotensive individuals [21]. In addition, daytime sleepiness has long been associated with high SBP and DBP and the development of hypertension 5 years later [22]. The high prevalence of hypertension in the elderly may be influenced by both insufficient and excessive sleep [23]. It is important to note that sleep deprivation in adolescents leads to an increase in heart rate, SBP and, to a lesser extent, DBP [24]. This confirms that changes in the sleep process - daytime sleepiness, and lack of nighttime sleep - lead to developing hypertension [25]. However, there are other data. Sleep disorders were not found to increase the risk of hypertension in a study conducted by Vozoris N.T. in 2014 [26]. Sleep disorders can be manifested by an imbalance of the autonomic nervous system in response to chronic stress, often accompanied by an increase in metabolic rate, an increase in heart rate, a decrease in heart rate variability, and an increase in cortisol secretion. Thus, dysregulation of the autonomic nervous system and the hypothalamic-pituitary axis contribute to the development of a mechanism linking sleep disorders and cardiovascular disease [27, 28]. The causal relationship

between sleep disorders and cardiovascular diseases is also experimentally confirmed, for example, sleep deprivation leads to an increase in blood pressure and the level of inflammatory mediators, as well as to a violation of carbohydrate metabolism and increased atherogenesis, and subsequently to cardiovascular diseases. In addition, sleep fragmentation can have a negative impact on blood flow to the brain and lead to cerebral circulation problems [29]. Women are more likely than men to complain about the quality of their sleep, especially as they age. 81% of women complain about insomnia, while 78% of men are likely to complain about sleep problems. Women are more likely to wake up early (50%) than men (41%) and have more difficulty falling asleep - 33 and 31% respectively [30].

Taking into account the above facts, the purpose of our study was to investigate the prevalence and thirty-year trends of sleep disorders, as well as to assess the impact of sleep duration and sleep disorders on the risk of cardiovascular diseases in the healthy population of Novosibirsk, Western Siberia, Russian Federation.

## 2. Materials and methods

The study results were obtained based on a survey of the able-bodied population of the Oktyabrsky district of Novosibirsk. The study included materials from 5 screening studies of representative samples of the population aged 25–64 years (budget topic Reg. No. FWNR-2024-0002). During the screening II in 1988–1989 1435 individuals were examined: 725 men, mean age 43.4 ± 0.4 years, response - 71.3% and 710 women, mean age 44.8 ± 0.4 years, response - 72%. During screening III in 1994–1995, 1038 individuals were examined: 647 men, mean age − 44.3 ± 0.4 years, response - 82.1%; 391 women, mean age - 45.4 + −0.4 years, response - 72.5%. During the screening IV in 2003–2005 1650 individuals were examined: 576 men, mean age - 54.23 ± 0.2 years, response - 61%; 1074 women, mean age - 54.27 + 0.2 years, response - 72%. During the screening V in 2013–2016, 975 individuals were examined: 427 men, mean age 34 ± 0.4 years, response - 71%; 548 women, mean age 35 ± 0.4 years, response - 72%. During the screening VI in 2016–2018, 665 individuals were examined: 275 men, mean age 49 ± 0.4 years, response - 72%; 390 women, mean age 45 ± 0.4 years, response - 75%.

The general examination in 1988–1989, 1994–1995, 2003–2005, 2013–2016, 2016–2018 was carried out according to the standard methods of the WHO program "MONICA-psychosocial (MOPSY)" [31]. Sleep disorders were assessed using the WHO "MONICA-psychosocial (MOPSY)" scales [31]. The respondents were asked the question: "How can you rate the quality of your sleep?" The range of responses included the following options: "very good", "good", "satisfactory", "bad", "very bad". There was another question: "How many hours a day do you usually sleep?" The range of responses included the following options: "5 hours and less", "6 hours", "7 hours", "8 hours", "9 hours", "10 hours and more". The analyzed level of the risk factor was taken as its value in the original study. The contribution of time dynamics was not taken into account. The methods were strictly standardized and met the requirements of the WHO "MONICA-psychosocial" protocol [31].

Processing of the findings under the WHO MONICA psychosocial program was carried out at the MONICA Information Collection Center in Helsinki, Finland. Quality control was performed at MONICA Quality Control Centers in Dundee (Scotland), Prague (Czech Republic), and Budapest (Hungary). The results presented were considered satisfactory [31].

All women and men with identified cardiovascular pathology (coronary heart disease, cerebral vascular disease, hypertension, myocardial infarction, diabetes mellitus) occurring before or during the screening period were excluded from the observation cohort.

The screening III materials were used to assess the effect of sleep disorders on the risk of developing CVD (hypertension, myocardial infarction, and stroke). Included in the analysis were 384 women and 190 men at the baseline age of 25 to 64 years. The period of the prospective observation of the participants lasted from the 1st of January 1996 to the 31st of December 2012.

The subject of the study of the risk of myocardial infarction (MI) in relation to sleep duration was an observational cohort (the screening IV) consisting of men and women initially aged 45–64 years. Included in the analysis were 428 men and 798 women with a baseline age of 45 to 64 years (the screening IV). The period of prospective observation of the participants was as follows: from January 1, 2006 to December 31, 2019.

The following "endpoints" were identified in the study: first-ever cases of arterial hypertension (AH) recorded during the follow-up period. Sources used to identify cases of hypertension included: annual examination of individuals in the population cohort, medical histories, inpatient discharge reports, district clinics, death certificates, interviews with relatives, and pathoanatomical and forensic reports. During the annual follow-up, a standardized measurement of blood pressure (BP) was performed with a mercury sphygmomanometer on the right hand (the first phase of Korotkov tones was recorded as SBP, the fifth phase as DBP), the average of two measurements was included in the analysis. Hypertension was defined as SBP of 140 mmHg or higher and/or DBP of 90 mmHg or higher in subjects who were not receiving antihypertensive therapy at the time of the examination. Men with normal blood pressure were also included in the hypertensive group if they were taking antihypertensive medication during the examination period or had stopped taking it less than 2 weeks before the examination (WHO, 1993).

First-time cases of myocardial infarction (MI) and stroke. Registration of all cases of MI was based on the WHO Acute Myocardial Infarction Registry Program; first-time cases of stroke were recorded during the follow-up period. Sources used to identify stroke cases included: annual examination of individuals in the population cohort, medical histories, inpatient discharge reports, district clinics, death certificates, interviews with relatives, pathoanatomical and forensic reports.

During cohort follow-up (the screening III), 229 cases of first-time hypertension were detected in women and 46 in men; 15 cases of first-time hypertension in women and 30 in men; and 35 cases of first-time stroke in women and 22 in men. During cohort follow-up (the screening IV), 44 new cases of MI were detected in men and 37 in women.

SPSS software package version 20 was used for statistical analysis [15]. The Pearson chi-squared criterion was used to test the statistical significance of the differences between the groups [32]. The risk of hypertension, MI, and stroke was assessed using a single-factor Cox proportional regression model [32]. The probability was assumed to be at a significance level of $p < 0.05$.

## 3. Results

The level of sleep disorders ("bad", "very bad" sleep) in men of 25–34 years of age in 1988–1989 was 5.4%; in 1994–1995-3.6%; in 2013–2016 - 4.3% ($p < 0.01$).

In women, the level of sleep disorders accounted for 13.7% in 1988–1989, 7.9% in 1994–1995; in 2013–2016-5.7% ($p < 0.001$). In men aged 35 to 44 years, the levels of sleep disorders were 9.5 percent from 1988 to 1989, 9.3 percent in 1994 to 1995, 4.2 percent in 2013 to 2016, and 11 percent in 2016 to 2018 ($p < 0.05$). The level of sleep disorders in women was 17.9% in 1988–1989, 20% in 1994–1995, 14.2% in 2013–2016, and 10.3% in 2016–2018 ($p < 0.001$). In the 45–54 age group of men, the level of sleep disorders was 11% in 1988–1989, 9.8% in 1994–1995, 12.5% in 2003–2005, and 4.9% in 2016–2018 ($p < 0.05$). In women aged 45–54 years, the level of sleep disorders was 24% in 1988–1989, 15.2% in 1994–1995, 17.9% in 2003–2005, and 22.8% in 2016–2018 ($p < 0.001$). In the older age group 55–64 years, the level of sleep disorders in men aged 55–64 years was - 20.8% in 1988–1989, − 12.1% in 1994–1995, − 11.8% in 2003–2005, and - 19.7% in 2015–2018 ($p < 0.001$). In women aged 55–64 years, the level of sleep disorders was 35.8% in 1988–1989, 27% in 1994–1995, 21.8% in 2003–2005, and 24.9% in 2016–2018 ($p < 0.001$). In the age group 25–64 years, the level of sleep disorders among men in 1988–1989 was 11%, in 1994-1995-8.6%; in the age group 45–64 years in 2003–2005 - 12.2%; in the age group 25–44 years in 2013–2016-4.2%; in the age group 35–64 years in 2016–2018-2113.1% ($p < 0.001$); in women in the age group 25–64 years in 1988-1989-21.8%, in 1994–1995 - 16.6%, in the age group 45–64 years in 2003–2005-2019.7%; in the age group 25–44 years in 2013–2016-2110.8%; in the age group 35–64 years in 2016–2018-2020.5% ($p < 0.001$) (see **Table 1**).

In the population aged 45–64 years, between 2003 and 2005 (the screening IV) and 2015–2018 (the screening VI), the number of people with 7 hours of sleep per night decreased from 44.9 to 31.9% (for men from 44.6–31% and for women from 45.1 to 32.4%); and with 8 hours of sleep per night - from 28.5 to 24.4% (for men from 27.8 to 23.2% and for women from 28.8 to 25.3%). The number of people sleeping less than 5 hours increased during the period from 2003 to 2005 to 2015–2018 from 4.9 to 9.9% (for men from 4.4 to 7.4% and for women from 5.1 to 11.6%); and 6 hours from 16.2 to 27.2% (for men from 17.2 to 31.5% in men and 15.7 to 24.2% in women). The number of people sleeping 9 hours per night increased from 3.7 to 5.4% (from 4.2 to 4.9% in men and from 3.4 to 5.8% in women) ($p < 0.001$) (see **Table 2**).

In 2003–2005 (the screening IV), in the population aged 55–64 years, sleep of less than 5 hours (5.5%), 7 hours (45.1%), 8 hours (29.4%), 9 hours (4.4%) and ≥ 10 hours (2.1%) was observed. On the contrary, in the group of people aged 45–54 years −18.9% ($p < 0.01$), a similar trend was observed in men ($p > 0.05$) and was significant in women ($p < 0.05$) (see **Table 3**). For the screening VI examination, there were no significant differences between sleep duration and age group. A comparative analysis between the two screenings showed that in the 45–54-year-old population group, 7-hour (44.7%), 8-hour (27.6%) and 10-hour (1.5%) sleep was more common at the screening IV, and 5-hour (9.5%), 6-hour (28.1) and 9-hour (5%) sleep at the screening VI ($p < 0.001$). In the 55–64-year-old group, 7-hour sleep (45.1%), 8-hour sleep (29.4%) and 10-hour sleep (2.1%) prevailed at the screening VI, whereas 5-hour sleep (10.2%), 6-hour sleep (26.5%) and 9-hour sleep (5.8%) prevailed at the screening VI ($p < 0.001$). In the 45–54-year-old men, sleep of less than 5 hours (9.9%), 6 hours (29.6%) and 9 hours (6.2%) prevailed at the screening VI, and 7 hours (44.3%) and 8 hours (27%) at the screening IV ($p < 0.01$). In the 55–64 age group, 7-hour (45%), 8-hour (28.6%), and 9-hour (5.2%) sleep predominated at the screening IV and 5-hour (5.7%), 6-hour (32.8%), and 10-hour (3.3%) sleep predominated at the screening VI ($p < 0.001$). In women in the 45–54 age group, 7-hour (44.9%) and 8-hour (27.9%) sleep was more common at the screening IV, and 5-hour (9.3%), 6-hour (27.1%) and 9-hour (4.3%) sleep was more common at the screening VI, as well as 10-hour (1.4%)

| Question/Attitude | | 25–34 | | | | 35–44 | | | | 45–54 | | | | 55–64 | | | | 25–64* | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Men | | Women | | Men | | Women | | Men | | Women | | Men | | Women | | Men | | Women | |
| | | N | % | N | % | N | % | N | % | N | % | N | % | N | % | N | % | N | % | N | % |
| How can you rate the quality of your sleep? | | | | | | | | | | | | | | | | | | | | | |
| 1. Very good | 1988–1989 | 35 | 17.2 | 10 | 5.5 | 16 | 8 | 8 | 3.9 | 10 | 5.8 | 6 | 3.3 | 8 | 5.4 | 4 | 2.9 | 69 | 9.5 | 28 | 3.9 |
| 2. Good | | 101 | 49.5 | 75 | 41 | 91 | 45.7 | 67 | 32.4 | 59 | 34.1 | 37 | 20.2 | 42 | 28.2 | 14 | 10.2 | 293 | 40.5 | 193 | 27.2 |
| 3. Satisfactory | | 57 | 27.9 | 73 | 39.9 | 73 | 36.7 | 95 | 45.9 | 85 | 49.1 | 96 | 52.5 | 68 | 45.6 | 70 | 51.1 | 283 | 39 | 334 | 47.1 |
| 4. Bad | | 10 | 4.9 | 23 | 12.6 | 17 | 8.5 | 31 | 15 | 15 | 8.7 | 33 | 18 | 30 | 20.1 | 46 | 33.6 | 72 | 9.9 | 133 | 18.7 |
| 5. Very bad | | 1 | 0.5 | 2 | 1.1 | 2 | 1 | 6 | 2.9 | 4 | 2.3 | 11 | 6 | 1 | 0.7 | 3 | 2.2 | 8 | 1.1 | 22 | 3.1 |
| Total | | 204 | 100 | 183 | 100 | 199 | 100 | 207 | 100 | 173 | 100 | 183 | 100 | 149 | 100 | 137 | 100 | 725 | 100 | 710 | 100 |
| | | $\chi2 = 24.08$ υ = 4 P = 0.001 | | | | $\chi2 = 15.1$ υ = 4 P = 0.01 | | | | $\chi2 = 16.4$ υ = 4 P = 0.001 | | | | $\chi2 = 19.2$ υ = 4 P = 0.001 | | | | $\chi2 = 66.6$ υ = 4 P = 0.001 | | | |
| 1. Very good | 1994–1995 | 9 | 5.4 | 8 | 6.3 | 11 | 6.4 | 5 | 3.2 | 8 | 5.6 | 3 | 6.5 | 8 | 4.8 | 1 | 1.6 | 36 | 5.6 | 17 | 4.3 |
| 2. Good | | 97 | 58.1 | 54 | 42.5 | 72 | 41.9 | 47 | 30.3 | 55 | 38.5 | 11 | 23.9 | 75 | 45.5 | 9 | 14.3 | 299 | 46.2 | 121 | 31 |
| 3. Satisfactory | | 55 | 32.9 | 55 | 43.3 | 73 | 42.4 | 72 | 46.5 | 66 | 46.2 | 25 | 54.3 | 62 | 37.6 | 36 | 57.1 | 256 | 39.6 | 188 | 48.1 |
| 4. Bad | | 5 | 3 | 7 | 5.5 | 14 | 8.1 | 29 | 18.7 | 13 | 9.1 | 6 | 13.0 | 17 | 10.3 | 14 | 22.2 | 49 | 7.6 | 56 | 14.3 |
| 5. Very bad | | 1 | 0.6 | 3 | 2.4 | 2 | 1.2 | 2 | 1.3 | 1 | 0.7 | 1 | 2.2 | 3 | 1.8 | 3 | 4.8 | 7 | 1 | 9 | 2.3 |
| Total | | 167 | 100 | 127 | 100 | 172 | 100 | 155 | 100 | 143 | 100 | 46 | 100 | 165 | 100 | 63 | 100 | 647 | 100 | 391 | 100 |
| | | $\chi2 = 8.35$ υ = 4 P > 0.05 | | | | $\chi2 = 11.89$ υ = 4 P < 0.05 | | | | $\chi2 = 3.902$ υ = 4 P > 0.05 | | | | $\chi2 = 23.577$ υ = 4 P < 0.001 | | | | $\chi2 = 32.202$ υ = 4 P = 0.001 | | | |
| 1. Very good | 2003–2005 | | | | | | | | | 10 | 3.3 | 23 | 4.2 | 10 | 3.7 | 11 | 2.1 | 20 | 3.5 | 34 | 3.2 |
| 2. Good | | | | | | | | | | 104 | 34.2 | 107 | 19.3 | 73 | 26.8 | 88 | 16.9 | 177 | 30.7 | 195 | 18.2 |
| 3. Satisfactory | | | | | | | | | | 152 | 50 | 325 | 58.7 | 157 | 57.7 | 308 | 59.2 | 309 | 53.6 | 633 | 58.9 |
| 4. Bad | | | | | | | | | | 37 | 12.2 | 94 | 17 | 29 | 10.7 | 108 | 20.8 | 66 | 11.5 | 202 | 18.8 |
| 5. Very bad | | | | | | | | | | 1 | 0.3 | 5 | 0.9 | 3 | 1.1 | 5 | 1 | 4 | 0.7 | 10 | 0.9 |
| Total | | | | | | | | | | 304 | 100 | 554 | 100 | 272 | 100 | 520 | 100 | 576 | 100 | 1074 | 100 |
| | | | | | | | | | | $\chi2 = 22.62$ υ = 4 P = 0.001 | | | | $\chi2 = 20.9$ υ = 4 P = 0.001 | | | | $\chi2 = 5.72$ υ = 4 P = 0.221 | | | |

| Question/Attitude | | 25–34 | | | | 35–44 | | | | 45–54 | | | | 55–64 | | | | 25–64* | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Men | | Women | | Men | | Women | | Men | | Women | | Men | | Women | | Men | | Women | |
| | | N | % | N | % | N | % | N | % | N | % | N | % | N | % | N | % | N | % | N | % |
| 1. Very good | 2013–2016 | 25 | 15.2 | 29 | 13.7 | 28 | 10.7 | 30 | 9.1 | | | | | | | | | 53 | 12.4 | 59 | 10.8 |
| 2. Good | | 78 | 47.6 | 105 | 49.5 | 126 | 48.3 | 137 | 41.4 | | | | | | | | | 205 | 48 | 243 | 44.3 |
| 3. Satisfactory | | 54 | 32.9 | 66 | 31.1 | 96 | 36.8 | 117 | 35.3 | | | | | | | | | 151 | 35.4 | 187 | 34.1 |
| 4. Bad | | 6 | 3.7 | 11 | 5.2 | 10 | 3.8 | 42 | 12.7 | | | | | | | | | 16 | 3.7 | 53 | 9.7 |
| 5. Very bad | | 1 | 0.6 | 1 | 0.5 | 1 | 0.4 | 5 | 1.5 | | | | | | | | | 2 | 0.5 | 6 | 1.1 |
| Total | | 164 | 100 | 212 | 100 | 261 | 100 | 331 | 100 | | | | | | | | | 427 | 100 | 548 | 100 |
| | | χ2 = 0.836 υ = 4 P = 0.933 | | | | χ2 = 16.918 υ = 4 P = 0.002 | | | | | | | | | | | | χ2 = 14.425 υ = 4 P = 0.006 | | | |
| 1. Very good | 2016–2018 | | | | | 6 | 8.3 | 6 | 6.2 | 3 | 3.7 | 1 | 0.7 | 0 | 0 | 4 | 2.6 | 9 | 3.3 | 11 | 2.8 |
| 2. Good | | | | | | 32 | 44.4 | 43 | 44.3 | 35 | 43.2 | 45 | 32.1 | 35 | 28.7 | 33 | 21.6 | 102 | 37.1 | 121 | 31.1 |
| 3. Satisfactory | | | | | | 26 | 36.1 | 38 | 39.2 | 39 | 48.1 | 62 | 44.3 | 63 | 51.6 | 78 | 51 | 128 | 46.5 | 178 | 45.6 |
| 4. Bad | | | | | | 8 | 11.1 | 10 | 10.3 | 4 | 4.9 | 31 | 22.1 | 24 | 19.7 | 35 | 22.9 | 36 | 13.1 | 76 | 19.5 |
| 5. Very bad | | | | | | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0.7 | 0 | 0 | 3 | 2.0 | 0 | 0 | 4 | 1 |
| Total | | | | | | 72 | 100 | 97 | 100 | 81 | 100 | 140 | 100 | 122 | 100 | 153 | 100 | 275 | 100 | 390 | 100 |
| | | | | | | χ2 = 0.396 υ = 3 P > 0.05 | | | | χ2 = 14.606 υ = 4 P < 0.01 | | | | χ2 = 7.304 υ = 4 P > 0.05 | | | | χ2 = 8.646 υ = 4 P > 0.05 | | | |
| Total | | χ2 = 14.858 υ = 8 P < 0.01 | | χ2 = 24.715 υ = 8 P < 0.001 | | χ2 = 12.67 υ = 12 P < 0.05 | | χ2 = 21.177 υ = 12 P < 0.001 | | χ2 = 14.280 υ = 12 P < 0.05 | | χ2 = 40.155 υ = 12 P < 0.001 | | χ2 = 41.093 υ = 12 P < 0.001 | | χ2 = 22.01 υ = 12 P < 0.001 | | χ2 = 122.061 υ = 16 P < 0.001 | | χ2 = 230.626 υ = 16 P < 0.001 | |

*2003–2005 - 45-64 y.o., 2013–2016 - 25-44 y.o., 2016–2018 - 35-64 y.o.*

**Table 1.**
*The prevalence of sleep disorders among the population aged 25–64 years from 1988 to 2018.*

| Hours slept | population screening IV 2003–2005 | | population screening VI 2015–2018 | | men screening IV 2003–2005 | | men screening VI 2015–2018 | | women screening IV 2003–2005 | | women screening VI 2015–2018 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | n | % | n | % | n | % |
| 5 hours | 79 | 4.9 | 49 | 9.9 | 25 | 4.4 | 15 | 7.4 | 54 | 5.1 | 34 | 11.6 |
| 6 hours | 263 | 16.2 | 135 | 27.2 | 97 | 17.2 | 64 | 31.5 | 166 | 15.7 | 71 | 24.2 |
| 7 hours | 727 | 44.9 | 158 | 31.9 | 252 | 44.6 | 63 | 31 | 475 | 45.1 | 95 | 32.4 |
| 8 hours | 461 | 28.5 | 121 | 24.4 | 157 | 27.8 | 47 | 23.2 | 304 | 28.8 | 74 | 25.3 |
| 9 hours | 60 | 3.7 | 27 | 5.4 | 24 | 4.2 | 10 | 4.9 | 36 | 3.4 | 17 | 5.8 |
| 10 hours | 29 | 1.8 | 6 | 1.2 | 10 | 1.8 | 4 | 2 | 19 | 1.8 | 2 | 0.7 |
| Total | 1619 | 100 | 496 | 100 | 565 | 100 | 203 | 100 | 1054 | 100 | 293 | 100 |
| | $\chi 2 = 61.285$ df = 5 $p < 0.001$ | | | | $\chi 2 = 25.306$ df = 5 $p < 0.001$ | | | | $\chi 2 = 38.99$ df = 5 $p < 0.001$ | | | |

**Table 2.**
*Dynamics of hours slept per day for the population aged 45–64 from 2003 to 2005 to 2015–2018.*

sleep ($\chi p < 0.05$). In the group of women aged 55–64 years, 7-hour (45.2%), 8-hour (29.8%) and 10-hour (2.4%) were more common for the screening IV, 5-hour (13.7%), 6-hour (21.6%) and 9-hour (7.2%) sleep for the screening VI ($\chi p < 0.001$) (see **Table 3**).

**Table 4** shows self-rated sleep quality depending on the time spent sleeping. In 2003–2005, 40.9% of people with 8 hours of sleep considered their sleep to be "good" ($p < 0.001$): 38.8% of men ($p < 0.001$) and 42.6% of women ($p < 0.001$). In 2015–2018, people with 7 hours of sleep were more likely to say their sleep was "good" - 35.3% ($p < 0.001$), among men there was a trend toward 6 hours of sleep - 38.4% ($p > 0.05$), and among women, 7 hours of sleep - 37.3% ($p < 0.01$). In 2015–2018, people who slept 7 hours a day were more likely to rate their sleep as "bad" - 36.7% ($p < 0.001$), the trend for men is 39.3% ($p > 0.05$), and for women, the trend for 6 hours of sleep is 35.7% ($p < 0.01$) (see **Table 4**).

| Number of hours slept | Both sexes, screening IV, 2003–2005 | | | | Men, screening IV, 2003–2005 | | | | Women, screening IV, 2003–2005 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 45–54 y.o. | | 55–64 y.o. | | 45–54 y.o. | | 55–64 y.o. | | 45–54 y.o. | | 55–64 y.o. | |
| | n | % | n | % | n | % | n | % | n | % | n | % |
| 5 hours | 35 | 4.3 | 44 | 5.5 | 12 | 4.1 | 13 | 4.8 | 23 | 4.4 | 31 | 5.8 |
| 6 hours | 155 | 18.9 | 108 | 13.5 | 57 | 19.3 | 40 | 14.9 | 98 | 18.7 | 68 | 12.8 |
| 7 hours | 366 | 44.7 | 361 | 45.1 | 131 | 44.3 | 121 | 45 | 235 | 44.9 | 240 | 45.2 |
| 8 hours | 226 | 27.6 | 235 | 29.4 | 80 | 27 | 77 | 28.6 | 146 | 27.9 | 158 | 29.8 |
| 9 hours | 25 | 3.1 | 35 | 4.4 | 10 | 3.4 | 14 | 5.2 | 15 | 2.9 | 21 | 4 |
| 10 hours | 12 | 1.5 | 17 | 2.1 | 6 | 2 | 4 | 1.5 | 6 | 1.1 | 13 | 2.4 |
| total | 819 | 100 | 800 | 100 | 296 | 100 | 269 | 100 | 523 | 100 | 531 | 100 |
| | $\chi 2 = 11.942$ df = 5 $p < 0.01$ | | | | $\chi 2 = 3.257$ df = 5 $p > 0.05$ | | | | $\chi 2 = 10.652$ df = 5 $p < 0.05$ | | | |

| Number of hours slept | Both sexes, screening IV, 2003–2005 | | | | Men, screening IV, 2003–2005 | | | | Women, screening IV, 2003–2005 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 45–54 y.o. | | 55–64 y.o. | | 45–54 y.o. | | 55–64 y.o. | | 45–54 y.o. | | 55–64 y.o. | |
| | n | % | n | % | n | % | n | % | n | % | n | % |
| | Both sexes, screening VI, 2015–2018 | | | | Men, screening VI, 2015–2018 | | | | Women, screening VI, 2015–2018 | | | |
| 5 hours | 21 | 9.5 | 28 | 10.2 | 8 | 9.9 | 7 | 5.7 | 13 | 9.3 | 21 | 13.7 |
| 6 hours | 62 | 28.1 | 73 | 26.5 | 24 | 29.6 | 40 | 32.8 | 38 | 27.1 | 33 | 21.6 |
| 7 hours | 75 | 33.9 | 83 | 30.2 | 28 | 34.6 | 35 | 28.7 | 47 | 33.6 | 48 | 31.4 |
| 8 hours | 50 | 22.6 | 71 | 25.8 | 16 | 19.8 | 31 | 25.4 | 34 | 24.3 | 40 | 26.1 |
| 9 hours | 11 | 5 | 16 | 5.8 | 5 | 6.2 | 5 | 4.1 | 6 | 4.3 | 11 | 7.2 |
| 10 hours | 2 | 0.9 | 4 | 1.5 | 0 | 0 | 4 | 3.3 | 2 | 1.4 | 0 | 0 |
| total | 221 | 100 | 275 | 100 | 81 | 100 | 122 | 100 | 140 | 100 | 153 | 100 |
| | $\chi 2 = 1.679$ df = 5 p > 0.05 | | | | $\chi 2 = 5.578$ df = 5 p > 0.05 | | | | $\chi 2 = 5.636$ df = 5 p > 0.05 | | | |

*45–54 y.o., both sexes $\chi 2 = 24.421$ df = 5 $p < 0.001$; men $\chi 2 = 12.876$ df = 5 $p < 0.01$; women $\chi 2 = 13.324$ df = 5 $p < 0.05$*
*55–64 y.o., both sexes $\chi 2 = 40.726$ df = 5 $p < 0.001$; men $\chi 2 = 20.73$ df = 5 $p < 0.001$; women $\chi 2 = 28.225$ df = 5 $p < 0.001$*

**Table 3.**
*Distribution of number of sleep hours per day by age group in the population aged 45–64 (screening IV 2003–2005 and screening VI 2015–2018).*

5 years after the start of the study, a single-factor regression analysis of Cox showed that among men with sleep disorders, the risk of hypertension was higher HR = 5.4 (95% CI 2.5–10.8; $p < 0.05$) than in women HR =4.35 (95% CI 1.29–14.58; $p < 0.05$). After 10 years, the risk of hypertension did not differ between women HR = 2.68 (95% CI 1.3–7.15; $p < 0.05$) and men HR = 2.3 (95% CI 1.2–8.8; $p < 0.05$). After 16 years, only a tendency to reduce the risk of developing hypertension remained: HR = 1.2 in men (95% CI 0.19–3.59; $p < 0.05$) and HR = 1.05 in women (95% CI 0.73–1.48; $p > 0.05$) (see **Table 5**).

Multivariate Cox regression analysis including age and social characteristics (marital status, educational level, occupational status) in the model showed an increased risk of hypertension among people with sleep disorders in men HR = 3.1(95% CI 1.2–8.2, $p < 0.01$) than in women HR = 2.5(95% CI 1.3–4.8, $p < 0.005$). Moreover, the risk of hypertension in the group of widowed individuals with sleep disorders was higher in men than in women HR = 14.6 (95% CI 3–27, $p < 0.01$) compared to married HR = 5.6 (95% CI 2.6–11.8; $p < 0.0001$). We found an increased risk of hypertension only in women with sleep disorders and with a secondary education HR = 3.3 (95% CI 1.3–8.3; $p < 0.008$) or incomplete secondary - primary education HR = 10.3 (95% CI 4–26; $p < 0.0001$). No similar patterns have been found in men. In people aged 45–64 years, the risk of hypertension was 3.2 (95% CI 1.7–8.6; $p < 0.05$) times higher in men compared with the 25–34-year age group, and there were no reliable results for women (see **Table 6**).

A single-factor Cox regression analysis showed that individuals with sleep disorders had a 2.4 (95%CI 1.1–5.3; $p < 0.05$) times increased risk of developing MI over a 16-year period compared to men without sleep disorders. Sleep disorders did not affect women's risk of having an MI (see **Table 7**).

| Number of hours slept | Both sexes, screening IV, 2003–2005 | | | | | | Men, screening IV, 2003–2005 | | | | | | Women, screening IV, 2003–2005 | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | good sleep | | satisfactory sleep | | bad sleep | | good sleep | | satisfactory sleep | | bad sleep | | good sleep | | satisfactory sleep | | bad sleep | |
| | n | % | n | % | n | % | n | % | n | % | n | % | n | % | n | % | n | % |
| 5 hours | 16 | 3.3 | 45 | 3.8 | 46 | 13.3 | 5 | 2.2 | 16 | 3.9 | 13 | 14.9 | 11 | 4.2 | 29 | 3.7 | 33 | 12.7 |
| 6 hours | 71 | 14.5 | 162 | 13.7 | 85 | 24.5 | 34 | 15.2 | 67 | 16.5 | 18 | 20.7 | 37 | 14 | 95 | 12.2 | 67 | 25.8 |
| 7 hours | 163 | 33.3 | 622 | 52.6 | 120 | 34.6 | 80 | 35.7 | 210 | 51.7 | 30 | 34.5 | 83 | 31.3 | 412 | 53.1 | 90 | 34.6 |
| 8 hours | 200 | 40.9 | 290 | 24.5 | 81 | 23.3 | 87 | 38.8 | 92 | 22.7 | 21 | 24.1 | 113 | 42.6 | 198 | 25.5 | 60 | 23.1 |
| 9 hours | 27 | 5.5 | 41 | 3.5 | 12 | 3.5 | 11 | 4.9 | 12 | 3 | 5 | 5.7 | 16 | 6 | 29 | 3.7 | 7 | 2.7 |
| 10 hours | 12 | 2.5 | 22 | 1.9 | 3 | .9 | 7 | 3.1 | 9 | 2.2 | 0 | 0 | 5 | 1.9 | 13 | 1.7 | 3 | 1.2 |
| | 489 | 100 | 1182 | 100 | 347 | 100 | 224 | 100 | 406 | 100 | 87 | 100 | 265 | 100 | 776 | 100 | 260 | 100 |
| | $\chi 2 = 137.314$ df = 10 $p < 0.001$ | | | | | | $\chi 2 = 48.4$ df = 10 $p < 0.001$ | | | | | | $\chi 2 = 100.071$ df = 10 $p < 0.001$ | | | | | |
| | Both sexes, screening VI, 2015–2018 | | | | | | Men, screening VI, 2015–2018 | | | | | | Women, screening VI, 2015–2018 | | | | | |
| Number of hours slept | good sleep | | satisfactory sleep | | bad sleep | | good sleep | | satisfactory sleep | | bad sleep | | good sleep | | satisfactory sleep | | bad sleep | |
| | n | % | n | % | n | % | n | % | n | % | n | % | n | % | n | % | n | % |
| 5 hours | 7 | 4.5 | 23 | 9.5 | 19 | 19.4 | 1 | 1.4 | 10 | 9.8 | 4 | 14.3 | 6 | 7.2 | 13 | 9.3 | 15 | 21.4 |
| 6 hours | 46 | 29.5 | 53 | 21.9 | 36 | 36.7 | 28 | 38.4 | 25 | 24.5 | 11 | 39.3 | 18 | 21.7 | 28 | 20 | 25 | 35.7 |
| 7 hours | 55 | 35.3 | 84 | 34.7 | 19 | 19.4 | 24 | 32.9 | 32 | 31.4 | 7 | 25.0 | 31 | 37.3 | 52 | 37.1 | 12 | 17.1 |
| 8 hours | 35 | 22.4 | 68 | 28.1 | 18 | 18.4 | 15 | 20.5 | 27 | 26.5 | 5 | 17.9 | 20 | 24.1 | 41 | 29.3 | 13 | 18.6 |
| 9 hours | 11 | 7.1 | 12 | 5 | 4 | 4.1 | 4 | 5.5 | 6 | 5.9 | 0 | 0 | 7 | 8.4 | 6 | 4.3 | 4 | 5.7 |
| 10 hours | 2 | 1.3 | 2 | 0.8 | 2 | 2 | 1 | 1.4 | 2 | 2 | 1 | 3.6 | 1 | 1.2 | 0 | 0 | 1 | 1.4 |
| | 156 | 100 | 242 | 100 | 98 | 100 | 73 | 100 | 102 | 100 | 28 | 100 | 83 | 100 | 140 | 100 | 70 | 100 |
| | $\chi 2 = 30.525$ df = 10 $p < 0.001$ | | | | | | $\chi 2 = 15.702$ df = 10 $p > 0.05$ | | | | | | $\chi 2 = 25.543$ df = 10 $p < 0.01$ | | | | | |

**Table 4.**
*Distribution of hours slept per night according to self-rated sleep quality in the population aged 45–64.*

| Sex | Age group | Male | | | | Female | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | p | HR | 95% CI for HR | | p | HR | 95% CI for HR | |
| | | | | lower | upper | | | lower | upper |
| 5 years | 25–34 | — | — | — | — | >0.05 | 2.17 | 0.22 | 20.92 |
| | 35–44 | — | — | — | — | >0.05 | 4.05 | 0.18 | 90.75 |
| | 45–54 | >0.05 | 2.2 | 0.7 | 4.2 | >0.05 | 1.32 | 0.13 | 12.95 |
| | 55–64 | >0.05 | 0.3 | 0.02 | 2.6 | >0.05 | 4.52 | 0.52 | 38.92 |
| | 25–64 | 0.05 | 5.4 | 2.5 | 10.8 | 0.05 | 4.35 | 1.29 | 14.58 |
| 10 years | 25–34 | — | — | — | — | >0.05 | 0.33 | 0.22 | 3.25 |
| | 35–44 | — | — | — | — | >0.05 | 6.44 | 0.8 | 51.82 |
| | 45–54 | >0.05 | 2.1 | 0.01 | 3.9 | >0.05 | 2.37 | 0.50 | 11.11 |
| | 55–64 | >0.05 | 0.02 | 0.008 | 2.5 | >0.05 | 1.13 | 0.09 | 13.26 |
| | 25–64 | 0.05 | 2.3 | 1.2 | 8.8 | 0.05 | 2.68 | 1.3 | 7.15 |
| 16 years | 25–34 | >0.05 | 1 | 0.08 | 1.4 | >0.05 | 1.21 | 0.68 | 2.16 |
| | 35–44 | >0.05 | 1.1 | 0.03 | 1.6 | >0.05 | 0.66 | 0.34 | 1.26 |
| | 45–54 | >0.05 | 2 | 0.9 | 4.7 | >0.05 | 1.9 | 0.84 | 4.34 |
| | 55–64 | >0.05 | 1.4 | 0.01 | 2.9 | >0.05 | 4.47 | 0.27 | 71.8 |
| | 25–64 | 0.05 | 1.2 | 0.19 | 3.59 | >0.05 | 1.05 | 0.73 | 1.48 |

**Table 5.**
*Single factor cox regression analysis of sleep disorders and risk of hypertension in the 25–64-year-old population.*

| Sex | | Male | | | | Female | | | |
|---|---|---|---|---|---|---|---|---|---|
| Reference group | Risk group | p | HR | 95% CI for HR | | p | HR | 95% CI for HR | |
| | | | | lower | upper | | | lower | upper |
| Good sleep | Bad sleep | 0.01 | 3.1 | 1.2 | 8.2 | 0.005 | 2.5 | 1.3 | 4.8 |
| Married | Never been married | 0.9 | 1.1 | 0.1 | 9.1 | 0.5 | 1.3 | 0.5 | 3.3 |
| | Divorced | 0.1 | 2.5 | 0.8 | 7.7 | 0.2 | 1.9 | 0.6 | 5.39 |
| | Widowed | 0.01 | 14.6 | 3 | 27 | 0.0001 | 5.6 | 2.6 | 11.8 |
| Higher education | n/higher or secondary vocational education | 0.5 | 1.6 | 0.3 | 7.5 | 0.18 | 1.8 | 0.7 | 4.4 |
| | Secondary education | 0.8 | 1.2 | 0.2 | 6.9 | 0.008 | 3.3 | 1.3 | 8.3 |
| | n/secondary - primary education | 0.4 | 1.7 | 0.4 | 7.1 | 0.0001 | 10.3 | 4 | 26 |
| Managers and engineers | Workers | 0.4 | 2.4 | 0.2 | 16 | 0.9 | 0.9 | 0.4 | 1.9 |
| 25–34 y.o. | 35–64 y.o. | 0.05 | 3.2 | 1.7 | 8.6 | 0.9 | 1 | 0.01 | 2.1 |

**Table 6.**
*Multivariate cox regression analysis of sleep disorders and risk of hypertension in the 25–64-year-old population 25–64 over 16-year period.*

| Sex | | Male | | | | Female | | | |
|---|---|---|---|---|---|---|---|---|---|
| 25–64 y.o. | CVD | p | HR | 95% CI for HR | | p | HR | 95% CI for HR | |
| | | | | lower | upper | | | lower | upper |
| | Myocardial infarction | 0.05 | 2.4 | 1.1 | 5.3 | >0.05 | 1.05 | 0.3 | 3 |
| | stroke | 0.05 | 3 | 1.2 | 7.6 | 0.05 | 1.9 | 1.03 | 3.7 |

**Table 7.**
*Single-factor cox regression analysis of sleep disorders and risk of CVD in the 25- to 64-year-old population.*

In a single-factor Cox regression analysis over a 16-year period in individuals with sleep disorders, the risk of stroke was higher among men HR = 3 (95% CI 1.2–7.6; $p < 0.05$) than among women HR = 1.9 (95%CI 1.03–3.7; $p < 0.05$) (**Table 7**).

In the multivariate Cox regression model, we also did not obtain an effect of sleep disorders on the risk of developing MI, and stroke in women HR = 2.09 (95% CI 0.23–18.75; $p > 0.05$). In men, when social parameters were included in the model: marital status, education, occupational level, and age, the risk of developing MI decreased, and there was only a tendency to increase the risk by 1.08 (95% CI 0.4–4.7; $p < 0.05$) times. The marital status of the men with sleep disorders had a major impact on their risk of developing an MI. The risk of MI was 3 (95% CI 1.9–9; $p < 0.0001$) times higher in men who had never been married, HR = 4.3 (95% CI 2.1–8.9) in divorced men, and the highest risk was in widowed men HR = 7.5 (95% CI 2.5–22; $p < 0.0001$). No similar pattern has been found in the women. It was found that in the presence of sleep disorders, the risk of developing MI is higher in men aged 55–64 years HR = 6.4 (95%CI 2–21; $P < 0.01$) than in women in the same age group HR = 2.6 (95%CI 1.06–6.5; $P < 0.05$), compared with people aged 25–54 years without sleep disorders (see **Table 8**).

| Sex | | Male | | | | Female | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Reference group** | **Risk group** | **p** | **HR** | **95,0% CI for HR** | | **p** | **HR** | **95,0% CI for HR** | |
| | | | | **lower** | **upper** | | | **lower** | **upper** |
| Good sleep | Sleep Disorder | 0.05 | 1.08 | 0.4 | 4.7 | >0.05 | 2.09 | 0.23 | 18.75 |
| Married | Never been married | 0.05 | 3 | 1.9 | 9 | >0.05 | 1.59 | 0.0001 | 2.47 |
| | Divorced | 0.0001 | 4.3 | 2.1 | 8.9 | >0.05 | 8.88 | 0.0001 | 13.83 |
| | Widowed | 0.0001 | 7.5 | 2.5 | 22 | >0.05 | 1.890 | 0.2 | 17.5 |
| Higher education | n/higher or secondary vocational education | >0.05 | 0.9 | 0.3 | 2.5 | >0.05 | 1.473 | 0.1 | 16.4 |
| | Secondary education | >0.05 | 1.7 | 0.6 | 5.1 | >0.05 | 1.367 | 0.08 | 21.8 |
| | n/secondary - primary education | >0.05 | 1.3 | 0.5 | 3.5 | >0.05 | 2.382 | 0.1 | 39.1 |
| Managers and engineers | Workers | >0.05 | 5.8 | 0.6 | 48 | >0.05 | 1.152 | 0.12 | 11.03 |
| 25–54 y.o. | 55–64 y.o. | 0.01 | 6.4 | 2 | 21 | 0.05 | 2.6 | 1.06 | 6.5 |

**Table 8.**
*Multivariate cox regression analysis of sleep disorders and risk of MI in the 25–64-year-old population over 16-year period.*

Multivariate Cox regression analysis including marital status, education level, occupational status, and age in the model showed that among people with sleep disorders, the risk of stroke is approximately the same for men HR = 2.8 (95% CI 1.1–7.1; P < 0.05) and women HR = 2.7 (95% CI 1.4–5.42; P < 0.01) (see **Table 9**).

We found that only widowed men with sleep disorders had an increased risk of stroke HR = 1.9 (95%CI 1.2–3; P < 0.01) compared to married men without sleep disorders. No significant results have been found for women. When comparing the risk of stroke among people with sleep disorders who differ in education level, it was found that the risk of stroke was higher in men with incomplete secondary/primary education HR = 5.3 (95%CI 1.4–19.1; p < 0.01) than in women HR = 4.2 (95% CI 1.25–14; p < 0.05). There was also an increased risk of stroke in women with secondary education and sleep problems HR = 3.7 (95%CI 1.1–11.9; P < 0.05). We found no differences in the risk of stroke in people with sleep disorders in the older age group 55–64 years between men HR = 2.1 (95% CI 1.09–5.6; p < 0.05) and women HR = 2 (95% CI 1.05–4.8; P < 0.001) (see **Table 9**).

A single-factor regression analysis showed that in a population of men aged 45–64 years, the risk of developing MI, over a 14-year period, in men with 5–6 hours of sleep was 1.689 higher (95%CI 1.124–2.537; p < 0.012) compared with men with 7–8 hours of sleep. The risk of MI in the group of men aged 45–54 years with 5–6 hours of sleep over a 14-year period was 2.416 (95%CI 1.311–4.452; p < 0.005) compared with men with 7–8 hours of sleep per night (see **Table 10**).

In the population of women aged 45–64 years, according to a single-factor Cox regression analysis, over a 14-year period, the risk of MI was 1591 (95%CI 1058-2392; p < 0.026) higher among people who slept 5–6 hours compared with women who slept 7–8 hours per night. In the 45–54-year-old group, the risk of MI was 4.44 (95%CI 2726-20,309; p < 0.0001) higher for women who slept 9–10 hours per night compared to women who slept 7–8 hours per night (see **Table 11**).

| **Sex** | | **Male** | | | | **Female** | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Reference group** | **Risk group** | **p** | **HR** | **95,0% CI for HR** | | **p** | **HR** | **95,0% CI for HR** | |
| | | | | **lower** | **upper** | | | **lower** | **upper** |
| Good sleep | Sleep Disorder | 0.05 | 2.8 | 1.1 | 7.1 | 0.01 | 2.7 | 1.4 | 5.42 |
| Married | Never been married | >0.05 | 1.1 | 0.1 | 9.1 | >0.05 | 0.7 | 0.2 | 2.44 |
| | Divorced | >0.05 | 2.5 | 0.8 | 7.7 | >0.05 | 0.9 | 0.2 | 3.8 |
| | Widowed | 0.01 | 1.9 | 1.2 | 3 | >0.05 | 0.2 | 0.02 | 2.2 |
| Higher education | n/higher or secondary vocational education | >0.05 | 1.8 | 0.4 | 7.9 | >0.05 | 2.4 | 0.78 | 7.54 |
| | Secondary education | >0.05 | 1.6 | 0.3 | 7.3 | 0.05 | 3.7 | 1.1 | 11.9 |
| | n/secondary - primary education | 0.01 | 5.3 | 1.4 | 19.1 | 0.05 | 4.2 | 1.25 | 14 |
| Managers and engineers | Workers | >0.05 | 3.4 | 0.3 | 35 | >0.05 | 1.8 | 0.9 | 2.2 |
| 25–54 y.o. | 55–64 y.o. | 0.05 | 2.1 | 1.09 | 5.6 | 0.001 | 2 | 1.05 | 4.8 |

**Table 9.**
*Multivariate cox regression analysis of sleep disorders and risk of stroke in the 25–64-year-old population over 16-year-period.*

| | Risk factor | Reference group | p | HR | 95% CI for HR | |
|---|---|---|---|---|---|---|
| Age group | number of hours slept | Number of hours slept | | | Lower bound | Upper bound |
| 45–64 y.o. | 5–6 hours | 7–8 hours | 0.012 | 1.689 | 1.124 | 2.537 |
| 45–54 y.o. | 5–6 hours | 7–8 hours | 0.005 | 2.416 | 1.311 | 4.452 |
| 55–64 y.o. | 5–6 hours | 7–8 hours | 0.870 | 1.067 | 0.491 | 2.322 |
| 45–64 y.o. | 7–8 hours | 9–10 hours | 0.355 | 1.218 | 0.802 | 1.850 |
| 45–54 y.o. | 7–8 hours | 9–10 hours | 0.086 | 1.965 | 0.910 | 4.245 |
| 55–64 y.o. | 7–8 hours | 9–10 hours | 0.433 | 0.775 | 0.409 | 1.467 |
| 45–64 y.o. | 9–10 hours | 7–8 hours | 0.282 | 0.578 | 0.213 | 1.570 |
| 45–54 y.o. | 9–10 hours | 7–8 hours | 0.289 | 0.045 | 0.001 | 13.840 |
| 55–64 y.o. | 9–10 hours | 7–8 hours | 0.310 | 1.709 | 0.607 | 4.809 |

**Table 10.**
*14-year risk of myocardial infarction in men aged 45–64 years (screening IV) by number of hours of night sleep (single-factor cox regression model).*

| | risk factor | reference group | p | HR | 95% CI for HR | |
|---|---|---|---|---|---|---|
| Age group | number of hours slept | number of hours slept | | | Lower bound | Upper bound |
| 45–64 y.o. | 5–6 hours | 7–8 hours | 0.026 | 1.591 | 1.058 | 2.392 |
| 45–54 y.o. | 5–6 hours | 7–8 hours | 0.628 | 0.764 | 0.257 | 2.270 |
| 55–64 y.o. | 5–6 hours | 7–8 hours | 0.487 | 0.688 | 0.239 | 1.977 |
| 45–64 y.o. | 7–8 hours | 8–10 hours | 0.747 | 0.938 | 0.634 | 1.386 |
| 45–54 y.o. | 7–8 hours | 8–10 hours | 0.006 | 0.292 | 0.121 | 0.706 |
| 55–64 y.o. | 7–8 hours | 8–10 hours | 0.398 | 1.420 | 0.629 | 3.207 |
| 45–64 y.o. | 9–10 hours | 7–8 hours | 0.105 | 1.712 | 0.894 | 3.280 |
| 45–54 y.o. | 9–10 hours | 7–8 hours | 0.0001 | 4.440 | 2.726 | 20.309 |
| 55–64 y.o. | 9–10 hours | 7–8 hours | 0.368 | 0.045 | 0.0001 | 38.406 |

**Table 11.**
*14-year risk of myocardial infarction in women aged 45–64 years (screening IV) by number of hours of night sleep (single-factor cox regression model).*

## 4. Discussion

According to our data, in the age group of 25–64 years, the level of sleep disorders is high and had the following trend: from 1988 to 1989 to 1994–1995, there was a decrease; however, an increase was observed in 2003–2018. The increase in sleep disorders between 2003 and 2018 was mainly due to older age groups (45–64 years). Our results on the increase in sleep disorders in 2003–2018 are consistent with data from other researchers. For example, Calem M. and co-authors conducted three cross-sectional mental health studies in 1993, 2000 and 2007 in the UK and found that the prevalence of sleep disorders in the adult population of England is slightly but steadily increasing [33]. In the United States, insomnia or sleep problems were reported to

have increased significantly in the adult population between 2002 and 2012 [34]. In addition, from 1999 to 2010, the number and percentage of outpatients who complained about sleep problems in the United States increased significantly, as did the number of prescriptions for sleep medications [35]. In Norway, the prevalence of several different symptoms associated with sleep disorders, as well as clinical cases of insomnia and the use of sleep medications, increased significantly in the adult population between 1999 and 2010 [36]. In Finland, symptoms related to insomnia and daytime sleepiness doubled from the mid-1990s to the late 2000s [37]. However, some of our results were unexpected, i.e., the level of sleeping disorders decreased in 1994–1995 (the screening III). For an explanation of the seemingly paradoxical indicators, we turned to our previous work on trends in self-rated health. It was during this period that the majority of the population lost their jobs, withdrew into the family circle, and looked for new jobs, which could affect the nature of sleep [38, 39]. But this does not mean that it was a healthier sleep, because we got a decrease in the number of "very good sleep" responses and an increase in "satisfactory" responses. The increase in sleep disorders in 2003–2015 is due to the fact that social and economic conditions have changed: socio-economic factors (income, level of education and employment status - an increase in the amount of work due to lack of financial resources, the need to work in shifts, shifting the time of falling asleep) naturally lead to sleep disorders [40]. Adequate uninterrupted sleep is becoming rare, especially in 24/7 communities [5], and short sleep (<6 hours/night) is increasingly observed, especially among full-time workers [6]. Women were found to have twice as many sleep disorders as men. This is in agreement with the results obtained by other authors [41]. According to our data, which is also emphasized by other authors [42, 43], the prevalence of sleep disorders increases with age. It should be noted that some age groups show trends different from the general trend. Thus, there is a trend toward a decrease in sleep disorders in women in the age groups 25–34 and 35–44. A decrease in sleep disorders in men aged 35–44 years was observed in 2013–2016. This is understandable, given that the frequency of sleeping problems also depends on psychosocial factors [44]. It was found that over 22 years (from 1994 to 1995 to 2013–2016), high levels of hostility, life exhaustion, and low levels of social support decreased significantly among women aged 25–44. Low levels of social support decreased significantly among men aged 35–44 years [39, 45].

Among the population aged 45–64, during the observation period from 2003 to 2005 to 2015–2018, the number of people sleeping 5 hours or less per day increased 1.6 times for men and more than 2 times for women. Although according to our data, mainly in the population studied, the population spent from 7 to 8 hours of sleep, we do observe an unfavorable trend: over the past period, the number of people spending the recommended ≥7 hours of sleep in our population has decreased [10]. The result obtained is not only typical for our population but also has a global trend. For example, Liu Y. and co-authors, 2016 [46] showed that nearly two-thirds of adults in the United States sleep ≥7 hours per day, and approximately 83.6 million adults in the United States sleep <7 hours. In a comparative analysis between two age groups, 45–54 years and 55–64 years, using the example of the screening IV, we found that 5, 7, 8, 9 and 10 hours of sleep were more common among people aged 55–64 years, and 6 hours of sleep was more common in the 45–54-year group. The need to adapt to a modern lifestyle is one of the possible reasons for the predominance of 6-hour sleep in the 45–54 age group. For example, short sleep duration (<6 hours/night) has become increasingly common in the active working-age population working full time [47]. Also, based on data from the world literature, one of the reasons for the increase in the

number of people aged 55–64 years who sleep ≤5 hours or ≥ 9 hours every night is lack of physical activity [48]. The duration of sleep is one of the many factors that may have a potential impact on physical activity [49]. In particular, Tsou [50] found that study participants who were "long sleepers" (≥9 hours) were less likely to engage in regular physical activity. Another study conducted among elderly people living in the Chinese community showed that both short and long sleep duration were associated with poor physical performance compared to people who reported 7–8 hours of sleep [51]. Looking at the dynamics of sleep for the period from 2003 to 2005 to 2015–2018, it was found that regardless of gender and age, there was an increase in 5–6 hours of sleep in 2015–2018 compared to 2003–2005, when sleep duration was more often 7–8 hours, which again confirms the global trend [51]. Our results are also consistent with the ESSE-RF study, the average age of the population is ±50 years, which showed that the average sleep duration in different regions of Russia was 7.3 ± 1.2 hours. At the same time, 22.5% of participants had a sleep duration of 6 hours or less per day, and 12.4% of respondents had more than 9 hours per day [41]. We also analyzed the effect of sleep duration on sleep quality. It turns out that in 2003–2005 those who slept 8 hours a day were more likely to think their sleep was "good"; in 2015–2018 those who slept 7 hours a day were more likely to think so. An unexpected trend was found in the male population: those who slept 6 hours were more likely to say their sleep was "good", and those who slept 7 hours were more likely to say their sleep was "bad". On the contrary, a comparative analysis of women showed that those who slept 7 hours per day rated their sleep as "good sleep", and those who slept 6 hours - as "poor sleep" [52]. We turned to the monograph of Horne J. A. *Journey Through the Science of Sleep* [53] for the explanation. For women, "poor sleep" is closely associated with high levels of psychological distress and increased feelings of hostility, depression, and anger; these feelings were not associated with the same level of sleep disturbance in men. Allowing the brain to recover is one of the primary functions of sleep. The more mental activity a person engages in during the day, the more time it takes for the brain to recover and, therefore, the more sleep that is needed. Women tend to be multi-taskers - they do a lot of things at the same time and they have more neuroplasticity - and so they use up more of their mental energy than men do. As a result, their need for sleep is greater. A man who has a difficult job that requires a lot of decision-making and outside-the-box thinking may also need more sleep than the average man, although probably not as much as a woman.

Our results are consistent with the data obtained by Swedish researchers. They conducted telephone interviews with 1550 men and women between the ages of 18 and 84. Women were found to report sleep problems twice as often as men [54]. This is confirmed by other authors such as Zhang B, Wing YK. In 2006, a meta-analysis of 31 sources concluded that women are 1.4 times more likely to suffer from sleep disorders than men [55]. As shown by Barsky AJ and coauthors in 2001, this is because women are more likely than men to express emotional experiences and somatic symptoms, including sleep complaints [56]. In addition, as an explanation for the discrepancy between men and women in the prevalence of insomnia, Lampio L. and co-authors have shown that in women, sleep disorders may occur due to a decrease in estrogen and progesterone levels. Thus, postmenopausal women (aged 53–58) were more likely to wake up at night compared to premenopausal women (aged 44–48) [57].

Widowed men were 2.6 times more likely than women to develop hypertension. This is explained by the fact that loneliness, especially as people get older, is usually associated with a stressful situation. These include retiring, separating from relatives, and losing a spouse [58]. Being widowed or bereaved ranks among the most stressful

situations. When a widowed person lives on his or her own, he or she has to face many practical and psychological problems. They have to manage their own household, maintain social contacts and make financial decisions. It is believed that men who are lonely in old age have a harder time bearing it than women do. The reason for this is not only the emotional restraint of men but also the fact that, unlike women, they adapt less well to the new situation. Widows tend to keep in touch with family and friends, and their social lives tend to be more intense. Widowers are more likely to become isolated and disrupt pre-existing social contacts because the relationship between fathers and children is less predictable than with the mother and can change for the worse. The loneliest widows are those with few or no children. Despite the fact that widowers tend to have higher incomes, they have fewer health problems than widows, but more emotional problems. The risk of social isolation increases for many older people who have experienced the death of a spouse. The different attitudes to loneliness among men and women support the view that the experience of loneliness is a purely individual feeling that does not transcend external conditions [59]. Thus, the combination of loneliness, dissatisfaction with life, and additional household chores contributes to poor sleep quality [54] and further increases the risk of developing hypertension [60, 61]. In our study, the risk of developing hypertension in women with incomplete secondary or primary education was three times higher than in women with secondary education. This is in line with the results obtained by Chen Y. in 2005: the higher the level of education of women, the better their sleep; on the contrary, men with a low level of education sleep better [62]. Only women, but not men, who rated their sleep as "bad" and had an average and low level of education, had an increased risk of developing hypertension. Our results are consistent with the conclusions of other authors who consider a low level of education as an independent risk factor for hypertension [63]. There were no gender-related differences in the occupational risk of hypertension. Our study has shown that sleep disorders are more common in women than they are in men. In addition, the presence of an unfavorable social gradient, e.g., widowhood or low educational level, contributes to an increased risk of hypertension. Nevertheless, we observe that the increased risk of hypertension is greater in men (HR = 5.4) than in women (HR = 4.35) during the first 5 years after the start of the study. Within 10 years, the risk of hypertension is about the same for men and women. It decreases by the 16th year. What is the reason for this? It is known from the literature that there are gender differences in coping with stress [64] and in the effects of stressful life events [65]. We believe that sleep disorders, as one of the psychosocial factors, contributes to the risk of hypertension, independent of other factors, in both men and women, but additional conditions, such as a negative social gradient, contribute to aggravate the situation.

The risk of myocardial infarction and stroke was higher in men with dysfunctional marital status and sleep disorders, while we did not find such patterns in women. Notably, the highest risk of heart attack and stroke was among widowed men with sleep disorders. One of the most stressful events in life is the loss of a loved one, which often leads to severe emotional disturbance, reduced financial security, and lifestyle changes, all of which contribute to poor sleep quality [66]. We also found that the risk of stroke was highest in people with low levels of education and sleep disorders, in both men and women. Sleep disorders increased the risk of myocardial infarction by 2.4 times in men aged 25–64. We found that in women with sleep disorders, the risk of myocardial infarction was 2.6 times higher only at the age of 55–64 years; in men in this age group, the risk of myocardial infarction was the highest - 6.4 times. The results obtained are confirmed by other researchers. For example, Gianfagna F.

together with co-authors, found that severe sleep disturbance increased the risk of CVD by a factor of 1.8 for first-time sleep disturbance and by a factor of 1.97 for those over 48 years of age [67]. Men who slept no more than 5 hours per night had a 2.3 times higher risk of developing a heart attack than men who slept 6 to 8 hours per night [68, 69].

The risk of stroke in people with sleep disorders was higher in men (HR = 3) than in women (HR = 1.9), but after adjusting for social gradient and age, the risk of stroke was similar in men (HR = 2.8) and women (HR = 2.7). It is known from literature that a stroke can be preceded by various sleep disorders. These include insomnia, fatigue, increased sleepiness, and parasomnia [70]. One of the major risk factors for stroke is sleep-disordered breathing, such as snoring. Sleep disorders and sleep-disordered breathing affect general and cerebral circulation. This leads to hypoxemia during the night. The high prevalence of morning strokes supports this theory. Oxygen demand is higher during REM sleep, and most apnea occur during this stage [71]. Eguchi K and coauthors conducted a study to determine the effect of sleeping time on stroke risk. The risk of stroke was more than doubled in hypertensive patients with less than 7.5 hours of sleep per night [72].

In our study, over a 14-year follow-up period, the risk of myocardial infarction was almost 1.7 times higher in men aged 45–64 years, and 2.4 times higher in the 45–54 years group, in those who slept 5–6 hours compared with those who slept 7–8 hours. In women aged 45–64, the risk of MI was almost 1.6 times higher among those who slept 5–6 hours compared to those who slept 7–8 hours. And the greatest risk of MI was in the 45–54-year-old group. The risk is 4.44 times higher in women who sleep 9–10 hours per night compared to women who sleep 7–8 hours per night. Our results are similar in many respects to those of the MONICA/KORA Myocardial Infarction Registry Study, Augsburg, Germany [68]. Over a 10-year follow-up period, compared with women who slept 8 hours, the relative risk (HR) of myocardial infarction was 2.98 (95% CI, 1.48–6.03) for women who slept less than 5 hours and 1.40 (95% CI 0.74–2.64) for women who slept ≥9 hours. The corresponding HRs for men were 1.13 (95% CI 0.66–1.92) and 1.07 (CI 95%, 0.75–1.53), respectively [68]. Another study confirming our results was conducted by Daghlas I. and coauthors [73]. They studied the relationship between sleep duration and MI, taking into account the genetic risk of coronary artery disease, as well as other parameters of sleep disorders. It turned out that compared with people who slept 6 to 9 hours every night, “short sleepers” had a 20% higher risk of MI (HR = 1.20; 95% CI, 1.07–1.33) and “long sleepers” had a 34% higher risk (HR = 1.34; 95% CI, 1.13–1.58), adjusted for several variables; associations were independent of other risk factors for sleep disorders. Healthy sleep duration reduced the risk of MI even in people with a high genetic predisposition to MI (HR = 0.82; 95% CI, 0.68–0.998) [74].

## 5. Conclusion

Summarizing the results of the study, we can conclude that there is an unfavorable trend - sleep duration in the population aged 45–64 years decreased between 2003 and 2018, both among men and women; there was an increase in sleep disorders. From the point of view of prevention of cardiovascular diseases, the duration of sleep from 7 to 8 hours a day may be optimal for health. However, sleeping for 9 hours or more per day can be a useful diagnostic tool in the detection of subclinical or unrecognized co-morbidities. People who report sleeping 5 hours or less per day should be considered

as a group at increased risk of all-cause mortality. In our study, "short" sleep duration was a potential risk factor for MI in men, and "short" and "long" sleep were found to be risk factors for MI in women. The question of whether sleep duration is a cause or a sign of poor health should be addressed in future research. To date, indirect evidence suggests that prolonged sleep deprivation may trigger biological mechanisms that contribute to poor health, while prolonged sleep duration may be a strong additional marker of poor health. Sleep duration should be considered as an additional behavioral risk factor or risk marker that is largely determined by the environment and may be amenable to change through education and counseling as well as public health interventions. It is necessary to seek favorable changes in the physical and work environment to ensure adequate sleep and to avoid habitual and prolonged sleep deprivation.

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Chapter 9

# Epilepsy and Sleep

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## Abstract

Epilepsy is one of the most common neurological disorders, characterized by spontaneous and recurring unprovoked seizures, affecting approximately at least 2% of the global population. Epileptogenesis involves complex and dynamic changes at the molecular, cellular, and network levels within the brain. A critical aspect of this process is the reorganization of neuronal networks, which plays an essential role in the development and perpetuation of epileptic activity. This reorganization includes alterations in synaptic connectivity, neurogenesis, and the balance between excitatory and inhibitory neurotransmission. The relationship between sleep and epilepsy is complex and bidirectional. Sleep can influence seizure occurrence and interictal epileptiform discharges (IEDs), and conversely, epilepsy and seizures can impact sleep architecture and quality. Insomnia in children with epilepsy is a complex and multifactorial condition involving intricate interactions between neurophysiological, genetic, psychological, and environmental factors. Understanding the pathophysiology of insomnia in this population requires a comprehensive approach considering the diverse mechanisms contributing to sleep disruption.

**Keywords:** epilepsy, epileptogenesis, insomnia, ASMs, brain network reorganization

## 1. Introduction

### 1.1 Epilepsy and epileptogenesis

#### *1.1.1 Background*

Epilepsy is one of the most common neurological disorders, characterized by spontaneous and recurring unprovoked seizures, affecting approximately at least 2% of the global population [1].

While there are various anti-epileptic drugs available in clinical practice, they are only effective in controlling seizures, and there is a noticeable lack of medications capable of preventing the onset of epilepsy [2]. Around 30–40% of epilepsy patients experience drug resistance [3], and it is crucial to research the mechanisms underlying epileptogenesis and to identify potential drug targets for preventing seizures.

Epileptogenesis refers to the process of structural and functional changes in the brain following potential epileptogenic lesions [4], which plays a crucial role in the development of epileptic seizures.

This process can be initiated by various insults such as traumatic brain injury, stroke, central nervous system infections, or prolonged febrile seizures. After the initial insult, there is a period of latency during which molecular and cellular changes occur, ultimately leading to the development of spontaneous seizures.

Epileptogenesis involves complex and dynamic changes at the molecular, cellular, and network levels within the brain. A critical aspect of this process is the reorganization of neuronal networks, which plays an essential role in the development and perpetuation of epileptic activity. This reorganization includes alterations in synaptic connectivity, neurogenesis, and the balance between excitatory and inhibitory neurotransmission [5].

During epileptogenesis, several fundamental pathological changes take place:

#### *1.1.1.1 Disorder in the neurovascular unit*

The neurovascular unit (NVU), consisting of astrocytes, microglia, neurons, vascular endothelial cells, vascular pericytes, and extracellular matrix, is central to epileptogenesis [6, 7]. Disorders within the NVU involve an imbalance of the neuronal excitation-inhibition system, the morphology and functional alteration of astrocytes, inflammatory activation of microglia, and increased activity of vascular endothelial cells [8].

Considering the difficulty of following individuals with brain damage that causes seizures over a long period, it can take months to years for seizures to develop after the initial injury. It is important to find reliable biomarkers during the epileptogenesis process. This will help to identify patients at risk of developing epilepsy and to choose effective drugs for treatment. This is essential for delaying epilepsy progression and preventing seizures, especially in cases of drug-resistant epilepsy. However, current research on epilepsy mainly focuses on seizures, with limited study of epileptogenesis.

#### *1.1.1.2 Neuroinflammation*

After an insult, inflammatory processes are activated, leading to the release of cytokines and other inflammatory mediators that can alter neuronal excitability.

Neuroinflammation refers to the inflammatory response within the central nervous system (CNS), involving the activation of glial cells, such as microglia and astrocytes, and the release of inflammatory mediators. Various factors, including infections, traumatic injuries, autoimmune disorders, neurodegenerative diseases, and systemic inflammation, can trigger this process. While acute neuroinflammation is a protective mechanism aimed at resolving injury or infection, chronic neuroinflammation can lead to detrimental effects on neuronal function and viability, contributing to the pathogenesis of various CNS disorders.

Microglia plays a central role in initiating and regulating neuroinflammatory responses as the resident immune cells of the CNS. In response to injury or infection, microglia undergoes morphological changes from a resting state to an activated state. Activated microglia releases pro-inflammatory cytokines (e.g., IL-1β, TNF-α, and IL-6), chemokines, reactive oxygen species (ROS), and nitric oxide (NO), which help to contain and eliminate pathogens and debris. The prolonged activation of microglia can result in excessive production of these inflammatory mediators, leading to neuronal damage and worsening of CNS pathology [9].

Astrocytes also contribute to neuroinflammation. Under pathological conditions, astrocytes become reactive, a process characterized by hypertrophy, proliferation, and the upregulation of intermediate filament proteins such as glial fibrillary acidic protein (GFAP). Reactive astrocytes secrete a range of inflammatory cytokines, chemokines, and growth factors, which can modulate the activity of other glial cells and neurons. While astrocyte reactivity is essential for wound healing and tissue repair, the chronic astrocytosis can disrupt the homeostatic functions of astrocytes, including neurotransmitter clearance and blood-brain barrier (BBB) maintenance, thereby contributing to neurodegeneration [10].

Neuroinflammation is both a consequence and a contributor to seizure activity in epilepsy. Seizures induce the release of pro-inflammatory cytokines and the activation of glial cells, which can alter neuronal excitability and promote further seizure generation. Interleukin-1β (IL-1β) and high-mobility group box 1 (HMGB1) are among the vital inflammatory mediators involved in this process. Targeting neuroinflammatory pathways has emerged as a potential therapeutic strategy for reducing seizure frequency and severity in patients with epilepsy [11].

#### *1.1.1.3 Neuronal network reorganization*

Neuronal network reorganization is a central aspect of epileptogenesis, involving synaptic changes, altered neurogenesis, cell death, and imbalances in excitatory and inhibitory signaling.

Recent developments in neuroimaging, molecular biology, and electrophysiology, in which you are actively involved, are helping to illuminate the complex changes happening in the brain affected by epilepsy. This research holds the potential to significantly impact the development of more effective treatments, providing a hopeful and motivating outlook for the future.

During epileptogenesis, significant changes occur in synaptic connectivity and plasticity. These changes include synaptic sprouting, where new synaptic connections form between neurons. A well-documented example is the mossy fiber sprouting in the hippocampus, commonly observed in temporal lobe epilepsy (TLE). This process involves the growth of axonal projections from granule cells in the dentate gyrus. These projections form aberrant connections with other granule cells, creating a recurrent excitatory circuit that can facilitate seizure activity [12].

Synaptic plasticity, the ability of synapses to strengthen or weaken over time, also plays a role. Long-term potentiation (LTP), a process that strengthens synaptic connections, and long-term depression (LTD), a system that weakens synaptic connections, are methods that modulate synaptic strength and are influenced by epileptic activity. Abnormal LTP and LTD in epileptic brains can contribute to the hyperexcitability and hypersynchrony characteristic of epileptic networks [13].

Epileptogenesis is associated with both increased neurogenesis and neuronal loss.

Neurogenesis, the process of generating new neurons, occurs primarily in the hippocampus and is upregulated following seizures. However, the integration of these new neurons into the existing network can be abnormal, leading to aberrant connectivity that promotes epileptic activity [14].

Seizure-induced neuronal loss, particularly of inhibitory interneurons, disrupts the balance between excitation and inhibition. The loss of GABAergic interneurons, which provide crucial inhibitory control over excitatory neurons, leads to a reduction

in inhibitory tone and enhances network excitability. This imbalance is a hallmark of epileptic networks and contributes significantly to the development of seizures. It is important to note that GABA, the primary inhibitory neurotransmitter, plays a vital role in this process.

#### *1.1.1.4 Network hyperexcitability and synchronization*

A defining feature of epileptic networks, which are networks of neurons that are hyperexcitable and hypersynchronous, is their propensity for hyperexcitability and hypersynchrony. Hyperexcitability refers to the increased likelihood of neurons firing action potentials, while hypersynchrony involves the excessive synchronization of neuronal firing across the network. These properties are a result of both intrinsic neuronal changes and alterations in network connectivity.

Changes in ion channel expression and function can alter the excitability of individual neurons. For instance, upregulation of voltage-gated sodium channels or downregulation of potassium channels can increase neuronal excitability. The alterations in neurotransmitter receptor expression, such as increased AMPA and NMDA receptor activity or decreased GABA receptor function, further contribute to the hyperexcitable state [15].

Network-level changes, including the formation of new excitatory pathways and the loss of inhibitory circuits, facilitate the synchronous firing of large groups of neurons. This hypersynchrony is critical for the generation and propagation of seizures. Exploring network dynamics using techniques like optogenetics and electrophysiology is vital for deepening our understanding of the mechanisms involved in epileptogenesis.

#### *1.1.1.5 Abnormal neurogenesis*

Neurogenesis, the process of generating new neurons, primarily occurs in the dentate gyrus of the hippocampus and the subventricular zone. Under normal conditions, neurogenesis contributes to learning, memory, and brain repair. In epilepsy, this process can become dysregulated, leading to abnormal neurogenesis, which significantly contributes to the development of epilepsy [16].

### *1.1.2 Abnormal hippocampal neurogenesis*

The hippocampus is a crucial brain region involved in memory formation and spatial navigation, and it is highly susceptible to seizures. In epilepsy, the dentate gyrus of the hippocampus shows abnormal neurogenesis. Seizures and status epilepticus can induce an increase in the proliferation of neural progenitor cells (NPCs). The integration of these new neurons into the existing hippocampal circuitry is often abnormal. The newly formed granule cells in the dentate gyrus may exhibit ectopic migration, forming clusters in inappropriate locations such as the hilus. These ectopic granule cells can integrate aberrantly, forming excitatory connections that contribute to the hyperexcitability and hypersynchrony of hippocampal networks.

The dendritic architecture and synaptic connectivity of these aberrantly integrated neurons can be abnormal. These neurons may form excessive excitatory synapses with other granule cells and mossy cells, leading to a positive feedback loop that exacerbates seizure activity. This aberrant network reorganization contributes to the recurrent excitatory circuits that are a hallmark of TLE [14].

### *1.1.3 Neurogenesis in other brain regions*

While the hippocampus is the most studied region in terms of neurogenesis and epilepsy, other brain regions also undergo changes in neurogenesis that contribute to the development of epilepsy. In the subventricular zone (SVZ), seizures can induce increased proliferation of NPCs, which migrate to various brain regions, including the olfactory bulb and cortex. These newly generated neurons can also integrate abnormally, potentially contributing to the development of seizures and the spread of epileptic activity.

In the cortex, the aberrant neurogenesis can lead to the formation of dysplastic neurons and glial cells, which can disrupt the cortical architecture and contribute to cortical dysplasia often observed in focal cortical dysplasia (FCD) and other forms of epilepsy [17]. These dysplastic neurons can form abnormal excitatory circuits, increasing the propensity for seizure generation and propagation.

### *1.1.4 Molecular mechanisms*

Several molecular mechanisms underlie the abnormal neurogenesis observed in epilepsy. Seizure-induced inflammation, characterized by increased levels of pro-inflammatory cytokines such as IL-1β and TNF-α, can alter the microenvironment of the hippocampus and other neurogenic niches, affecting NPC proliferation, differentiation, and survival [18]. The alterations in signaling pathways, such as the mTOR (mechanistic target of Rapamycin) pathway, can influence neurogenesis. Hyperactivation of the mTOR pathway has been implicated in epilepsy and can lead to increased proliferation and abnormal differentiation of NPCs [16].

### *1.1.5 Therapeutic implications*

Understanding the role of abnormal neurogenesis in epileptogenesis has significant therapeutic implications. Targeting the processes that lead to abnormal neurogenesis, such as inflammation and mTOR pathway activation, holds the potential for developing treatments that could mitigate or prevent the development of epilepsy [19]. Pharmacological agents that modulate neurogenesis or promote the integration of new neurons in a controlled manner may offer new avenues for therapy.

#### *1.1.5.1 Ion channel alterations*

Defects in ion channels play a crucial role in the development of epilepsy. Mutations and dysregulation of voltage-gated sodium, potassium, and calcium channels, as well as ligand-gated ion channels, disrupt the balance of neuronal excitability and inhibition, leading to hyperexcitable and hypersynchronized neuronal networks. Understanding these alterations provides crucial insights into the mechanisms underlying epileptogenesis and highlights potential therapeutic targets for preventing or mitigating epilepsy.

Changes in the expression and function of ion channels can result in an imbalance between excitatory and inhibitory neurotransmission.

Epileptogenesis involves a series of alterations at the molecular and cellular levels. Among the most critical contributors to this process are changes in ion channels, which play a pivotal role in regulating neuronal excitability and network synchronization. These alterations can boost neuronal excitability, disrupt the balance between excitation and inhibition, and lead to the hyper-synchronization of neuronal activity characteristic of seizures.

*Voltage-gated sodium channels (Nav)* are crucial for the initiation and propagation of action potentials. Mutations and dysregulation of these channels are commonly associated with epilepsy. Gain-of-function mutations in the SCN1A gene, encoding the Nav1.1 channel, can lead to hyperexcitability of neurons by increasing the persistent sodium current, thereby lowering the threshold for action potential generation [20]. These mutations are implicated in various forms of epilepsy, including Dravet syndrome and generalized epilepsy with febrile seizures plus (GEFS+).

*Voltage-gated potassium channels (Kv)* are essential for repolarizing the membrane potential and terminating action potentials. Loss-of-function mutations in potassium channel genes, such as KCNQ2 and KCNQ3, which encode subunits of the Kv7 channel, result in prolonged neuronal depolarization and increased excitability [21]. These mutations are associated with benign familial neonatal seizures (BFNS) and other epileptic encephalopathies. Additionally, downregulation of Kv channels has been observed in acquired epilepsy, contributing to hyperexcitability in affected neuronal networks.

*Voltage-gated calcium channels (Cav)* regulate neurotransmitter release and various intracellular signaling pathways. Alterations in these channels can significantly impact neuronal excitability. The mutations in the CACNA1H gene, encoding the Cav3.2 channel, have been linked to idiopathic generalized epilepsy. These mutations can lead to increased calcium influx, enhancing neurotransmitter release and neuronal excitability. The Cav3.2 channels have been shown to be upregulated in animal models of TLE, suggesting a role in acquired forms of the disease [22].

*Ligand-gated ion channels*, such as the GABA-A receptors and NMDA receptors, also play vital roles in maintaining the excitatory/inhibitory balance in the brain. GABA-A receptors mediate inhibitory neurotransmission, and their dysfunction is a common feature in epilepsy. Mutations in GABA-A receptor subunits, such as GABRA1, can reduce inhibitory currents, leading to an imbalance that favors excitability [23]. The NMDA receptors, which mediate excitatory neurotransmission, can contribute to epileptogenesis when overactivated. Increased expression or hyperfunction of NMDA receptors can lead to excessive calcium influx and excitotoxicity, further promoting neuronal hyperexcitability and network reorganization [24].

*Beyond genetic mutations*, changes in the expression and function of ion channels due to environmental factors, brain injury, or prolonged seizures can contribute to epileptogenesis. The status epilepticus, a condition of protracted seizures, can lead to the downregulation of GABA-A receptors and upregulation of Nav and Cav channels, perpetuating a cycle of increased excitability and seizure susceptibility.

#### *1.1.5.2 Epigenetic modifications*

Epigenetic modifications are critical contributors to the complex process of epileptogenesis. DNA methylation, histone modifications, and non-coding RNAs collectively influence gene expression patterns that underlie neuronal excitability, inflammation, and synaptic plasticity, thereby promoting the development and progression of epilepsy. Understanding these epigenetic mechanisms provides valuable insights into potential therapeutic targets for preventing and treating epilepsy.

Epigenetic modifications, such as DNA methylation, histone modifications, and non-coding RNA regulation, are crucial in the development of epilepsy [25]. These modifications do not change the DNA sequence but can impact gene expression and neural function, contributing to the onset and progression of the condition [26].

DNA methylation involves adding a methyl group to the cytosine residues of DNA, typically at CpG dinucleotides, which leads to gene silencing. Abnormal DNA

methylation patterns have been observed in epilepsy. The hypermethylation of the Reelin gene, involved in neuronal migration and synaptic plasticity, has been linked also to TLE. This hypermethylation decreases Reelin expression, contributing to abnormal neuronal connectivity and hyperexcitability. The hypomethylation of genes involved in inflammatory pathways can lead to their overexpression, promoting a state of increased inflammation that worsens seizure activity.

The histone modifications, such as acetylation, methylation, phosphorylation, and ubiquitination, affect chromatin structure and gene expression. Altered histone acetylation patterns have been implicated in the regulation of genes associated with neuronal excitability and inflammation in epilepsy. The increased histone acetylation at the promoters of pro-inflammatory cytokine genes can enhance their expression, contributing to the observed neuroinflammatory environment in epileptic brains. The HDAC inhibitors have been shown to reduce seizure frequency and severity in animal models by restoring standard gene expression patterns. Histone methylation also plays a role, with specific patterns of histone H3 methylation being associated with either activation or repression of epilepsy-related genes [27].

Non-coding RNAs, including microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), regulate gene expression post-transcriptionally. Dysregulation of miRNAs has been implicated in epilepsy. The miR-146a, involved in the regulation of inflammation, is upregulated in epilepsy, leading to enhanced expression of pro-inflammatory cytokines and contributing to seizure susceptibility. Other miRNAs, such as miR-34a and miR-128, have been found to regulate neuronal excitability and synaptic plasticity, further implicating their role in the development of epilepsy [28]. LncRNAs, which can modulate chromatin structure and gene expression, also play a role in epilepsy. Altered expression of specific lncRNAs has been associated with changes in the expression of genes involved in synaptic function and neuronal excitability, highlighting their potential involvement in the development of epilepsy [29].

## 2. Sleep and epilepsy

### 2.1 Relationship between sleep and seizure activity

The relationship between sleep and epilepsy is complex and bidirectional. Sleep can influence seizure occurrence and IEDs, and conversely, epilepsy and seizures can impact sleep architecture and quality.

### 2.2 Influence of sleep on seizures

#### *2.2.1 Sleep stages and seizure occurrence*

Certain sleep stages are more prone to seizure activity. Seizures are more likely to occur during non-rapid eye movement (NREM) sleep than rapid eye movement (REM) sleep. NREM sleep is characterized by synchronous neuronal activity, which may provide a conducive environment for seizure propagation. REM sleep is associated with desynchronized neuronal activity, which may help inhibit seizure spread.

- Circadian rhythms: The occurrence of seizures also follows circadian rhythms. Some types of epilepsy, such as juvenile myoclonic epilepsy (JME), have a higher incidence of seizures upon awakening or shortly after waking up.

- Sleep deprivation: Lack of sleep is a well-known trigger for seizures in individuals with epilepsy. Sleep deprivation can lead to increased neuronal excitability and lowered seizure threshold, thereby increasing the likelihood of seizures.

*2.2.2 Impact of epilepsy on sleep*

Epilepsy and seizures can adversely affect sleep architecture and quality, leading to various sleep disorders, including insomnia, excessive daytime sleepiness, and parasomnias. Some of the ways epilepsy impacts sleep include the following:

- Nocturnal seizures: Seizures that occur during sleep can lead to frequent awakenings, fragmented sleep, and reduced sleep efficiency.

- Interictal epileptiform activity: IEDs can disrupt standard sleep patterns, particularly during NREM sleep, leading to alterations in sleep architecture.

- Effects of antiseizure medications (ASMs): While ASMs are essential for controlling seizures, some can have sedative effects or cause sleep disturbances as side effects, which can further impact sleep quality.

**2.3 Sleep disorders in epilepsy patients**

Patients with epilepsy are at an increased risk of various sleep disorders, which can further exacerbate their condition. Some common sleep disorders in epilepsy patients include the following:

- Obstructive sleep apnea (OSA): OSA is prevalent among epilepsy patients and can worsen seizure control. Continuous positive airway pressure (CPAP) therapy for OSA has been shown to improve seizure control in some patients.

- Restless legs syndrome (RLS): RLS is characterized by an irresistible urge to move the legs, particularly during rest, and is more common in individuals with epilepsy.

- Insomnia: Difficulty falling asleep or maintaining sleep is common in epilepsy patients, often exacerbated by nocturnal seizures and anxiety related to the condition.

**2.4 Pathophysiology of insomnia in children with epilepsy**

Insomnia, a prevalent sleep disorder characterized by difficulty in falling asleep, staying asleep, or achieving restorative sleep, significantly affects children with epilepsy. The pathophysiology of insomnia in this population is multifactorial, involving complex interactions between neurological, genetic, psychological, and environmental factors. This comprehensive analysis examines the underlying mechanisms contributing to insomnia in children with epilepsy, focusing on recent advancements and research findings in this field.

## 3. Neurophysiological mechanisms

### 3.1 Epileptic activity and sleep disruption

Epileptic seizures and IEDs profoundly disrupt standard sleep architecture. Seizures can occur during sleep, leading to frequent awakenings and a fragmented sleep pattern. IEDs can interfere with sleep continuity and reduce the amount of slow-wave sleep (SWS), which is crucial for restorative sleep, even in the absence of overt seizures. Studies have shown that children with epilepsy often exhibit decreased SWS and rapid eye movement (REM) sleep, coupled with increased light sleep stages (N1 and N2) [30, 31]. This alteration in sleep architecture results from the brain's abnormal electrical activity, which disrupts the normal progression of sleep stages.

### 3.2 Role of the thalamocortical network

The thalamocortical network, which plays a pivotal role in generating and maintaining sleep rhythms, is often disrupted in epilepsy. This disruption can result from structural abnormalities and functional impairments within the network. The thalamus, a key relay center for sensory and motor signals, regulates sleep spindles and SWS. In children with epilepsy, thalamic dysfunction can impair the generation of these sleep rhythms, contributing to insomnia [32]. Functional imaging studies have revealed altered thalamic connectivity in patients with epilepsy, correlating with sleep disturbances [33].

### 3.3 Neurotransmitter imbalance

Neurotransmitter systems regulate sleep-wake cycles, particularly gamma-aminobutyric acid (GABA) and glutamate. Epilepsy is associated with an imbalance between excitatory and inhibitory neurotransmission, with an overall increase in excitatory glutamatergic activity and a decrease in inhibitory GABAergic activity. This imbalance can lead to hyperexcitability of cortical and subcortical networks, promoting wakefulness and reducing sleep propensity [34]. The use of ASMs that modulate these neurochemical pathways can further influence sleep patterns, either improving or exacerbating insomnia depending on the specific medication and individual response [35].

## 4. Genetic and molecular factors

### 4.1 Genetic predisposition

Genetic factors play a significant role in both epilepsy and insomnia. Specific genetic mutations and polymorphisms have been linked to an increased risk of epilepsy and associated sleep disturbances. For instance, mutations in genes encoding ion channels, such as SCN1A, have been implicated in epilepsy syndromes like Dravet syndrome, which are often accompanied by severe sleep disturbances [36]. Similarly, polymorphisms in clock genes that regulate circadian rhythms, such as PER3, have been associated with insomnia and disrupted sleep patterns [37]. These genetic predispositions highlight the interplay between genetic factors influencing epileptogenesis and sleep regulation.

### 4.2 Circadian rhythm disruption

Circadian rhythms, governed by the suprachiasmatic nucleus (SCN) of the hypothalamus, play a crucial role in regulating the sleep-wake cycle. Disruptions in circadian rhythms are commonly observed in children with epilepsy. Epileptic seizures themselves can disrupt the normal functioning of the SCN, leading to irregular sleep patterns. Moreover, genetic mutations affecting circadian clock genes can misalign the sleep-wake cycle, contributing to insomnia [38]. Studies have shown that children with epilepsy often exhibit delayed sleep phase syndrome (DSPS), characterized by a delayed onset of sleep and difficulty waking up in the morning.

## 5. Psychological and behavioral factors

### 5.1 Anxiety and depression

Psychological comorbidities, particularly anxiety and depression, are highly prevalent in children with epilepsy and significantly contribute to insomnia. Anxiety can lead to hyperarousal, making it difficult for children to initiate and maintain sleep [39]. Depression is associated with alterations in sleep architecture, including reduced SWS and REM sleep and increased nighttime awakenings [40]. The bidirectional relationship between epilepsy and psychological comorbidities complicates the management of insomnia, as seizure control can improve psychological well-being and vice versa.

### 5.2 Behavioral sleep disorders

Behavioral factors, such as poor sleep hygiene and conditioned arousal, can also contribute to insomnia in children with epilepsy. Inadequate sleep hygiene practices, including irregular sleep schedules, excessive screen time before bed, and consumption of caffeine or sugar, can disrupt the sleep-wake cycle. Additionally, children with epilepsy may develop conditioned arousal, where they associate the bed and sleep environment with wakefulness and anxiety due to previous negative experiences, such as nocturnal seizures [41]. Addressing these behavioral factors through education and cognitive-behavioral therapy for insomnia (CBT-I) can significantly improve sleep outcomes in this population.

## 6. Environmental and social influences

### 6.1 Impact of antiseizure medications (ASMs)

ASMs, the primary treatment for epilepsy, can have variable effects on sleep. Some ASMs, such as benzodiazepines and barbiturates, have soothing properties and can promote sleep. However, others, like stimulants and specific mood stabilizers, can exacerbate insomnia by increasing arousal and reducing sleep efficiency [31]. ASMs such as phenytoin and carbamazepine have been reported to cause alteration in sleep microstructure, although the effects do not seem to be continuous [42]. The choice of AEDs must be carefully considered, balancing seizure control with the potential impact on sleep quality.

### 6.2 Sleep environment and routine

The sleep environment and routine play critical roles in sleep quality. Children with epilepsy may have disrupted sleep environments due to the need for monitoring and medical interventions. Frequent nocturnal awakenings for medication administration or seizure monitoring can fragment sleep and contribute to insomnia. Creating a stable and comfortable sleep environment, establishing consistent bedtime routines, and minimizing disruptions can help improve sleep quality in children with epilepsy [43].

### 6.3 Family and social dynamics

Family and social dynamics also influence sleep in children with epilepsy. Parental anxiety about seizures, inconsistent caregiving practices, and stress within the household can contribute to sleep disturbances. Family-based interventions that address parental stress, provide education on sleep hygiene, and promote consistent caregiving practices can improve sleep outcomes for children with epilepsy [44]. Support networks, such as groups for families of children with epilepsy, can offer valuable resources and strategies for coping.

## 7. Neuroendocrine and immune system contributions

### 7.1 Hormonal regulation

The neuroendocrine system, particularly the hypothalamic-pituitary-adrenal (HPA) axis, significantly regulates sleep. Dysregulation of the HPA axis, often observed in children with epilepsy, can lead to increased cortisol levels and a state of hyperarousal, contributing to insomnia. Chronic stress and frequent seizures can exacerbate this dysregulation, creating a vicious cycle of stress and sleep disruption [45]. Interventions aimed at reducing stress and regulating cortisol levels, such as mindfulness-based stress reduction (MBSR) and relaxation techniques, can be beneficial in managing insomnia in this population.

### 7.2 Immune system involvement

The immune system is increasingly recognized as a critical player in the pathophysiology of sleep disorders. Inflammatory processes and immune dysregulation have been implicated in both epilepsy and insomnia. Elevated levels of pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), have been associated with poor sleep quality and increased seizure frequency [46]. This bidirectional relationship suggests that targeting inflammation and immune dysregulation may be a potential therapeutic avenue for improving sleep in children with epilepsy.

## 8. Recent advances and future directions

### 8.1 Advances in neuroimaging

Recent advances in neuroimaging techniques, such as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET), have provided

more profound insights into the brain mechanisms underlying insomnia in children with epilepsy. These techniques allow for visualizing functional and structural abnormalities in the brain regions involved in sleep regulation, such as the thalamus, hypothalamus, and brainstem [47]. Longitudinal neuroimaging studies are needed to understand the dynamic changes in brain networks associated with insomnia and epilepsy over time.

### 8.2 Genetic and epigenetic research

Genetic and epigenetic research continues to uncover the complex interactions between genes, environment, and sleep regulation. Studies exploring the epigenetic modifications that occur in response to seizures and chronic sleep disruption can provide insights into the long-term impact of epilepsy on sleep. Additionally, identifying genetic biomarkers associated with susceptibility to insomnia in children with epilepsy can facilitate early diagnosis and personalized treatment approaches [48].

### 8.3 Novel therapeutic approaches

The development of novel therapeutic approaches for managing insomnia in children with epilepsy is a growing area of research. Non-pharmacological interventions, such as neurofeedback and transcranial magnetic stimulation (TMS), promise to modulate brain activity and improve sleep quality. Pharmacological advancements, including developing new AEDs with fewer sleep-disrupting side effects and using melatonin and other sleep-promoting agents, are also being explored [49].

### 8.4 Integrative and holistic approaches

Integrative and holistic approaches, combining pharmacological treatments with behavioral and environmental interventions, are increasingly recognized as effective strategies for managing insomnia in children with epilepsy. Multidisciplinary care teams, including neurologists, sleep specialists, psychologists, and social workers, can provide comprehensive care tailored to each child's individual needs. Implementing integrative approaches that address the multifaceted nature of insomnia can improve overall health outcomes and quality of life for children with epilepsy [50].

## 9. Conclusion

Insomnia in children with epilepsy is a complex and multifactorial condition involving intricate interactions between neurophysiological, genetic, psychological, and environmental factors. Understanding the pathophysiology of insomnia in this population requires a comprehensive approach considering the diverse mechanisms contributing to sleep disruption. Recent advancements in neuroimaging, genetic research, and novel therapeutic approaches hold promise for improving the management of insomnia in children with epilepsy. Future research should continue to explore these areas, aiming to develop targeted and personalized interventions that address the unique needs of this vulnerable population.

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Section 4

# Sleep Measurement and Drug Therapy

Chapter 10

# Perspective Chapter: Assessment of Subjective and Objective Sleep Quality from Wrist-Worn Wearable Data

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## Abstract

Researchers are interested in measuring both objective and subjective assessments of sleep, and associated phenomena such as sleepiness, quality and restoration. Predicting perceived sleep quality accurately from objective measurements remains an unsolved and interesting problem. Previous studies using polysomnograms and actigraphy have shown poor concordance between objective metrics and subjective sleep quality, but were often limited by study duration (e.g., one or two nights of PSG, study population in low 100 s). In this chapter, we consider whether consumer sleep trackers could significantly improve the assessment of subjective sleep quality through longer periods of assessment and larger data scale. We describe a recent study that modeled two subjective sleep quality metrics (PROMIS Sleep-Related Impairment (SI) and Sleep Disturbance (SD) Index) from objective sleep metrics acquired from a consumer wearable device (Fitbit). However, the goodness-of-fit parameter remains relatively low, even with the increased data availability and scale of data provided by consumer wearables. Specifically, for a well-characterized normative population of 2106 adults, we see that a linear multivariate model produces an $R^2$ of 0.107 for predicting SI and $R^2$ of 0.147 for SR, consistent with prior results using PSG and actigraphy. We conclude that subjective sleep quality remains broadly a psychological construct that cannot be fully modeled solely by objective sleep metrics.

**Keywords:** sleep quality, wearables, total sleep time, PROMIS, actigraphy

## 1. Introduction

### 1.1 Assessing sleep: quality or quantity?

Within the field of sleep research, there have been parallel efforts to quantify both objective and subjective aspects of sleep. Objective metrics of sleep are defined

as those in which the subject's feedback or assessment is not required, and have been driven initially by polysomnography [PSG] (laboratory based sleep studies), and the resulting parameters derived therefrom. For example, we now have well codified rules [1] for the scoring of various sleep stages [wake, N1-N3 non-REM sleep, and REM sleep], and while there is often imperfect agreement between individual scorers, in general, metrics such as total sleep time (TST), wake after sleep onset (WASO), and total duration of various sleep stages, provide robust and repeatable measurements that can be used to explore sleep. Objective metrics from PSG can also be used to quantify clinical sleep disorders such as apnea or periodic limb movements, where reliable assessment can be done independently of the user's own perceptions.

The field of objective sleep measurement was further expanded by the adoption of actigraphy in the 1980s [2] - these are typically wrist worn devices that have the advantage that they can be worn in a free-living environment for longer periods of time. They are based on the use of 1D or 3D accelerometry to measure motion, coupled with specialized algorithms to map the movement to estimates of sleep and wake state. Actigraphy allows investigation of multi-night sleep phenomena such as sleep regularity, circadian phase, and longitudinal changes of TST, WASO, sleep onset latency, etc. in a natural setting. Actigraphy has been adopted by sleep clinicians as a reliable way to characterize circadian sleep disorders [3], and for more general use in sleep research.

A newer entry to the field of sleep assessment are consumer-based sleep trackers, which have seen increased adoption and popularity in the last 10–15 years [4]. These can take the form of wrist-watches or trackers (e.g., devices such as Fitbit Charge, Apple Watch, Samsung Galaxy Gear, etc.), "smart" rings (e.g., Oura), under-mattress sensors (e.g., Withings Sleep Tracking Pad), bedside, non-contact - "nearable" monitors (Nest Hub, ResMed S+, etc.), and even electroencephalographic consumer devices (e.g., Dreem, Zeo, etc.). A benefit of consumer sleep trackers is the ability to measure sleep longitudinally and under free-living conditions, and at large scale. They also measure additional signals compared to actigraphy (such as heart rate, SpO2, electrodermal activity, etc.), and given their mass consumer nature, are available at significantly lower cost than specialized actigraphy devices. Consumer devices have already given new insights into population sleep dynamics [5], or as useful outcome metrics for sleep improvement programs [6].

In parallel to devices and rules/algorithms that measure sleep objectively, there has been development of subjective ratings of sleep itself, or of sleep-related phenomena such as sleepiness, insomnia, restlessness or restoration, and even sleep satisfaction. These vary from the comprehensive (e.g., the Pittsburgh Sleep Quality Index [7]), to the more disease-focused such as the Insomnia Severity Index [8]. A subjective sleep metric implicitly requires a user's feedback, and can be thought of as a psychological construct, with all of the challenges associated with psychometrics (such as reliability and construct validity). Such constructs assume an underlying latent variable ("sleep quality", "restoration", etc.) which cannot be directly accessed but nevertheless has value as a predictor of other factors (e.g., higher risk of depression) or as a target in itself for improvement. The constructs also have implicit time dependence (e.g., how you feel about last night's sleep could differ significantly from your perspective on your long term average).

For users and sleep researchers, there is value in both objective and subjective sleep metrics, as they reflect different aspects of sleep's importance to overall health. There is a complex relationship between objective sleep, subjective sleep quality (and associated daytime function) and overall health, and most sleep clinicians and researchers would regard both types of metrics as important. For example, the

clinical definition of insomnia in the Diagnostic and Statistical Manual's fifth edition, text revision, DSM-5-TR [9], implicitly includes both subjective ("dissatisfaction with sleep quality or quantity") and objective criteria ("occurs more than three times per week"). Indeed many patients with insomnia manifest objective sleep metrics considered within normal range [10]. Furthermore, in the area of mental health and wellness, subjective sleep quality has often been shown to be more highly correlated with mental wellness than objective sleep metrics [11].

In this chapter, we will give a brief survey of the most commonly used objective and subjective sleep quality metrics, discuss attempts to model subjective sleep quality from objective metrics (including an example from a recent study on digital wellbeing), and draw some general conclusions about the need for both types of metrics.

## 2. A brief survey of objective and subjective sleep quality metrics

### 2.1 Commonly used objective sleep metrics

Many objective sleep metrics can be derived from a laboratory based polysomnogram (PSG or "sleep study"). In a PSG, the person's sleep state is determined on an arbitrary, 30-second-epoch basis over the duration of the sleep period. Since a PSG study is typically observed by a technician, the moment at which a person begins to attempt to sleep can be directly elicited from the subject. This is much harder in an unattended, real-world setting, where individuals may typically read, watch TV, etc. before intentionally deciding to fall asleep, resulting in misestimation of the intent to sleep because of periods of relatively inactive wake, as well as unintentional lapses into sleep (i.e., "dozing").

Commonly used summary objective metrics derived from a night of PSG are shown in **Table 1**. Even for these objective metrics there can be some degree of ambiguity (e.g., determining the point at which a person "attempts to sleep" is ambiguous, and in most cases the "Lights Out" time is used as a surrogate metric. Similarly sleep onset latency (SOL) can be measured to the first observed epoch of N1 sleep, the earliest of 3 consecutive N1 epochs, or to the first non-N1 sleep stage epoch, depending upon the protocol.

A disadvantage of objective sleep metrics from a PSG study are that they represent a single night's record, so may not reflect typical sleep patterns for an individual (indeed since they are taken in an unusual environment, and with the participant wearing many physiological sensors, they are highly unlikely to represent normal sleep for that individual [12]). In particular, they are unlikely to capture information about sleep regularity or circadian phase.

Actigraphy (sometimes referred to as actimetry) is a technique that emerged in the 1980s [2] to enable objective sleep measurements without the need for a laboratory-based assessment. Actigraphy uses 1D or 3D accelerometers to measure body movement (typically at the wrist, but other body sites such as the ankle or hip are also used). A variety of algorithms were developed that mapped the observed accelerometer patterns to the sleep state observed by a PSG, and reasonable levels of accuracy can be obtained (e.g., typical commercial actigraphy devices provide sleep sensitivity (percent of true sleep epochs detected as sleep) of ~95–98% and wake specificity (percent of true wake epochs detected as wake) of approximately 40–50% on a per-epoch basis, with the exact performance dependent on algorithm choice and population [13, 14]. However, actigraphy has the considerable advantage of being deployable

| Metric | Unit | Description |
|---|---|---|
| Time-in-Bed | minutes | The total time when a person is in bed during a sleep session |
| Bed-Entry Time | hh:mm:sec | The time when a person enters bed |
| Bed-Exit Time | hh:mm:sec | The time when a person exits bed for the final time in a night. |
| Time-Attempting-To-Sleep (TATS) onset | hh:mm:sec | The time when a person first decides to attempt sleeping |
| Total Wake Time | minutes | Total time recorded as wake state using AASM sleep scoring rules |
| Initial Sleep Onset Time | hh:mm:sec | The time at which the person is first recorded in a sleep state |
| Final Awakening Time | hh:mm:sec | The time at which the person is considered to have completed their sleep |
| Hypnogram | A sequence of labels (Wake, N1,N2,N3, REM, unclassified) with associated timestamps | This is the overall sequence of sleep stages throughout a night |
| Total Sleep Time (TST) | minutes | The sum of N1-N3 and REM sleep stages throughout a night, scored on non-overlapping 30-sec epochs |
| Total Wake Time, Total time in N1, N2, N3, REM | minutes | The cumulative duration of time spent in individual stages |
| Wake After Sleep Onset (WASO) | minutes | The time recorded in the wake state after the Initial Sleep Onset Time up to the Final Awakening Time |
| Sleep Onset Latency (SOL) | minutes | The time between TATS-onset and the first recorded epoch of sleep (alternative definitions possible). |

**Table 1.**
*An illustrative set of commonly used objective sleep metrics typically observed by laboratory studies (not intended to be comprehensive).*

in a free-living environment, over multiple nights and is therefore recommended in clinical practice for assessment of circadian rhythm disorders [3]. Actigraphy also allows for the development of multi-night objective metrics such as average bed-time or sleep regularity index [15].

Beyond standard summary metrics characterizing typical sleep patterns, the mid-term monitoring duration (typically 7–14 days) of actigraphy offers opportunities to identify patterns of stability and change within individuals. In particular, the continuous measurement of rest-activity patterns from actigraphy can highlight relevant bidirectional influences on and from the circadian system that are otherwise impractical to study [16], due to the highly controlled nature of the study environments. This property is especially valuable as studies exploring both the typical sleep/wake and circadian patterns as well as their changes over time have revealed some of the genetic underpinnings of individuals' sleep patterns [17], and highlighted important associations with health and disease [18].

Building upon the value imparted by actigraphic monitoring of longitudinal, real-world sleep-and-activity data, consumer wearable technology has added various sensors to their devices to offer a more detailed picture of sleep. While the accuracy of sleep tracking technologies evidences several limitations, such that no technology is truly a replacement for a polysomnogram [19–21], their multimodal sensors do provide meaningful assessments of body states during sleep. This has recently been demonstrated in a large (over 6700 participants, sharing over 6.5 million nights of Fitbit sleep data) study, which highlighted meaningful associations between clinical disorders and consumer wearable sleep-wake and sleep quality (e.g., sleep stages, restlessness, etc.) metrics [22]. So, while no two consumer sleep trackers are necessarily measuring the same physiologic parameters or mapping directly to clinical measurements, it appears that these proprietary metrics do still provide valuable insights into important aspects of sleep, beyond just the proportion and timing of sleep and wake.

## 2.2 Commonly used subjective sleep metrics

In contrast to the objective sleep metrics listed above, subjective sleep metrics explicitly require an individual to provide retrospective self reported feedback on their subjective experience, considering time periods as short as a single night or ecological momentary assessments, up to significantly longer time periods such as the last two weeks, or last month. A significant number of such subjective questionnaire instruments have been developed, and the ones listed below are among the more commonly used (listed in order of assessment period from one night to one month or longer).

### *2.2.1 Consensus sleep diary (CSD)*

The consensus sleep diary [23] is targeted at standardizing a sleep diary for reporting on *individual nights*, and is particularly aimed at evaluating individuals with insomnia. It asks 8 structured questions, including subjective estimates of objective metrics such as bed-entry-time, bed-exit-time, sleep onset latency, etc. It also includes one question "How would you rate the quality of your sleep" which is scored on a 5-point Likert scale from "Very Poor" to "Very Good".

### *2.2.2 PROMIS sleep related impairment and PROMIS sleep disturbance indices*

The Patient-Reported Outcomes Measurement Information System (PROMIS) is an NIH initiated project to assemble standardized patient reported outcomes across a range of clinical fields. There are two PROMIS related questionnaires which are relevant for assessing aspects of sleep quality [24]. The PROMIS Sleep-Related Impairment questionnaire focuses on self-reported perceptions of alertness, sleepiness, and tiredness during usual waking hours, and the perceived functional impairments during wakefulness associated with sleep problems or impaired alertness. In its full form, it is a sixteen-item questionnaire, with each aspect measured on a 5 point scale. The PROMIS Sleep Disturbance questionnaire is composed of twenty-seven questions and assesses perceptions of restlessness, restoration, difficulty falling asleep and overall quality. Short forms of both these questionnaires are available as 4 or 8 question panels, and have been validated [25] while also presenting less of a burden on individuals completing them. The raw score from the questionnaire can be mapped to a T-score from 0 to 100. It is intended for the user to consider the *prior seven days* of sleep.

*2.2.3 The insomnia severity index (ISI)*

This is widely used to assess the presentation and severity of insomnia symptoms, and is a seven-question survey [MOR93]. Three questions focus on specific experiences of not being able to sleep as desired, and four questions are focused on an individual's perception of how that affects them. The overall score can range from 0 to 28, with higher scores indicating the presence of more severe insomnia symptoms, with scores of 15 and above generally considered to represent moderate-to-severe insomnia. It is intended for participants to review their *preceding two weeks* of sleep history.

*2.2.4 Pittsburgh sleep quality index (PSQI)*

This is probably the most widely used metric of subjective sleep currently, and has the advantage that due to its longevity, there are many reference studies on different populations available. It consists of a 19-item, self-report assessment of sleep quality, which details seven components of sleep (quality, onset latency, duration, efficiency, disturbance, use of sleep medication, and daytime dysfunction) [BUY89]. It is intended for participants to review their *prior month* of sleep history, and provides a global score that ranges from 0 to 21, where higher scores (e.g., >6) indicate reduced sleep quality.

*2.2.5 Karolinska sleep questionnaire (KSQ )*

This is a comprehensive tool which addresses sleep difficulties, napping behavior, chronotype, estimated sleep need, perceived sleep quality, etc. [26] It is intended for participants to consider their *last 3 months* of sleep in answering the questionnaire. A subset of 4 questions from the KSQ is sometimes used to develop a sleep quality index.

*2.2.6 National Sleep Foundation sleep satisfaction tool (SST)*

The SST aimed to provide a broad simple tool for assessing sleep health, and focuses on nine items: sleep quality, sleep duration, ease of falling asleep, ease of going back to sleep after waking, feelings after waking up, feelings during the day, relaxation, and sleeping environment [27]. *No time period* of evaluation is specified, just a request for a "typical" value.

*2.2.7 The RU-SATED framework*

This was intended to provide a simple overall metric of sleep health and satisfaction [28], and includes six questions on sleep regularity (R), satisfaction (S), alertness in the day (A), timing of sleep (T), efficiency of sleep (E) and duration of sleep (D) and is intended to be applied retrospectively on a person's typical sleep. *No time period* of evaluation is specified. While this measure has been derived from various combinations of objective sleep data and self-report questionnaires, a 6-question-based instrument was recently developed and validated [29].

In addition to these instruments specified above, there are a significant number of additional questionnaires that provide insight into people's perceptions of sleep or associated phenomena: for example the Epworth Sleepiness Scale assesses symptoms of daytime sleepiness [30], the Karolinska Sleepiness Scale assesses sleepiness at a particular moment in time [31], the Morning-Eveningness Questionnaire estimates

chronotype [32], and the Sleep Self Efficacy scale provides insights on individuals' confidence in their sleeping patterns, etc. [33]. Depending on the context of a study or population, these may also provide insight into "sleep quality". The National Sleep Foundation's Sleep Health Index is an interesting recent tool which combines elements of subjective sleep quality together with a clinical sleep disorder assessment and sleep duration [34]. This is intended as a potential population-level tool, so that sub-populations with higher or lower sleep health can be identified. A more in-depth review of the various subjective sleep metrics that have been explored can be found in [35].

## 3. Predicting subjective sleep quality from objective measures

### 3.1 Current state of the art

At a surface level, it seems reasonable that accurate assessment of objective sleep metrics should lead to quite robust estimates of subjective sleep quality, and many studies have attempted to find an optimal mapping from objective to subjective sleep, using objective metrics obtained through either polysomnography or actigraphy.

#### *3.1.1 Polysomnography-based studies*

While polysomnography remains a gold standard for characterizing a single night of sleep (e.g., for detection of sleep disorders such as sleep apnea, periodic limb movements, etc.), at face value it is not necessarily suited to characterize a person's overall sleep quality (e.g., people are sleeping in a novel environment, heavily instrumented, and often offset from their natural circadian rhythm). Nevertheless, some studies have considered whether a PSG study can help predict overall subjective sleep quality. In [36], researchers studied a cohort of 45 insomnia sufferers. They used the PSQI as an assessment of sleep quality, and saw modest correlations between the global PSQI score and some objective sleep metrics (e.g., TST minus time spent in Stage N1 was a significant predictor). Correlations were in the order of 0.1–0.3 (i.e., small to medium effect sizes) at highest. Similarly, in a larger scale study [37] of 1483 older adults, researchers used a variety of linear and non-linear models to predict subjective, single-night sleep quality ratings (in terms of restfulness and sleep depth). They reported that even quite complex models based on random forest, non-linear classifiers were able to explain only about 11–17% of the variance. The most predictive objective variables were TST, sleep efficiency (SE), and WASO.

#### *3.1.2 Actigraphy and sleep quality studies*

In general, actigraphy devices (such as the Actiwatch) do not provide a single, consolidated sleep quality score, but focus on providing objective measures such as TST, SOL, sleep efficiency, and fragmentation. Actigraphy has been primarily positioned as a clinical/scientific research tool, and in most use cases, the objective sleep metrics are not directly provided to the participant during trials. Many trials do ask participants to provide assessments of sleep quality, and these can then be compared, retrospectively, with the actual objective sleep metrics measured, where the participant's ratings are blind to the objective data. In [38], a cohort of 313 subjects was studied using 7 nights of actigraphy, and the PSQI was used as a measure of subjective sleep quality. An $R^2$ of 0.14 was reported, with variability of total sleep time

as the most significant factor in predicting the PSQI. Similarly, in [39], the authors considered whether objective metrics from a week of actigraphy data in 489 adults could provide reasonable predictions of the PSQI score. They observed single- factor correlations in the range of 0.0–0.05, and even when they used a composite objective sleep metric (number of awakenings plus sleep efficiency plus WASO), the correlation remained low (0.03). In [40], researchers used a subset of 4 metrics from the validated Karolinska sleep diary, and actigraphic metrics to compare objective and subjective sleep measurements in 54 subjects over 7 nights. They reported low correlation between sleep quality and three objective metrics (total sleep time, sleep efficiency, and sleep percent) with correlation coefficients ranging in the 0.0–0.4 range (null to medium effect sizes). They also recommended at least 6 nights of actigraphic recorded data to obtain reliable objective metrics of sleep, and for weekend and weekday nights to be processed separately if feasible. As a final example, in [41], the authors considered both the PSQI and the CSD sleep quality metrics compared across 14+ nights of actigraphy data in a cohort of older adults. They also demonstrated low correlation between any objective metric of sleep and the PSQI global score or the CSD sleep quality (highest individual correlation of 0.3 was achieved by considering the start time of the 5 least active hours of a person's day). An insight of this paper was there was a high level of correlation between individual nights of CSD sleep quality assessment, and the overall global PSQI score, which at least suggests that the concept of "sleep quality" is quite stable over a time period of a month for an individual user, even if it was not well predicted by objective metrics.

*3.1.3 Consumer sleep trackers*

In the last ten-to-fifteen years, the field of consumer sleep tracking has grown considerably, and offers a variety of options to consumers to measure their sleep objectively via smartwatches, trackers, under-mattress sensor pads, or non-contact radiowave or ultrasound sensors. Such devices allow the observation of sleep patterns outside clinical or research settings, and over extended periods of time. The users also receive daily feedback on objectively measured sleep parameters, so this raises the possibility that such devices could provide more robust or insightful measurements of subjective sleep quality. A number of studies have considered whether the component factors measured by a wearable device (e.g., Total Sleep Time, Time-in-Bed, etc.) can provide useful assessments of subjective sleep quality. In [42], the authors compared objective sleep parameters from Fitbit devices with the Korean language version of the PSQI, and showed that the sleep efficiency, total sleep time, and number of awakenings were significantly correlated with the PSQI score (correlations ranged from −0.07 to −0.24). This was in a cohort of 268 adults. In [43], the authors used objective sleep metrics from a Samsung Galaxy watch to generate a sleep habit score for a cohort of 714 subjects. They focused on using the sleep habit score to classify subjects into "good" and "bad" sleepers, based on objective metrics obtained from the watch such as regularity, duration, timing and efficiency, and also augmented the overall score with daytime data such as steps. In this way, they were able to provide an overall sleep score which they believed was useful for behavior change and motivation.

In addition to component level objective sleep metrics, many consumer sleep trackers provide a consolidated single number to assess the overall quality of an individual's night, a holistic "sleep score" (this could also be referred to as a composite objective sleep metric). The Fitbit range of products provides a number between 0 and 100, which combines three components of sleep: total sleep time relative to a

person's desired TST, the sleep architecture (i.e., appropriate amounts of deep and REM sleep), and a restoration metric (which combines the degree of restlessness during the night together with the observed reduction in heart rate during the night) (https://support.google.com/fitbit/answer/14236513?hl=en#zippy=). Conceptually this can be thought of as a composite objective score that uses expert judgment on what is a "good night of sleep" to compose a single objective metric. In a recent small scale study (103 subjects), researchers evaluated the Fitbit Sleep Score versus the global PSQI and saw a negative correlation $r = -0.598$ as expected (e.g., higher Sleep Scores should be associated with lower PSQI), and is consistent with the prior art [44], It is encouraging that composite objective metrics from a wearable device can be directionally useful indicators of expected sleep quality in a population.

The Garmin range of smartwatches and trackers provides a similar sleep score between 0 and 100, with broadly similar inputs, but includes an estimated "stress index" during the sleep period, which is based on heart rate variability [45]. The Samsung range of smartwatches also has a sleep score between 0 and 100, with similar inputs. The Apple Watch does not provide any single numerical metric relating to sleep quality, though consumers may use third party apps to provide such metrics. The Oura ring also provides a proprietary composite objective sleep metric based on combinations of resting heart rate, body temperature, movement, and time spent in specific sleep stages, including light, deep, and REM.

https://support.ouraring.com/hc/en-us/articles/360025445574-Sleep-Score As of the time of writing, there do not appear to be any studies linking these proprietary sleep score indices to other accepted sleep quality metrics.

### 3.2 Case study: predicting PROMIS sleep disturbance index and sleep related impairment index from consumer wearable devices

As one example of a research study which considered subjective sleep quality in parallel with objective metrics from a smartwatch, we will discuss the Digital Wellbeing (DWB) Project [46], which is a joint research study of the University of Oregon and Google. The overall objective of this IRB-approved study was to provide normative data on objective patterns of smartphone use and associated lifestyle factors such as typical sleep, activity levels, and mental wellness. As part of the study, a cohort of Fitbit users were enrolled, and were asked about their subjective sleep quality as well as contributing their objective sleep metrics as assessed by the Fitbit wearable device over a period of four weeks. Specifically, the users were asked to complete the 8-question, short-form PROMIS Sleep Disturbance and Sleep Related Impairment questionnaires both at enrollment into the study and at study end. This allowed comparisons of actual objective sleep metrics acquired from the wearable device with the baseline PROMIS scores.

While the overall DWB study enrolled approximately 8000 participants, the analysis was restricted to the subset of participants who completed the PROMIS SRI and SD short-forms at enrolment, and who had sufficient Fitbit sleep data (4 days) in the 7-days prior to completing the survey, resulting in a sample size of 2106. **Tables 2** and **3** illustrates the demographic breakdown of the larger set of participants who completed enough of the surveys and with sufficient mobile phone usage for analysis (4932), of which approximately 44% also had the required level of Fitbit sleep data.

The observed distributions of PROMIS scores are broadly similar with previous population studies [47], as are the distributions of total sleep time and WASO, so we

| | Description | N | % |
|---|---|---|---|
| Age | 18–29 | 541 | 11.0 |
| | 30–49 | 2658 | 53.8 |
| | 50–69 | 1574 | 31.9 |
| | 70+ | 159 | 3.2 |
| Gender | Female | 3483 | 70.6 |
| | Male | 1274 | 25.8 |
| | Queer/Non-Conforming | 115 | 2.3 |
| | Trans | 55 | 1.1 |
| | Not specified | 5 | 0.1 |
| Ethnicity | Not Hispanic or Latino | 4571 | 92.7 |
| | Hispanic or Latino | 353 | 7.2 |
| | Not specified | 8 | 0.2 |

**Table 2.**
*Demographics for participants in the study who had sufficient smartphone usage and questionnaire completion for analysis (including both Fitbit and non-Fitbit participants).*

| Parameter | Mean (s.d.) |
|---|---|
| PROMIS Sleep Disturbance Index raw-score | 19.0 (6.5) [corresponding T-score = 49.0] |
| PROMIS Sleep Related Impairment raw-score | 18.3 (7.3) [corresponding T-score = 53.3] |
| Total Sleep Time (mins) | 385.6 (98.2) |
| Wake After Sleep Onset (mins) | 42.5 (19.5) |
| Sleep Efficiency (%) | 0.82 (0.14) |
| Bed Entry Time | 11:26 PM (2.24 hrs) |

**Table 3.**
*Associated sleep parameters of sub study population with sufficient Fitbit sleep data.*

believe that the study population is broadly representative of a general free-living population under "normal" sleeping conditions, albeit with a higher than representative bias towards female users. The mean SDI T-score is 49.0 (i.e., report marginally less sleep disturbance than estimated population mean) and the mean sleep related impairment T-score is 53.3 (i.e., report more sleep impairment than average). To place this in context, a recent study on the impact of an audio-based intervention to improve sleep quality found a baseline value of approximately 60 for both SD and SRI T-scores at baseline in a population of poor sleepers [48], so in general we can consider our cohort to represent a sample showing non-clinical (i.e., normative) levels of sleep disturbance and impairment.

We conducted some simple analyses to determine if the sleep quality metrics assessed by the PROMIS measures are associated with objective metrics. Specifically, we generated a set of 14 predictor variables to represent each individual, namely the mean and standard deviation of seven variables (calculated over 7 nights prior to survey): total sleep time, WASO, sleep efficiency, long awakening counts, resting heart rate (defined as estimated heart rate at rest prior to waking up), restlessness

(defined as percentage of time with significant movement during the night), and percentage heart rate below RHR during the main sleep log. The association of these predictor variables with the SD and SRI scores was evaluated using two methods; (a) on an individual feature basis to determine the most significant predictor variables beyond age and sex, and (b) in a greedy step-forward multivariate linear regression model, which included variables in the model in the order of the strength of their contribution, starting from a baseline model of age, gender, and population mean score. For (a), the single variables most associated with overall estimation of sleep related impairment were variation in total sleep time (standard deviation of recorded TSTs over the week), and mean bed-entry-time. For sleep disturbance, the most significant predictors were mean total sleep time and the variation in restlessness (standard deviation of the nightly restlessness values). For (b), a greedy multivariate linear model was constructed, and the weights and significance of each contributor variable are shown in **Tables 4** and **5**. Even with this more complex model, the adjusted $R^2$ (amount of variance explained) for Sleep Disturbance and Sleep Related Impairment were 0.107 and 0.147, respectively. While it is probable that more sophisticated non-linear multivariate models could produce higher goodness-of-fit, given this low starting point, it's unlikely that a substantial amount of the variance would be adequately explained by objective sleep metrics alone. However, these are not atypical goodness-of-fit variables for psychological constructs (e.g., studies which used passively-tracked smartphone usage patterns to predict personality type had similar $R^2$ to what is reported here [49]). It is also worth reflecting that the interpretation of $R^2$ needs to be carefully considered [50], as the typical interpretation of the seemingly

| **Independent Variable** | **Slope** | **Std Error** | **t-value** | **p > \|t\|** |
|---|---|---|---|---|
| mean(Total Sleep Time) | −0.1482 | 0.024 | −6.097 | 0.000 |
| mean(Long WASO Count) | 0.1243 | 0.024 | 5.196 | 0.000 |
| mean(Time Entered Bed) | 0.0986 | 0.022 | 4.428 | 0.000 |
| mean(Resting Heart Rate) | 0.0901 | 0.022 | 4.095 | 0.000 |
| std (Total Sleep Time) | 0.0782 | 0.022 | 3.577 | 0.000 |
| std(Restlessness) | 0.0510 | 0.023 | 2.173 | 0.030 |
| std(Resting Heart Rate) | 0.0456 | 0.021 | 2.157 | 0.031 |
| Age | −0.0525 | 0.022 | −2.387 | 0.017 |
| Female | 0.3324 | 0.048 | 6.870 | 0.000 |
| | | | | |
| Intercept | −0.2448 | 0.041 | −5.944 | 0.000 |
| | | | | |
| $R^2$ | 0.111 | | | |
| Adjusted $R^2$ | 0.107 | | | |
| F-statistic | 29.06 | | | |
| N (no. of observations) | 2110 | | | |

**Table 4.**
*Prediction of PROMIS-Sleep Disturbance Index raw score (dependent variable) from a set of candidate independent variables using Ordinary Least Squares regression.*

| Independent Variable | Slope | Std Error | t-value | p > \|t\| |
|---|---|---|---|---|
| mean(Time Entered Bed) | 0.1160 | 0.022 | 5.357 | 0.000 |
| std (Total Sleep Time) | 0.1213 | 0.021 | 5.691 | 0.000 |
| mean(Total Sleep Time) | −0.0757 | 0.022 | −3.405 | 0.001 |
| mean(Resting Heart Rate) | 0.0840 | 0.021 | 3.992 | 0.000 |
| std(Restlessness) | 0.0627 | 0.022 | 2.887 | 0.004 |
| Age | −0.2303 | 0.021 | −10.952 | 0.000 |
| Female | 0.2452 | 0.047 | 5.192 | 0.000 |
| Intercept | −0.1809 | 0.040 | −4.496 | 0.000 |
| $R^2$ | 0.149 | | | |
| Adjusted $R^2$ | 0.147 | | | |
| F-statistic | 52.66 | | | |
| N (no. of observations) | 2106 | | | |

**Table 5.**
*Prediction of PROMIS-Sleep Related Impairment raw score (dependent variable) from a set of candidate independent variables using Ordinary Least Squares regression.*

low amount of variance explained can mask us to the fact that the model has uncovered some useful truth or phenomenon. For example, a linear model which uses gender to predict body weight has an $R^2$ of about 0.07, but most people would agree that knowing whether a person is a man or woman would be useful information if you had to guess a person's weight at random.

To illustrate how a simple model can predict the reported PROMIS metrics, **Figure 1** shows the best fit Ordinary Least Squares regression for SD and SRI raw

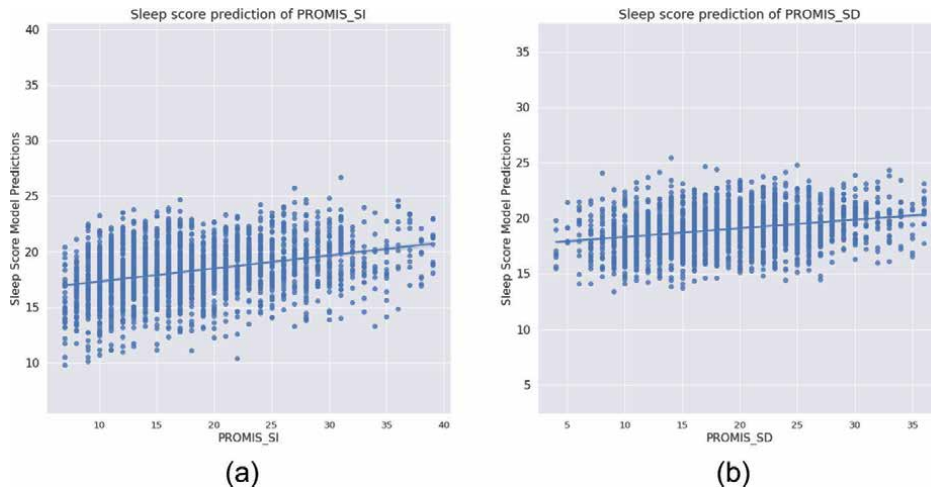


**Figure 1.**
*A graphical illustration of predicting a subjective sleep score from a linear model of objective inputs. In this case, the model inputs are age, gender and the Fitbit Sleep Score. The modeled variables are (a) the PROMIS SF-8 Sleep Related Impairment raw scores, and (b) the PROMIS SF-8 Sleep Disturbance raw scores. Note that for both these scales, higher values are "bad", and that typically these values are mapped to a normalized T-score with mean of 50 and standard deviation of 10.*

values. In both cases, the model is based on the optimal linear combination of age, gender and the Fitbit sleep score (the Fitbit sleep score is itself a composite metric of TST, WASO, deep sleep duration, percentage REM, and percentage time with heart rate below RHR). The goodness-of-fit for mean sleep score (augmenting age and gender) is $R^2$ = 0.09 for sleep disturbance and $R^2$ = 0.12 for sleep related impairment, which were the highest values obtainable for the set of single objective sleep values we explored. These data show that there is value to combining demographics and objective sleep metrics in predicting the subjective sleep metrics, but also reinforces the fact that the fit is at a population level, so for any individual the estimated SD or SRI index can differ radically from their perception.

Overall, the fact that objective variables derived from a smartwatch provide broadly similar predictive capability as prior studies that have examined objective variables from either polysomnography to actigraphy is not surprising. Consumer sleep trackers provide a similar or higher level of accuracy to actigraphy in terms of core metrics such as TST, WASO, bed-entry-time, bed-exit-time etc. [51], and can also provide similar longitudinal periods of measurement (e.g., 7 days, a month etc.)

## 4. Discussion and conclusions

In this chapter, we outlined different types of sleep metrics that can be used to answer the question of "how is a person sleeping". The evidence suggests that while objective metrics of sleep and subjective sleep quality have some correlation, the level is likely to be modest at a "predictive level", but comparable with other estimates of psychological constructs from objective variables. Both types of assessment are useful and complementary. For example, subjective sleep quality is more highly correlated with depressive symptoms than objective sleep metrics [52] (however it is worth noting that this can sometimes be tautological if the depression scale includes items on sleep disturbance, which are cardinal symptoms of depression). The literature also demonstrates that subjective sleep quality is inherently a psychological construct that is influenced by a number of cognitive and affective processes in addition to objective sleep behaviors, and the ability to predict exact values of subjective sleep quality with objective metrics alone will be limited, regardless of how fine-grained the objective information about an individual's sleep patterns is. This may be due, in part, to the known misperception/misestimation of sleep [53] and alertness among individuals, a fact that can readily be manipulated to improve sleep perceptions or sometimes - and inadvertently - worsen them (e.g., "orthosomnia"). Given these conceptual limitations, the models presented in the new analyses described here (as with prior models), which show moderate effect sizes in terms of how much variance in subjective sleep measures can be explained by objective and demographic metrics, suggest that while objective measurement cannot fully explain subjective sleep quality judgments, they do explain a non-trivial amount of the variance. In particular, they can provide directionally useful information about the factors most likely to influence a person's judgment of their sleep. Based on the evidence, directionally important components of objective sleep that appear most meaningful to map to subjective sleep assessments are: total sleep time (increased amounts are better), WASO (more is generally perceived as "bad"), bed-time (later may be worse, particularly if curtailing sleep duration), and regularity of sleep patterns (irregularity leads to lower quality perception).

From the technological perspective, a potential advantage of consumer sleep trackers is the ability to more easily collect objective and subjective sleep parameters in parallel (e.g., through questionnaires deployed on a mobile app or on a smartwatch), and also to provide improved insight to users of the complementary value of both types of metrics.

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Chapter 11

# Pharmacotherapy of Sleep Disorders

*Shreshth Khanna*

## Abstract

Sleep is a very integral part of our functioning with normal adults sleeping for about 1/3rd of their lives. Sleep disorders are a group of conditions that alter the ability of a person to get appropriate sleep which can alter the day-to-day functioning. In the present day and age sleep disorders irrespective of the reason the growth in the sleep disorders is alarming. Although many people tend to experience sleep disturbances on an occasional basis owing to stressful life situations, alterations in job schedules, traveling, and many other external influences, but when these issues occur regularly and become an impedance in the day-to-day activities, it may be suggestive of a sleeping disorder. A deficiency of a good quality sleep can have overall undesirable consequences on the vitality, temperament, attentiveness, and well-being of an individual. Sleep difficulties are linked to both physical and emotional problems. Sleep problems can both contribute to and exacerbate existing mental problems as well as serve as an important indicator of other mental health conditions. While the various sleep problems may resolve on its own or eventually conclude after a successful course of therapy, in a few resistant cases the treatment normally involves a combination of medical treatments and lifestyle changes.

**Keywords:** sleep, sleep disorders, NREM, REM, benzodiazepines, melatonin

## 1. Introduction

Sleep disorders are a group of various clinical commonly encountered medical issues in the outpatient settings. Sleep disorders can have a plethora of differentials; hence, standardized definitions and classifications are indispensable in delineating a diagnosis. Sleep disorders are a group of conditions that disturb usual sleeping patterns. Insufficient and/ or sound sleep can affect normal physical, psychological, social, and emotional functioning and overall quality of life of an individual and a community at large. Sleep disorders can occur across all the genders, races, and age groups. However, the clinical presentation of children with sleep disorders may be different than adults. The International Classification of Sleep Disorders (ICSD) provides a methodical and structured differentiation and definitions for sleep disorders [1].

Specifically, as per the third edition of the international classification of sleep disorders (ICSD-3), various categories of sleep disorders have been described, including:

- Insomnia
- Sleep-disordered breathing

- Central disorders of hypersomnolence
- Circadian rhythm sleep–wake disorders
- Parasomnias
- Sleep-related movement disorders.

## 2. Historical significance

The serendipitous discovery of electroencephalography (EEG) by Hans Berger in Germany heralded the new era of modern sleep medicine. In 1937, Alfred Lee Loomis discovered the electrophysiological correlates of the NREM sleep including vertex waves, sleep spindles, k-complexes, and delta waves. Eugene Aserinsky serendipitously discovered REM sleep in Chicago in 1952 and conceptualized its association with dreaming [2].

In 1957, Dement and Kleitman characterized human sleep cycling between NREM and REM sleep [2].

## 3. Sleep architecture

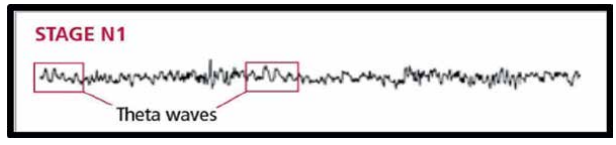
The normal sleep architecture comprises NREM and REM phases of sleep alternate cyclically throughout the sleep. Polysomnography (PSG) is the gold standard for assessing sleep and classifying the various stages of sleep. The sleep staging on a polysomnogram occurs in a 30 second period known as epochs using electroencephalography (EEG), muscle tone by electromyography, and eye movements by electromyography (EMG) and eye movements by electrooculography. NREM is marked by a synchronous EEG including sleep spindles, K complexes, and slow wave complexes in association with reduced muscle tone and minimal psychological activity. It is further divided into wake stage, N1, N2 & N3, and REM stages [3].

The non-rapid eye movement (NREM) phase of sleep is comprised of stages N1, N2, and N3. The depth of the sleep gradually increases from stage N1 to stage N3. On an average 75% of the total sleep is spent in the NREM stages, of these stages with stage N2 being the majority.

An average night's sleep usually comprises 4 to 5 sleep cycles, with the sleep progressing in the following order: N1, N2, N3, N2, and REM. The REM phase in the first sleep cycle is particularly short in duration. As the sleep advances, longer REM periods and decreased time in the NREM phase is characteristically observed [3].

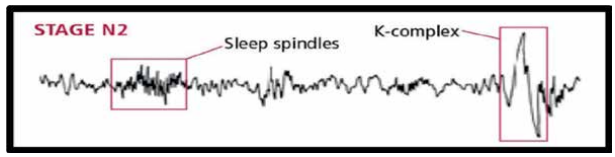
### 3.1 N1 (stage 1): Light sleep

EEG recording: theta waves—low voltage.



It is the lightest stage of sleep compared to the other different sleep stages. This stage marks the appearance of slower theta, delta waves in the 30 second epoch, replacing more than 50% of the alpha waves observed in the wake phase of the sleep. Breathing takes place regularly, and the muscle tone is present. This stage is a short stage lasting around 1 to 5 minutes in duration, comprising about 5% of total sleep time. During the transition into stage-1 sleep, it is common to experience hypnic jerks.

### 3.2 N2 (stage 2): Deeper sleep




*EEG recording*: this stage shows more delta waves emergence, and the cardinal features of N2 sleep, i.e., the sleep spindles, k- complexes, and posterior occipital sharp transients of sleep (POSTS) are seen in this phase.

Sleep spindles are thought to reflect the regulated activity facilitated by thalamo-cortical neuronal networks. This phase-II represents a relatively deeper stage of sleep as the heart rate and body temperature drops.

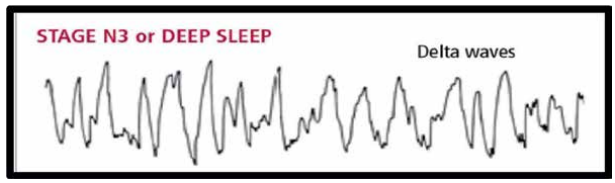
Sleep spindles are brief, powerful spurts of neuronal oscillatory activity in the thalamic reticular nucleus, thalamo-cortical cells, superior temporal gyrus, anterior cingulate nuclei and insular cortices, causing influx of calcium ions into cortical pyramidal cells. This mechanism is believed to be fundamental in synaptic plasticity.

Several researches have proposed a crucial role of sleep spindles in memory consolidation of factual and procedural memory [4]. Similarly, K-complexes that are longest brief high voltage and most distinct of all the brain waves have shown to function in memory consolidation [5].

The Stage 2 of the NREM sleep typically lasts about 25 minutes in the first sleep cycle, and the duration gradually extends with the passage of each successive cycle, which ultimately comprises about 45% of total sleep duration. This is the sleep stage where bruxism or teeth grinding occurs.

### 3.3 N3 (stage 3): Deepest non-REM sleep

Stage 3 NREM sleep comprises 25% of the total time duration spent in sleep.




NREM stage 3 is the deepest stage of sleep. Delta waves are the lower frequencies higher amplitude signals that are characteristically observed in this stage of NREM sleep. N3 is also known as slow-wave sleep (SWS).

EEG recording: lowest frequency, highest amplitude delta waves are characteristically observed in N3 stage. This stage is the most difficult to awaken from in some cases even from loud noises (> 100 decibels).

As the age advances, more time is spent in the stage 2 of the NREM sleep, and less time is spent in this slow, delta wave NREM stage 3 sleep. One of the cardinal features of stage 3 NREM sleep is the greatest arousal threshold. If awoken during this stage of NREM sleep, the person will experience a transient phase of mental fogginess called as sleep inertia.

Individuals aroused during this period of sleep experience mildly diminished cognitive performance for up to 1 hour. In this stage, the tissues regrow, bones and muscles develop, and the immune system strengthens. Sleepwalking, night terrors, and bedwetting occur are also observed in this stage of NREM sleep [6].

### 3.4 Rapid eye movement (REM) sleep


Rapid eye movement sleep makes up to 25% of the total sleep time. Characteristic EEG patterns observed in the REM sleep are the beta waves that are present during the wakeful state. Hence, the REM sleep is also called paradoxical sleep. Since REM sleep is associated with dreaming, it is not considered as relaxing sleep. The EEG pattern is like that of awake individual, the skeletal muscles are in a state of atonia, and an exception are the muscles of the eyes and the diaphragm. The respiratory rate is more inconsistent and asymmetrical. This stage usually follows cyclical patterns with the first cycle starting 90 minutes after falling asleep. The duration of each subsequent REM cycle increases throughout the night. The first REM cycle classically persists for a short duration of 10 minutes, and the duration of the final REM cycle lasts up to 1 hour. This stage is associated with nightmares, and penile/clitoral swelling occur [7].

Important features of REM sleep:

- Dreaming accompanied with irregular muscle as well as rapid eye movements.
- Spontaneous awakenings in some people during an episode of REM sleep in morning hours.
- Atonia, increased brain $O_2$ consumption, increased and inconsistent pulse and blood pressure.
- The brain metabolism is increased by up to 20% is throughout REM sleep during increased activity [8].

### 3.5 Sleep physiology

The synchronization between the sleep–wake cycle is hypothesized to be regulated by an interplay of two major processes, process S promoting sleep and process C that maintains wakefulness [9]. Process S is the sleep drive, which keeps increasing all the day, and is at its maximum just before the bedtime at night. Many of the neurons related with process S are found in the pre-optic area of the hypothalamus containing the endogenous chemicals which inhibit the neuronal interplay and turn off the arousal systems during sleep. Loss of these neurons is associated with significant insomnia [10]. Several inputs from the other regions of the brain also send direct

outputs to the lower brainstem, spinal cord, hypothalamus, and forebrain that cause muscle atonia and REM sleep. Whereas, the neurons in the pons are responsible for the intermittent switch from NREM to REM sleep over the course of the night and dysregulated autonomic activity that are characteristic of REM sleep [11].

Similar to the sleep generating process S, the process C which is generated by an ascending arousal system from the brainstem that activates the forebrain is associated with promotion of wakefulness and alertness. It builds across the day to counter the process S and is regulated by the circadian system. However, this wake-promoting system begins to decline at bedtime [9].

Some fibers originate from the cholinergic neurons in the pons, some from the upper brainstem which ultimately transmits the information to the cerebral cortex for the interpretation of the sensory information.

With adequate relaxation, the sleep drive is decreased, the diurnal waking drive increases, and the cycle initiates all over. Since the process C works to consolidate sleep and wake into discrete periods, the absence of process C leads to disseminated but unaltered total sleep time over the day and night; also, the process C works to synchronize the circadian systems with the environmental light-dark cycles [9].

## 4. Circadian rhythms, the 24-hour clock

Circadian rhythms are the daily rhythms which are responsible for maintenance of various physiological systems and behavior changes. It is responsible for regulating the sleep–wake cycle, modulating the physical functioning, and feeding habits, and over the course of the day regulates the basal body temperature, pulse, tone of the muscles, and the hormonal secretion. The rhythm generator in the brain are the neural structures in the hypothalamus which essentially functions as a biological clock [12].

Series of molecular pathways involving the "clock" genes that are expressed in a nearly 24-hour rhythm forms the physiological basis for these clocks [13].

In mammals, the Clock and Bmal1 proteins, hetero-dimerize and proceeds toward the nucleus, where they bind to the specific sites in the DNA thereby and activating precise genes including the *Period* and *Cryptochrome genes.*

The products of these genes through the feedback loop the move back into the nucleus, wherein they interrupt the attachment of the Clock and Bmal1 proteins to the DNA, thus inhibiting their own production. This regulation of the products of the *Period* and *Cryptochrome* genes follows an oscillating pattern mimicking the 24 hr. periodicity. Similarly, several other genes are also regulated by Clock and Bmal1, in many tissues of the body, giving rise to daily patterns of activity. Among the various homeostatic functions, these synchronously expressed genes contribute to various cellular function, including but not limited to "lipid & glucose metabolism, signal transduction, oxidative metabolism" emphasizing the significance of the diurnal system in various aspects of life [13].

### 4.1 The suprachiasmatic nucleus (SCN)

The SCN is a bilateral structure located in the hypothalamus which is responsible for regulating circadian rhythms in almost all organ functions. It receives its direct inputs from a class of neurons in the retinal tissue which acting as brightness detectors, thereby resetting the clock genes present in the SCN on a consistent basis. The SCN then communicates the signals to the rest of the brain and body which aligns all the regular rhythmic cycles in synchrony to the exterior diurnal cycles. The key stimulus of the

SCN on the sleep is due to a series of neural cell relays through the dorsomedial nucleus and posterior areas of the hypothalamus and the VLPO, which promote and maintain wakefulness during day and somnolence at night. It is also responsible for coordinating the diurnal cycles of feeding, locomotion, and hormonal synthesis and release [14].

Among the various other major outputs of the SCN, an important pathway is to the pineal gland which is responsible for controlling the secretion of melatonin, which is mainly secreted at night, to consolidate the circadian rhythms.

## 5. Endogenous molecules that regulate sleep

Several endogenous molecules are implicated in the regulation of sleep. Various endogenous molecules can be grouped as:

- Wake-promoting/sleep-suppressing, e.g., Catecholamines, orexin, and histamine.
- Sleep-promoting/wake-suppressing, e.g., γ-aminobutyric acid [GABA], adenosine, serotonin, melatonin, and prostaglandin D2 [15].

Increased and as well as decreased GABA in the occipital cortex of patients suffering from insomnia has been a consistent finding associated with the hyperarousal model of insomnia [15].

Endogenous molecules that regulate sleep interact with each other in complex ways, and many of their effects are reliant on the internal milieu of the brain [15].

## 6. Sleep disorders: Causes and treatment

### 6.1 Insomnia

DSM-5 classifies insomnia disorders as "dissatisfaction with sleep quantity/quality due to difficulty initiating sleep, maintaining sleep, or inability to return to sleep despite adequate opportunity for sleep". Insomnia, defined as insufficient quantity or quality of sleep, is the most prevalent sleep disorder with about 1/3rd of the adults reporting some sleep disorder. Insomnia may present as difficulty in falling asleep and/or staying asleep. The diagnosis of insomnia requires the presence of reduced daytime functioning, also including one or more symptoms like fatigue, daytime somnolence, poor attention, aggressive and irritable behavior, reduced motivation, and lethargy. Although the exact etiology remains ambiguous, many contributing factors like environmental changes, genetic make-up various medical, psychiatric, and psychosocial stressors play a pivotal role and lead to a hyperarousal states causing insomnia. Insomnia is often considered to be a disorder of increased somatic, cognitive and cortical activation, with hyperarousal occurring in both central (cortical) and peripheral (autonomic) nervous systems interfering with the natural "disengagement from the environment" as suggested by several theories [16].

Primarily insomnia is divided into transient, short-term and long-term insomnia.

#### *6.1.1 Transient insomnia*

Transient insomnia accounts for up to 15% of the total cases and lasts for less than 7 days. The causes for transient insomnia include jet lag, shift work, and new work place.

*6.1.2 Short-term insomnia*

Insomnia is defined as short term if it lasts for up to 3 weeks. It is caused by an expected but self-limiting problem such as pain, anxiety provoking occupational problems. Patient may have difficulty in induction of sleep, frequent nocturnal awakenings, and/or early morning awakenings.

*6.1.3 Chronic insomnia*

Insomnia occurring for more than 3 weeks is classified as chronic or long-term insomnia and indicates an underlying pathological or a personality disorder.

1. "Difficulty in sleep initiation or maintenance".

2. "Adequate opportunity to sleep, and"

3. "Presence of daytime consequences due to difficulty sleeping".

These conditions should last for at least three months and should be present thrice weekly.

Early identification to the cause of insomnia is vital, and the factors predisposing and precipitating insomnia symptoms should be identified from proper history [17].

**6.2 Non-pharmacological treatment of insomnia**

Cognitive–behavioral therapy for insomnia (CBT-I): This includes a set of psychological and behavioral techniques employed particularly in individuals who may not tolerate pharmacological treatment, due to increased risk of side effects [17].

Sleep restriction therapy (SRT): Limiting the total time allowed in bed to increase the drive to sleep.

Stimulus control therapy: Patients should avoid going to bed until drowsy and tired. Also, the use of bed should be restricted only for sleeping and having sex.

Relaxation therapy: Involves meditation and breathing exercises prior to bedtime.

Sleep hygiene: It includes tutoring about normal sleep patterns, avoiding substance use, exercising regularly, clean, and quaint bedroom environment, sleep, and wake times, and avoiding daytime naps.

*6.2.1 Pharmacotherapy of insomnia*

- Anti-histaminics—H1 receptor blockers due to their potential to cross the blood brain membrane are commonly used as sleeping aids due to their sedative effects.

- Benzodiazepines—These drugs cause depression of the CNS neurons, leading to confusion, dizziness, lethargy. These drugs suppress the REM sleep and reduces the stage 3 NREM sleep while increasing Stage 2 NREM sleep [18].

- Non-benzodiazepines—Like the BZDs these drugs also interact with the GABA-BZD receptor, causing sedation with slight increase in latency to REM sleep.

- Melatonin receptor (MT1, MT 2) agonist: Ramelteon (3–16 times more effective than melatonin). The use of ramelteon may be associated with decrease in sleep latency, increase in total sleep duration, no significant change in overall sleep quality, and increase in N2 phase of NREM sleep. These drugs are used in circadian rhythm sleep disorders, jet lag, and delayed sleep–wake phase disorder [19].

- Orexin receptor antagonists: orexin promotes wakefulness. Thus, the antagonism of this receptor helps in sleep. These agents antagonize the histaminergic and orexinergic wake-promoting nuclei and enhance both NREM and REM sleep and reduce wakefulness.

- Tricyclic antidepressants like amitriptyline and selective serotonin reuptake inhibitors (SSRIs) like fluoxetine may benefit the patients with resistant insomnia or insomnia associated with depression.

- The drugs used in the treatment of insomnia are summarized in **Table 1**.

### 6.3 Hypersomnia

Patients with hypersomnia complain of disabling excessive daytime sleepiness difficulty in maintaining alertness during significant waking hours, with a tendency to fall asleep at unsuitable periods during the day which tend to interfere with the daily

| Medications | Brand name | Dose | Half-life (hr) | DEA schedule |
|---|---|---|---|---|
| **BZD Receptor agonist** | | | | |
| Estazolam | ProSom | 1, 2 | 8–24 | IV |
| Flurazepam | Dalmane | 15, 30 | 48–120 | IV |
| Quazepam | Doral | 7.5, 15 | 48–120 | IV |
| Temazepam | Restoril | 7.5, 15, 22.5, 30 | 8–20 | IV |
| Triazolam | Halcion | 0.125, 0.25 | 2–4 | IV |
| **Non-BZDs** | | | | |
| Eszopiclone 1, 2, 3 5–7 IV | Lunesta | 1, 2, 3 | 5–7 | IV |
| Zaleplon 5, 10 1 IV | Sonata | 5, 10 | 1 | IV |
| Zolpidem 5, 10 1.5–2.4 IV | Ambien | 5, 10 | 1.5–2.4 | IV |
| **Selective Melatonin Receptor Agonist** Ramelteon | Rozerem | 8 | 1–2.6 | None |
| **H1 Receptor Antagonists** | | | | |
| Diphenhydramine | Benadryl | 25, 50 | 7–12 | None |
| Doxylamine | Unisom | 25 | 10 | None |
| **Orexin Antagonist** | | | | |
| Suvorexant | Belsomra | 5–20 | 12 | IV |
| Lemborexant | Dayvigo | 10–30 | 17–55 | IV |

**Table 1.**
*List of drugs approved for the treatment of insomnia.*

routine. Many patients describe a significant aftermath on their mental functioning, calling it brain fog.

### *6.3.1 Central disorders of Hypersomnolence*

Central hypersomnia is usually divided into three main subtypes:

- "Narcolepsy type 1",
- "Narcolepsy type 2", and
- "Idiopathic hypersomnia (IH)".

#### *6.3.1.1 Narcolepsy*

Narcolepsy is a sleep cycle disorder with persistent daytime sleepiness and brief episodes of cataplexy, sleep paralysis, and hypnagogic hallucinations. Individuals with narcolepsy have a disorder of REM phase of sleep, with a tendency to have dreams during the short naps, thereby reducing the sleep in the N3 stage and thus leading to an asymmetrical sleep pattern. There is a sudden loss of muscle strength as the body lapses into REM sleep which can happen anytime during the day and usually last seconds to minutes [20].

##### *6.3.1.1.1 Hypocretin (orexin)*

The hypocretin system has now been seen to play a pivotal role especially in narcolepsy -I patients. Normally, the hypocretin neurons in the hypothalamus moderate the activity of the reticular activating system (RAS), which increases the sleep-inhibiting chemicals in the cortical neurons and inhibits the sleep-promoting ventrolateral preoptic area (VLPO), thereby suppressing GABA, which is responsible for stimulating the activity of motor neurons and increasing the muscle tone. During normal REM sleep, orexin decreases, which decreases RAS activity and promotes atonia [20].

#### *6.3.1.2 Narcolepsy type 1*

Previously known as narcolepsy with cataplexy, characterized by excessive daytime somnolence, with a sudden loss of muscle tone that occurs during waking hours. Muscle weakness pattern is similar to that observed during REM sleep. Narcolepsy type 1 is characterized by deficiency of orexin which is responsible for separating wake from sleep. The RAS does not constantly increase the release of sleep-inhibiting neurochemicals to the cortical neurons and hinder the activity of the VLPO inconsistently. This leads to rapid alterations between the wake and the sleep cycle which leads to REM-based phenomena into wakefulness. The diagnosis is based on the individuals having low levels of a brain hormone (hypocretin) in the CSF, reporting cataplexy and having excessive daytime sleepiness on a special nap test [21].

#### *6.3.1.3 Type 2 narcolepsy*

Described earlier as narcolepsy without cataplexy.

The people presenting with this disorder usually experience immense daytime drowsiness and somnolence sans the muscle weakness in response to intense

emotions. They usually also have less severe symptoms and have normal levels of the brain hormone hypocretin. The exact pathophysiology of narcolepsy type 2 not remains to be elucidated [22].

*6.3.1.4 Idiopathic hypersomnia (IH)*

IH has characteristically distinct clinical features in addition to the severity of hypersomnia, such as sustained nocturnal somnolence (typically more than 10 hours) and sleep inertia. Additionally, there have been associations between excessive sleepiness, depressive symptoms, and low quality of life [22].

Drugs that promote the wakeful state are used as primary treatment.

Modafinil, a non-amphetamine stimulant promotes wakefulness, has fewer sleep disturbances with no REM sleep deficit and less abuse potential compared to traditional stimulants and hence is considered first-line therapy for narcolepsy replacing amphetamines and methylphenidate.

*6.3.1.5 Newer therapies*

- "Orexin receptors antagonists: Almorextant"
- "Orexin neurons transplantation, and"
- "Orexin targeted gene therapy"
- "Histamine H3 receptor antagonists/inverse agonists: Ciproxifan or Tiprolisant, Pitolisant" are in the pipeline for the treatment of disorders causing excessive daytime sleepiness like narcolepsy, somnolence seen in Parkinson's disease, and other degenerative CNS diseases.
- The drugs used in the treatment of hypersomnia are summarized in **Table 2**.

### 6.4 Restless leg syndrome (RLS) and periodic limb movements (PLM)

These are the most common movement disorders resulting in sleep disturbance affecting about 10% of the general population. Primary RLS, idiopathic RLS,

| Medication | Brand name | Dose | Half-life | DEA schedule |
|---|---|---|---|---|
| Modafinil | Modalert | 100–200 | 10–12 | IV |
| Armodafinil | Nuvigil | 150–250 | 15 | IV |
| Sodium Oxybate | Xyrem | 6–9 | 30–60 | I |
| Solriamfetol | Sunosi | 75 | 2.5 | IV |
| Methylphenidate | Ritalin | 20–30 | 2–7 | II |
| Amitriptyline | Elavil | 50–100 | 21 | None |
| Dextroamphetamine | Dexedrine | 5–60 | 7–34 | II |
| Pitolisant | Wakix | 8.9 | 10–12 | None |

**Table 2.**
*List of drugs used in the treatment of hypersomnia.*

| Medication | Dose | Time to peak plasma level | Half life | Mode of elimination |
|---|---|---|---|---|
| Levodopa | 100–400 | 30 | 1.5–3 | Hepatic |
| Carbidopa/ Levodopa | 10/100–25/250 | 120 | 6–8 | Hepatic |
| Bromocriptine | 2.5–10 | 45–60 | 3–4 (up to 40) | Hepatic |
| Pergolide | 0.1–0.75 | 60 | 27 | Renal |
| Cabergoline | 0.25–3.0 | 120 | 63–68 | Hepatic |
| Pramipexole | 0.25–1.5 | 120 | 8–12 | Renal |
| Ropinirole | 0.5–4.0 | 60–120 | Approx. 6 | Hepatic |
| Gabapentin enacarbil | 600 | 5–8 | 5–7 | Renal |

**Table 3.**
*List of drugs used in the treatment of restless leg syndrome and periodic limb movements.*

Willis-Ekbom disease also known as restless leg syndrome is a neurological disorder that causes unpleasant sensations like aching, throbbing, crawling, and creeping in the legs. The symptoms usually start in the evening and are intense in the night, while resting often occurring on both the sides of the body. RLS may severely disrupt initiation and maintenance of sleep. Movement in the legs or walking typically relieves symptoms but the sensations often recur once the movement stops. RLS is both a sleep disorder and a movement disorder as the symptoms subside only with the movement of legs. Mood changes, excessive day time somnolence, exhaustion, difficulty concentrating and memory impairment, diminished productivity, anxiety, and depression may be accompanying symptoms of RLS. Dopamine deficiencies have been seen to contribute to RLS and PLMD since the motor component is the hallmark feature of the disorder.

Reductions in the extracellular dopamine levels or reduced post synaptic response to dopamine within the CNS may contribute to the overall symptoms of RLS and PLMD.

Drugs used in the treatment of restless leg syndrome and periodic limb movements are summarized in **Table 3**.

### 6.5 Parasomnias

Parasomnias are the sleep disorders that may occur in between wakefulness and sleep state. These sleep disorders are explained as unwanted and disruptive movements, perceptions, events, or experiences occurring at the initiation, throughout or during awakening from sleep. The overall prevalence of parasomnias follows a wide variation, i.e., 2–3% for sleep walking, sleep-related violence to more than 40% for nightmares. The etiology of parasomnias may vary markedly from environmental factors, genetic factors, and an interplay between the genetic and the environmental interactions, all of which in conjunction may play a significant role in the causation of parasomnias [23].

Parasomnias are majorly distinguished into the following categories:

Non-rapid eye movement (NREM)-related parasomnias, and.

Rapid eye movement (REM)-related parasomnias.

"NREM-related parasomnias include:

- Confusional arousal,
- Sleepwalking,
- Sleep terrors, and
- Sleep-related eating disorder [23]".

"REM-related parasomnias include

- REM sleep behavior disorder (RBD) and
- Nightmare disorder [24]".

### *6.5.1 NREM parasomnia*

Non-rapid eye movement (NREM) parasomnias are described as atypical behavioral patterns originating predominantly throughout the phase three of non-REM (N3) sleep. Several subtypes including "sleep terrors", sleepwalking, sexsomnia, "confusional arousals", and "sleep-related eating disorder (SRED)" have been described. Modulation of these factors and ensuring safety are the mainstay in the management of NREM parasomnias. The various factors implicated in the causation of NREM parasomnias are primarily hypothesized to be genetic in origin, with several patients reporting a strong family history, lately a strong genetic linkage between dissimilar phenotypes has been established.

The treatment and management of NREM parasomnias focuses on several groups of drugs including benzodiazepines or benzodiazepine receptor agonists, and antidepressants. A few concerns that these groups of medications pose are the exacerbation of NREM parasomnias, worsening of precipitating factors for parasomnias (such as SDB and PLMS), and an increase daytime drowsiness of the patient [25].

Clonazepam is commonly the first-line pharmacotherapy NREM parasomnias. Antidepressants, including the selective serotonin reuptake inhibitors (SSRIs), tricyclic anti-depressants (TCAs) may be employed in managing NREM parasomnias. Melatonin might be efficient in re-aligning altered circadian rhythm, treating insomnia and REM behavior disorder, and theoretically addressing issues of NREM sleep disorders like terrors and sleep walking [26].

### *6.5.2 REM behavior disorder (RBD)*

RBD involves unrestrained and dysregulated bodily movements and acting out of the dream sequences leading to fragmentation of sleep with a predisposition to injure either the patients and/or their sleeping bed partners. Benzodiazepines (Clonazepam) and melatonin prior to bedtime are the mainstay treatment of the disorder. Enhanced EMG activity is typically observed during sleep, whereas other aspects of REM sleep are normal. Slightly male preponderance the disorder is common in the age group of over 50 years. RBD may be induced by various medications (e.g., antidepressants acting to increase serotonergic or noradrenergic tone). Occurrence of REM disorder has been noticed to herald the development of neurodegenerative diseases like Parkinson's disease, Lewy bodies dementia, and multiple system atrophy in later stages of life.

Withdrawal of the offending medications is a mainstay modality of treatment in the acute form of RBD, whereas the benzodiazepines and melatonin are employed in the chronic forms of illness [27].

### 6.6 Sleep breathing disorder

#### *6.6.1 Obstructive sleep apnea (OSA)*

Affecting approximately 7% of the population OSA is characterized by irregular and intermittent cessation in breathing spells occurring during sleep primarily due to closure of the airway, for at least 10 second interval, and which is usually accompanied by hypoxia and hypercarbia. The apneic moment is generally terminated by a slight provocation, as well as an increase in sympathetic tone, as the airway patency is reestablished.

OSA is a mechanical problem where there is a partial or complete blockage of the upper airways. Upper airway obstruction during sleep is often due to negative collapsing pressure during inspiration; however, progressive expiratory narrowing in the retro palatal area plays an important role. The body mass index plays a crucial role in determining the magnitude of upper airway narrowing during sleep. The sleep profile in the patient of OSA includes fragmentation of sleep and decreased prevalence of both NREM phase3 and REM sleep. Hallmark of OSA is excessive daytime somnolence with snoring and fragmented sleep occurring in the night time accompanied by attention and cognitive deficits. Additionally, OSA is an independent risk factor for the development of hypertension, diabetes, stroke, and cardiac rhythm abnormalities.

OSA impacts the individual, the sleeping bed-partner, and the society overall at large due to increased risk of occupational injury. Thus, it is imperative to consider OSA as a significant modern public health issue, thus making therapeutic treatment options for OSA patients of high importance. Effective treatments for apnea include: the continuous positive airway pressure (CPAP) device, dental devices, weight loss, and bariatric surgery. PSG is the gold standard for diagnosing OSA and other sleep disorders. Pharmacological therapies employed in the management of OSA targets the upper airway muscles, as well as the respiratory drive. Drugs targeting the noradrenergic system, e.g., protriptyline, serotonergic agents, e.g., fluoxetine, paroxetine, and bronchodilators, e.g., salbutamol are commonly used. Since there is an increased tendency to experience apneic episodes in the REM sleep, therefore pharmacotherapy which suppresses the REM sleep by targeting the serotonergic system may be beneficial. Certain stimulant medications like Modafinil have been long used to address the daytime hypersomnia commonly experienced in a patient of OSA [28].

### 6.7 Post-traumatic stress disorder (PTSD)

Affecting approximately 8% of the adult population PTSD is a common sleep disorder which occurs either because of emotional and / or physical trauma. Hyperarousal and disturbed sleep including sleep-onset insomnia, inability to stay asleep, excessive daytime somnolence, and traumatic nightmares are usually diagnostic of PTSD. Various groups of medications including SSRIs, atypical anti-depressants, and beta blockers have been used in PTSD to decrease the hyperarousal states associated with PTSD, with varying degrees of improvement of sleep disturbances [29].

Drugs used in the treatment of post-traumatic stress disorder are summarized in the **Table 4**.

| Medication | Dose | Time to peak plasma level | Half Life | Mode of Elimination |
|---|---|---|---|---|
| **SSRIs** | | | | |
| Sertraline | 50–200 | 4–10 hrs | 26 hrs | Hepatic |
| Paroxetine | 20–60 | 3–8 hrs | 21 hrs | Hepatic |
| Fluoxetine | 20–60 | 220 hrs | 2–4 days | Renal |
| **SNRIs** | | | | |
| Venlafaxine | 75–300 | 1–2 hrs | 5–7 hrs | Renal |
| **TCAs** | | | | |
| Amitriptyline | 15–300 | 4 hrs | 25 hrs | Renal |
| Imipramine | 100–200 | 2–3 hrs | 12 hrs | Renal |
| **Atypical Antidepressants** | | | | |
| Nefazodone | 200 | 2 | 2–4 hrs | Hepatic |
| Mirtazapine | 15 | 2 | 0.5–2 hrs | Renal |
| Risperidone | 2–8 | 4–6 | 7–15 hrs | Hepatic |
| Olanzapine | 5–15 | 4–6 | 30 | Hepatic |

**Table 4.**
*List of drugs for the treatment of post-traumatic stress disorder.*

## 7. Evaluation

Analysis of sleep disorders is carried out using various comprehensive modalities including the medical and medication history of the patient, sleep diary, sleep studies including home sleep apnea testing (HSAT) or poly-somnography (PSG), and usage of elaborate clinical and exploratory self-assessment questionnaires like the Epworth sleepiness scale (ESS), Fatigue Severity Scale (FSS) and Insomnia Severity Index (ISI) to narrow down and delineate the diagnosis [30].

## 8. Prognosis

Insufficient/ disturbed sleep can affect overall physical and mental health of an individual and society at large. The sequelae of various sleep disorders may result in industrial or motor vehicle accidents, decreased work performance, cognitive dysfunction, and an increased risk of depression, anxiety, and altered quality of life. The prognosis of sleep disorders depends widely on the cause of the sleep disorder. Early detection and treatment initiation is of paramount importance in the management of sleep disorders and improving the overall prognosis and quality of life of the individual.

## 9. Conclusion

A sound sleep constitutes an integral part life of a person, with approximately one-third to a quarter of life spent in sleep. Sound sleep is indispensable in maintaining the mental, physical well-being as well as optimal functioning of various

homeostatic functions including cognitive abilities, problem solving abilities, maintenance of cardiovascular functions, endocrinal regulations, cell growth, and repair, besides many others. Normal sleep pattern comprises two phases of sleep, i.e., the REM or the dream sleep phase and the NREM sleep or the quiet or the restful sleep phase. Various sleep phases repeat during the night, one after the other, i.e., NREM phase is followed by REM phase. Each phase of sleep lasts about 90 minutes in duration and usually repeats 6–7 times in a cyclical manner in a 7–8 hours' of sleep. As per the international classification of sleep disorders (ICSD-3) several sleep disorders have been categorized including: insomnia, sleep-disordered breathing, disorders of hypersomnolence, circadian rhythm sleep disorders, parasomnias, sleep-related movement disorders, etc. Untreated sleep disorders may culminate into a variety of serious short-term and long-term complications. Treatment of sleep disorders usually comprises non-pharmacological treatment modalities including practicing and encouraging good sleep hygiene, sleep scheduling, yoga, meditation techniques, and avoiding consumption of online social media while lying down on the bed. Pharmacotherapy varies depending on the reason and duration of the sleep disorder and the regime is generally tailor made for every patient. Proper management of sleep disorders requires a thorough effort from the inter-professional healthcare teams including clinicians, pharmacists, nursing staff, and psychological professionals by maintaining accurate and updated records regarding interactions held and interventions taken in individual cases, thereby delivering optimal outcomes in every case.

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