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Investigating the Relationship Between Circadian Rhythm and Learning-Memory

Sirkadiyen Ritim ile Öğrenme ve Bellek İlişkisinin Araştırılması

Tayfun Başer, Mustafa Saygın

Süleyman Demirel University School of Medicine, Department of Physiology, Isparta, Türkiye

Abstract

The circadian rhythm creates many metabolic changes in our body by influencing the activities of suprachiasmatic nucleus and other centers in the cerebrum according to the light-dark conditions within a 24-hour period. In these mechanisms, melatonin is particularly important in terms of its inhibition in light, and its secretion in the dark. The circadian rhythm, which operates with a negative feedback mechanism, can contribute to various metabolic and genetic functions with oscillations in the cerebrum. Melatonin has a special role in the circadian rhythm; it is controlled by neural, hormonal and genetic factors. The effects of circadian rhythm on learning and memory are determined by observed chemical activities. In particular, there is a strong link between cyclic adenosine monophosphate responsive element binding protein and pre1, and pre2 activation. This link is the most well-known feature of the molecular mechanism of circadian rhythm in memory and learning. As the circadian rhythm is affected by experiences, there may be remarkable changes in molecular mechanisms as well as neuronal activations and genetic mechanisms involved in learning processes and memory formation. Many experimental models on learning and memory have been created so far. The general conclusion is the necessity of the circadian rhythm for learning and memory formation. At the same time, melatonin to provide a healing effect on learning and memory in various dysfunctions.

Keywords: Circadian rhythm, suprachiasmatic nucleus, learning, memory

Öz

Sirkadiyen ritim, 24 saatlik zaman dilimi içerisinde aydınlık-karanlık şartlarına göre serebrumda bulunan suprakiazmatik nukleus ve bezlerin aktiviteleri sonucu vücudumuzda birçok metabolik değişiklikler oluşturmaktadır. Bu mekanizmalarda melatonin hormonunun, ışıkta inhibe olması ve karanlıkta salgılanması açısından ayrı bir önemi vardır. Negatif feedback mekanizmasıyla çalışan sirkadiyen ritim, serebrumda osilasyonlarla çeşitli metabolik ve genetik fonksiyonlara katkıda bulunabilmektedir. Sirkadiyen ritimde özel bir rolü olan melatonin; sinirsel, hormonal ve genetik faktörler tarafından kontrol edilmektedir.

Sirkadiyen ritmin öğrenme ve bellek üzerine etkileri, gözlemlenen kimyasal aktivitelerle tespit edilmiştir. Özellikle siklik adenozin monofosfat duyarlı element bağlayıcı protein ile *Per1* ve *Per2* aktivasyonu arasında güçlü bir bağ vardır. Bu bağ sirkadiyen ritmin bellek ve öğrenme üzerine olan moleküler mekanizmanın en bilinen özelliğidir. Deneyimler sonucu sirkadiyen ritmin etkilenmesiyle moleküler mekanizmaların yanı sıra nöronal aktivasyonlar ile öğrenme süreçleri ve bellek oluşumunda görev alan genetik mekanizmalarda da dikkat çekici değişiklikler olabilmektedir. Şimdiye kadar öğrenme ve bellek üzerine birçok deneysel modellemeler oluşturulmuştur. Bunlardan genel olarak çıkarılan sonuç, öğrenme ve bellek oluşumu için sirkadiyen ritmin gerekliliğidir. Aynı zamanda melatonin hormonu, öğrenme ve bellek üzerinde çeşitli disfonksiyonlarda iyileştirici etki sağlamaktadır.

Anahtar Kelimeler: Sirkadiyen ritim, suprakiazmatik nukleus, öğrenme, bellek

Introduction

Circadian Rhythm

The term "circadian rhythm" refers to the daily oscillations in various biological and physiological processes that are regulated by the transcription-translation of circadian *CLOCK* genes and proteins. Sleep-wake cycles, cognitive functions, and intrinsic clock functions are largely in accordance with circadian rhythm. Disruptions in circadian processes can lead to many pathologies, and therefore, understanding the molecular mechanism of circadian rhythm may help to eliminate many of these pathologies. The molecular mechanism underlying the circadian rhythm is encoded by the twenty-four-hour autoregulatory cycle in the cerebrum, forming a time-determining network in nearly all body tissues.[1] Disorders in the circadian cycle or alterations in genetic activations can result in circadian rhythm disorders. According to the International classification of sleep disorders, third edition, six distinct circadian rhythm disorders have been delineated: delayed sleep phase syndrome, early

Address for Correspondence/Yazışma Adresi: Tayfun Başer, Süleyman Demirel University School of Medicine, Department of Physiology, Isparta, Türkiye
E-mail: fizyolojitayfun@gmail.com **ORCID-ID:** orcid.org/0000-0002-8526-7737
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sleep phase syndrome, independent sleep phase syndrome, irregular sleep-wake rhythm, jet lag, and shift work disorder.[2]

Suprachiasmatic Nucleus

The suprachiasmatic nucleus (SCN) is a structure that contains approximately 20,000 neurons, glia, and pacemaker neurons. It is responsible for regulating the circadian rhythm through changes in the day-night cycle, spontaneous firing, and changes in membrane resting potential.[3] Impulses generated by light rays reaching the retinal ganglion cells stimulate the SCN through the retinohypothalamic pathway. The impulse generated by the entry and exit of sodium and potassium ions through the membrane of pacemaker neurons in the SCN reaches the paraventricular nucleus (PVN) and, subsequently, the superior cervical ganglion (SCG) through the intermediolateral column of the medulla spinalis. The post-ganglionic fibers from the SCG extend to the pineal gland, leading to the inhibition of melatonin synthesis.[4] The signals emanating from the SCN stimulate the pineal gland in a dark environment. However, light exposure during the day (it has recently been stated that it is especially blue light) inhibits the pineal gland, decreasing melatonin synthesis and moving away from the appropriate physiological conditions required for circadian rhythm.[5] The SCN is stimulated by the initial light exposure, which subsequently activates cortisol secretion, body temperature regulation, and hormonal mechanisms throughout the diurnal cycle.[6] Stimuli from the SCN then direct the work of peripheral tissues, such as the liver, pancreas, skeletal muscle, and numerous others. It is postulated that each of these tissues possesses an autonomous circadian clock, the regulation of which is facilitated by impulses generated from reactions within the SCN in response to light exposure or absence.[7] It is noteworthy that circadian rhythm exhibits interindividual variability, and SCN activity can be influenced by external signals called zeitgebers, which modulate numerous endogenous and genetic factors. The external signals, termed zeitgebers, play a crucial role in the regulation of circadian rhythm and the perception of the light/dark cycle.[8]

Pacemaker Neurons

These neurons constitute groups that function as the fundamental nodes in the initiation and regulation of circadian rhythm in the SCN of the hypothalamus. Pacemaker neurons have been identified as the site of molecular mechanisms that initiate intrinsic clocks and circadian rhythms.[9] It has been demonstrated that these neurons orchestrate the synchronization of oscillatory movements. Recent studies have demonstrated that the regulation of cellular multiple oscillatory movements is also provided by pacemaker neuron groups. These neurons generate signals that are phase-specific, with each signal contributing to the realization of distinct multi-oscillatory movements across diverse tissues.[10] Lesions or idiopathic dysfunction of these neurons have been demonstrated to induce circadian rhythm disturbances. The SCN astrocytes and neurons have been identified as potential contributors to these disturbances, given their role as distinct branches of the network formed by pacemaker neurons. The SCN, in conjunction with the pituitary gland, the autonomic nervous system, and the brain, plays a pivotal role in regulating the circadian rhythm of oscillatory movements through the reception of light rays.[11]

Melatonin

It is a hormone that is secreted by the pineal gland, which plays a regulatory role in both seasonal and diurnal rhythms, as well as the sleep-wake cycle. The secretion of this hormone is primarily derived from pinealocytes, which are characterized by the presence of lobulated and irregularly shaped nuclei. This phenomenon is attributed to the activation of the SCN in the absence of light. The pinealocytes are accompanied by numerous synaptic bodies, which play a crucial role in axo-dendritic synaptic communications.[12] Melatonin is synthesized from serotonin, and two important enzymes act as catalysts in this synthesis process. These enzymes are N-acetyl transferase (NAT) and hydroxyindole-O-methyltransferase. Norepinephrine, a significant transmitter in the pineal gland, binds to β1 and β1 receptors present on the pinealocyte membrane. It has been observed that 85% of melatonin hormone is secreted in response to stimulation of β1 receptors, while approximately 15% is released following binding to β1 receptors.[13] Upon binding to the designated receptors, norepinephrine elevates the concentration of cyclic adinosine monophosphate (cAMP) and NAT enzyme through the activation of adenylate cyclase in the pinealocyte cell membrane, thereby stimulating melatonin release. The released melatonin is not stored, but rather, it is released directly into the bloodstream.[8] The neural mechanism of melatonin synthesis involves signals originating from the retinohypothalamic pathway, which are transmitted to the hypothalamus. Within the hypothalamus, these signals undergo a series of chemical reactions in the SCN and the PVN. Subsequently, these signals are relayed to the medial forebrain bundle. From there, they pass to the medulla spinalis, where norepinephrine is released from the SCG via post-ganglionic fibers, and enzymatic reactions begin.[14] Numerous models have been developed through the use of chemical induction. In general, after memory and learning dysfunction are induced by using chemicals such as ethanol, thinner, okadaic acid, D-galactose, isoflurane, and its derivatives, experimental studies are performed with melatonin administration. Two salient points emerge from this research. Firstly, the impact of various chemicals when administered concomitantly with melatonin is observed. Secondly, the route of administration plays a pivotal role in the experimental outcomes. It is noteworthy that the outcomes observed through intracerebroventricular (ICV) and intraperitoneal (IP) administration can vary significantly in many experimental models.[15]

Per1 and Per2 Proteins

From a genetic perspective, the *Period proteins1 (Per1)* gene is an important clock factor in the regulation of circadian rhythms. Critical physiological pathways in cellular divisions are subject to the influence of circadian rhythms. The *Per1* gene has been identified as a crucial regulator of these circadian pathways, thereby establishing a link between circadian rhythms and cell division cycles.[16] The *Per2* gene has been identified as a tumor

suppressor gene. Disruption of the circadian rhythm has been shown to lead to the up-regulation and down-regulation of genes that contribute to the development of cancer cells.[4] The *Per1* gene, in particular, has been identified as a critical regulator of the connection between the circadian rhythm and the cell cycle, functioning through the actions of proteins such as brain and muscle ARNT-like protein (BMAL1) and Wee1, which are derived from CLOCK complexes.[7]

Activation of *BMAL1* and *CLOCK* genes leads to transcription of *Per* and *cryptochrome (CRY)* genes in the SCN. The resulting *Per* and *CRY* bind to each other to form a complex. The *Per-CRY* complex inhibits the genes they transcribe, and then this complex degrades, and the twenty-four-hour cycle is completed (Figure 1).

Learning

All the outcomes of education, training, and experiences that lead to long-lasting behavioral changes that are dependent on neural mechanisms are called learning. Many neuronal activations occur with experiences, and the main behavioral changes are due to changes in these neural mechanisms.[17] Perception, understanding, and comprehension are important factors in learning. Therefore, many theories have been put forward about how the complex process of learning takes place. Some of them are behavioral, sensory, cognitive, and neurophysiologically based learning theories.[18] It is a fact that the vast majority of human behaviors are learned behaviors. This dynamic process, involving different types of learning, continues throughout life and is also a determinant of human lifestyle.[19] All formations that emerge as a consequence of learning are considered behaviors. This encompasses a wide spectrum of behaviors, including but not limited to shouting, writing, walking, blushing, and speaking. Subsequent to the acquisition of knowledge, cognitive functions such as thinking, planning, and, most notably, decision-making abilities undergo development. The learning process unfolds through the mechanisms of classical and operant learning. In this process, the nervous system develops a selective adjustment mechanism against special stimuli within intense stimuli.[20] This dynamic process persists throughout the lifespan and is contingent on changes in neural functions. Consequently, learning can be succinctly defined as a phenomenon and/or the process that produces a phenomenon.[21]

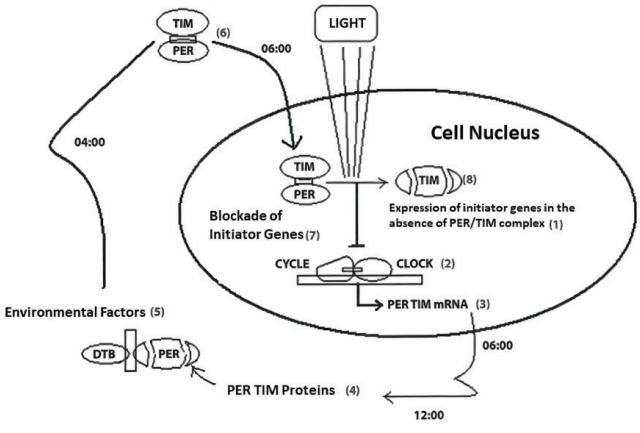

Figure 1. Genetic Mechanism of Circadian Rhythm[2]
TIM: Timeless proteins, PER: Period proteins, DTB: Doubletime proteins, mRNA: messenger-RNA

Memory

Memory can be defined as the cognitive process of storage and retrieval of information. It is not the content of what is read that determines our level of knowledge; rather, it is the retention and subsequent recollection of that information that contributes to our cognitive understanding. The classification of memory is typically based on criteria such as the manner in which information is stored and retrieved, the nature of the information stored, and the duration over which it is retained.[17] Each memory system has a different anatomical organization (Table 1). In different parts of the cerebrum, memory systems exhibit storage activations, which involve dynamic reactions with highly intense neuronal interactions. At the neuronal level, memory mechanisms extend into the cerebrum through chemical channels.[22] When neurons are in close proximity to stimulate each other and one neuron fires repeatedly and persistently, structural and metabolic changes occur in both neurons. Given the substantial number of synapses, it can be posited that memory capacity is potentially infinite. The neocortex, for instance, contains between 1014 and 1017 synapses, suggesting a capacity to retain information over an individual's lifetime. Furthermore, these synapses exhibit a remarkable efficiency in energy utilization. The various categories of memory are associated with distinct functions. These functions encompass the recognition and storage of objects, events, and other information, as well as the facilitation of various physiological processes, including conditioned responses, reflexes, and specific learning mechanisms.[22,23]

Circadian Rhythm and Learning-Memory Relationship

Molecular Mechanism

Many experimental studies so far have shown that circadian rhythm affects learning and memory. Dysfunctions in circadian rhythm exacerbate some neurodegenerative diseases and cause significant regressions in learning and memory mechanisms.[24] Molecular, genetic, and different systemic factors play a role in the relationship between circadian rhythm and memory. In particular, there is a strong link between cAMP-responsive element binding protein (CREB) and *Per1* and *Per2* activation.

Table 1. Classification of memory

Based on retention and retrieval of acquired knowledge	Based on the type of information stored	Based on duration
Declarative memory	Annotated memory	Short term memory
Reflexive memory	Skill memory	Intermediate-term memory
		Long term memory

This link is the most well-known feature of the molecular mechanism of circadian rhythm on memory and learning.[25]

Melatonin, Learning, and Memory

All molecular, genetic, and even epigenetic phenomena related to the circadian rhythm vary according to the day-night cycle, and each peripheral organ has a different clock-zone activation capability. One of these organs is the brain. For comprehensive intellectual thinking, learning, and storage of information in memory, there are ideal night and/or day times. For example, for thinking, learning, and comprehension, the late afternoon hours of the circadian rhythm are ideal, while for short-term memory, the early morning hours are ideal. For long-term memory, the circadian rhythm is ideal later in the day.[26] At every hour of the twenty-four-hour circadian rhythm, interesting vital, intellectual, cognitive, behavioral, and learning reactions take place. The most enigmatic of these is the secretion of the hormone melatonin, which also contributes to learning and memory formation.[27] Melatonin, a hormone secreted exclusively during the nocturnal phase of the day-night cycle, plays a substantial role in the development of memory in the hippocampus. It does so by binding to melatonin receptors (MT1/MT2), which are believed to be present in the hippocampus.[28] Melatonin's regulatory function extends to the circadian rhythm, with its synthesis originating from the amino acid tryptophan. While its memory-related functions are realized by binding to MT1 and MT2 receptors in the hippocampus, it also contributes significantly to learning processes by binding to MT1 and MT2 receptors distributed in the central nervous system (CNS) (especially the thalamus and cerebellum).[6] Following the secretion of melatonin from the pineal gland, the hormone binds to its receptors. This binding activates cAMP, which is formed from ATP through the process of adenylate cyclase activation. In turn, CREB is formed through phosphorylation by protein kinase. This results in a negative feedback loop that affects cAMP-responsive element (CRE). Consequently, the Per1 and Per2 proteins, which are formed by stimuli to CLOCK and BMAL complex through a chain of reactions at the molecular level that restart from CRE, establish a significant link between circadian rhythm and cellular cycle.[8]

Table 2. Experimental models demonstrating the effect of melatonin on learning and memory

Model	Impact on learning and memory
Down syndrome model	In the Morris Water Maze test, a significant improvement in melatonin, spatial learning and memory
Alzheimer's disease model	Slowing the progression of learning and memory dysfunctions
	Activating mechanisms to protect learning, memory, and different mnemonic functions
	Slowing down memory in the process of deterioration
	Reducing spatial and non-spatial cognitive deficits
	Regulating and improving learning, memory, and cognitive functions
	Improvement of working memory on T-maze of rats induced by bacterial lipopolysaccharide
Sleep deprivation model	Reversing the process of cognitive impairment
	Preventing dysfunction of memory formation mechanisms

Ideal Time Frames for Learning and Memory Activation

The hippocampus contains a large number of MT1/MT2 and also has a major role in learning, memory, and different intellectual functions. In addition, the hippocampus, which has multifaceted circadian information integrations, has gene expressions, neurogenesis activities, and epigenetic components that have not yet been explained. Therefore, it is possible to talk about the most active hours of learning and memory in the day/night cycle in the limbic system parts that contain many complex components related to circadian rhythm.[29] As has been previously reported, there are optimal periods during the day and/or night for comprehensive intellectual thinking, learning, and information storage in memory. Specifically, the early morning hours are conducive to short-term memory, later in the day is optimal for long-term memory, and late afternoon is the most favorable circadian time for learning.[26] However, it appears to be physiologically implausible to sustain the same pace of work, learning, and memory activation throughout the day. Personal motivations have been demonstrated to be ineffective when confronted with learning patterns that do not align with the circadian rhythm. The period of greatest learning and memory activation occurs a few hours after the onset of the day, but this level diminishes shortly after noon.[30] A multitude of studies have demonstrated that the optimal temporal windows for enhancing learning and memory within the circadian rhythm are early morning and late afternoon. Apart from these phenomena, which may vary according to physiological functions, there may also be different time periods in which individual efficiency is in question due to molecular and genetic functions in other limbic system components, especially hippocampal reactions.[31] A more thorough examination of the general concept of "learning" reveals its many facets, including behavioral learning, life learning, mathematics, literature, and language learning. For each of these learning modalities, optimal circadian rhythm times and distinct functional areas of the cerebrum are activated. For instance, in the context of language learning and memory, the optimal time for the most efficient recording function varies according to chronotype and is in the morning and evening.[32]

Chronotype and Learning

Chronotype, defined as an individual's preferred timing for activities based on their circadian rhythm, is a behavioral manifestation that underlies circadian rhythm. That is to say, it is a personality trait that affects circadian rhythm preference. Physiological measurements have categorized individuals into three chronotypes: morning people, evening people, and those who do not fit neatly into either category. Individuals identified as evening types typically engage in nocturnal activities later in the evening and experience higher levels of alertness and cognitive function in the afternoon, which corresponds with

the period of peak memory and learning skills. Conversely, morning people tend to retire early and rise early. The time frame in which optimal learning and memory activation occurs may vary according to chronotypes.[33] The initiation of learning is typically influenced by innate, need-based, and personal motivations. In the chronobiological framework, innate, cue-based learning motivations are of particular relevance.[34] It has been demonstrated that there is a relationship between the propensity for chronotypic behaviors in learning and the presence of need-driven and personal motivations. The hypothesis that the activation of *CLOCK* and *BMAL1* genes in the SCN is the catalyst for these behaviors is supported by research findings. Notably, the optimal learning periods are observed across genders. The genetic reaction cycle of *CLOCK* and *BMAL1* genes in the SCN persists for a designated period following the dissipation of daylight in the evening hours, thereby enabling males to engage in learning activities during these nocturnal periods. This phenomenon is referred to as the eveningist chronotype.[35] A more detailed examination of the relationship between chronotype and learning reveals that the pivotal factor is the interplay between sex and genetic configurations. The temporal framework for chronotypic behaviors is delineated by the activation time of the primary genes in the circadian rhythm mechanism and the subsequent reaction timings that persist after light. It is noteworthy that chronotypic behaviors are implicated in a wide array of physiological and psychological mechanisms. From the vantage point of connectivity with components involved in learning mechanisms, the involvement of disparate pathways accentuates the significance of all data that can be obtained in the chronotype-learning relationship.[36] Genetic arrangements and timings in the SCN, where the time frames of all physiological changes are determined, affect behaviors for innate and different personal needs. The genetic arrangements that underpin these behaviors are shaped by the interplay of *CLOCK*, *BMAL1*, *Per*, and *CRY* genes within the SCN, which undergo a series of chain and cyclic reactions.[37]

Studies on Circadian Rhythm, Learning and Memory

The effects of circadian rhythm on learning and memory have been shown in many studies, and any dysfunction related to circadian rhythm significantly reduces learning and memory ability. Some peptides cause this dysfunction; the most well-known of these is the molecule called Aβ31-35. It has been shown that learning and memory processes are favorable with other molecules that act as antagonists to this molecule. Aβ31-35-induced memory and learning dysfunctions may improve with exendin-4 administration.[24] A normal circadian rhythm is essential for learning and memory. Disruptions to the circadian rhythm, whether caused by neurodegenerative diseases, environmental factors, or pathophysiological conditions, have been shown to have a detrimental impact on learning and memory processes. Amyloid β1-42 (Aβ1-42) molecules have demonstrated efficacy in various neurodegenerative conditions, notably Alzheimer's disease. These peptides have the potential to enhance learning and memory processes by mitigating various circadian rhythm-disrupting factors within the CNS. Aβ peptides, which exist in multiple forms, have been shown to reduce oxidative stress and neurotoxicity and have been found to be effective in other dysfunctions that cause circadian rhythm disruption and positively affect learning processes according to chronotype characteristics. Aβ peptides have been shown to facilitate functional recovery by reducing stress and toxicity in specific receptor areas, particularly within the limbic system. It is imperative to note that a healthy circadian rhythm is a prerequisite for optimal learning and memory. Disruptions to the circadian rhythm, whether induced by neurodegenerative diseases, environmental factors, or pathophysiological conditions, have been shown to have a detrimental impact on learning and memory processes. Aβ1-42 molecules have demonstrated efficacy in various neurodegenerative conditions, particularly Alzheimer's disease. These peptides have the potential to enhance learning and memory processes by mitigating various circadian rhythm-disrupting factors within the CNS. Aβ peptides, which exist in multiple forms, have been shown to reduce oxidative stress and neurotoxicity and have been found to be effective in other dysfunctions that cause circadian rhythm disruption and positively affect learning processes according to chronotype characteristics. Aβ peptides have been shown to facilitate functional recovery by reducing stress and toxicity in specific receptor areas, particularly within the limbic system.[38] The hippocampus and amygdala play a fundamental role in learning, memory, and storage of acquired information. Memory activations in these regions are the result of electrical currents mediated by long-term potential spiking (LTP) and long-term potential depression (LTD). Briefly, a different definition of memory is LTP/LTD refers to the strengthening/weakening of synaptic connections between neurons. This dynamic process of synaptic connections is called synaptic plasticity.[39] Increasing the concentration of melatonin, which binds to a large number of MT1/MT2 receptors in the hippocampus, and perhaps the routes of administration (such as ICV and IP) in rats used in the experiments may be effective in regulating memory mechanisms affected by sleep disorders.[40] LTP and LTD activations or substitution or inhibition of different molecular mechanisms may be effective in this regulation. Studies show that the melatonin hormone contributes to memory formation mechanisms and even provides an effective learning, memory, and storage opportunity despite dysfunctions such as various sleep disorders.[41] The enzyme photolyase, which plays a fundamental role in DNA repair, is absent in many species of animals, plants, and microorganisms but can be found in some viruses. The enzyme photolyase has the ability to utilize photons of blue light. This ability enables it to repair pyrimidine dimers on DNA. Humans lack the enzyme photolyase; however, they possess two structurally analogous essential proteins that do not possess any repair functions. These proteins, designated as *CRY*, function as photoreceptors to regulate the circadian rhythm.[42]

The fundamental cascade of the photolyase enzyme in DNA repair can be elucidated as follows, given the presence of proteins that are absent in humans but share some structural similarities: ultraviolet radiation converts two adjacent pyrimidines into

cyclobutane pyrimidine dimer. The adjacent pyrimidines include thymines, and the enzyme photolyase is activated. This enzyme utilizes the energy of blue light to break the abnormal bond that causes this adjacency. Following this process, the enzyme photolyase converts the adjacent thymine dimer into two normal thymines, thus completing the DNA repair process. This repair process also eliminates the potentially harmful effects of DNA when the thymines are adjacent.[43] It is noteworthy that proteins analogous to the enzyme photolyase, a cryptic enzyme absent in placental mammals, have been identified in humans. As previously mentioned, these enzymes are classified as *CRYs.* CRY proteins exhibit two distinct forms, designated as *CRY1* and *CRY2*. These proteins have been demonstrated to function as receptors, contributing to the regulation of the circadian clock. The impact of *CRYs* on learning and memory remains to be fully elucidated.[44] The primary conclusion of the studies demonstrating the effects of melatonin and circadian rhythm on learning and memory with various models is that learning, memory, and different storage functions can be enhanced by affecting LTP/LTD activations, different molecular mechanisms, and genetic and neuronal factors.[45,46] It is important to note that experimental studies are ongoing, and these studies are guided by models that demonstrate the effects of melatonin on learning and memory.[47,48] Experimental models used in the complex processes of circadian rhythm maintenance are the Down syndrome model, sleep deprivation model, and Alzheimer's disease model (Table 2).

Conclusion

The regulation of circadian rhythm is the result of genetic activations and inhibitions in the SCN. The circadian rhythm, initiated by pacemaker neurons, is influenced by genetic factors. While melatonin, secreted from the pineal gland, acts as the primary regulator of this process, different neurophysiological mechanisms also contribute to the circadian rhythm. The genetic regulation of the circadian rhythm is generally understood to occur as follows: *CLOCK* and *BMAL1* genes in the SCN are activated by daylight through the retino-hypothalamic pathway, which then transcribe *Per* and *CRY* genes. The resulting *Per* and *CRY* genes bind to each other, resulting in the inactivation of the transcribed *Per* and *CRY* genes. Subsequently, especially in the absence of light, the Per and *CRY* genes linked to each other degrade, and the inactive *Per* and *CRY* genes become active again. It is very important to examine the phenomenon of learning, which is defined as behavioral changes that occur as a result of changes in neuronal activations, formation of new connectivities and consolidations, together with memory. Because the first stage of learning, short-term memory, and different memory mechanisms are intertwined. The effects of circadian rhythm on neuronal activations and inhibitions that activate learning memory are manifested by chronotypic behaviors. Genetic, molecular, and endocrine systems that enable the realization of circadian rhythm play a role in innate, need-based, and self-motivated learning. Genetic mechanisms constitute the main framework of the twenty-four-hour cycle of the circadian rhythm in chronotype behaviors that enable better learning. The fact that *CLOCK/BMAL1* genes, which are activated by light, still continue light-related reactions for a while in the dark environment may be the cause of chronotypic behaviors in learning. The impact of the circadian rhythm on learning and memory is dependent on molecular, neuronal, and genetic factors. Hormones such as melatonin have been shown to have significant effects on memory and have been found to ameliorate certain dysfunctions. Consistent with the findings, all studies on circadian rhythm demonstrate its definitive impact on memory. Notably, the 2015 Nobel Prize in Chemistry was bestowed upon Professor Dr. Aziz Sancar for his seminal contributions to this field. The restorative effect of the photolyase enzyme on pyrimidines, as discovered in recent studies, holds significant promise for further research on the enzyme's potential impact on learning and memory. Clinical studies have demonstrated that individuals in specific occupational groups are predisposed to shift-lag circadian rhythm disorders. In a study conducted in 2019, the sleep quality of nurses working in a shift system was investigated. The results obtained from this study demonstrate that sleep quality is impaired in individuals belonging to this specific occupational group. A similar study stated that shift work has harmful effects on cognitive health. The impact of sleep quality on learning and memory is unavoidable; therefore, circadian rhythm disturbances should be regarded as the primary factor influencing learning-memory mechanisms.

In the pandemic affecting the whole world, COVID and its variants cause anomalies in the sleep-wake cycle and circadian rhythm disorders as well as special occupational groups. In addition, COVID-19 anxiety and fear significantly reduce sleep quality and quality of life. Comprehensive and different studies are needed better to define the dimensions and types of circadian rhythm disorders.

Footnotes

Authorship Contributions

Concept: T.B., Design: M.S., Data Collection or Processing: T.B., Analysis or Interpretation: T.B., M.S., Literature Search: T.B., Writing: T.B., M.S.

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The Relationship Between Insomnia Symptoms, Night Sleep of Less than 7 Hours, and Impaired Fasting Glucose in Shift Workers

Vardiyalı Çalışanlarda Uykusuzluk Belirtileri, 7 Saatten Az Gece Uykusu ve Bozulmuş Açlık Glikozu Arasındaki İlişki

Elaheh Kabir-Mokamelkhah, Saber Mohammadi, Omid Asghari, Niloofar Safaei

Iran University of Medical Sciences, Occupational Medicine Research Center, Department of Occupational Medicine, Tehran, Iran

Abstract

Objective: The aim of this study was to examine the relationship between insomnia symptoms, night sleep of less than 7 hours, and the prevalence of impaired fasting glucose (IFG) in healthcare personnel in workplaces with shifting hours.

Materials and Methods: In this study, a total of 410 healthcare workers from an educational hospital were included. The presence of insomnia symptoms, difficulty initiating sleep (DIS), difficulty maintaining sleep (DMS), and early morning awakening (EMA) were assessed using the Insomnia Severity Index questionnaire. The participants' average sleep duration was categorized into three groups: <7 hours (short sleep), 7-8 hours (normal), and ≥9 hours (long). The diagnosis of glucose intolerance IFG was made following the recommendations of the American Diabetes Association. The relationship between sleep duration, insomnia symptoms, and IFG was evaluated using multivariate logistic regression analysis.

Results: The frequency of IFG was significantly higher among healthcare workers with DIS [OR=4.28, 95% confidence interval (CI): 3.28-5.19], DMS (OR=2.14, 95% CI: 1.78-3.86), EMA (OR=4.54, 95% CI: 1.09-5.63), and night sleep <7 hours (OR=1.84, 95% CI: 1.08-1.89) compared to others. Furthermore, according to logistic regression analysis, the presence of DIS, DMS, and EMA with night sleep <7 hours significantly increased the likelihood of IFG by 5.16 (adjusted OR=5.16), 2.15 (adjusted OR=2.15), and 5.26 (adjusted OR=5.26) times, respectively.

Conclusion: This study revealed that short night sleep (less than 7 hours) with insomnia symptoms in shift workers increases the risk of developing IFG. Therefore, it is important to focus on sleep hygiene, conduct regular screenings for insomnia, and promote access to healthy foods and physical activity to prevent the occurrence of IFG.

Keywords: Health personnel, glucose intolerance, insomnia, sleep duration

Öz

Amaç: Bu çalışmanın amacı, vardiyalı çalışanlarda uykusuzluk semptomları, 7 saatten az gece uykusu ve bozulmuş açlık glukozu (BAG) prevalansı arasındaki ilişkiyi incelemektir.

Gereç ve Yöntem: Bu çalışmaya bir eğitim hastanesinden toplam 410 sağlık çalışanı dahil edilmiştir. Uykusuzluk semptomlarının varlığı, uykuya geçmede zorluk (UGZ), uykuyu sürdürme güçlüğü (USG) ve sabah erken uyanma (SEU), Uykusuzluk Şiddet İndeksi anketi kullanılarak değerlendirilmiştir. Katılımcıların ortalama uyku süresi üç gruba ayrılmıştır: <7 saat (kısa uyku), 7-8 saat (normal) ve ≥9 saat (uzun). BAG tanısı Amerikan Diyabet Derneği'nin önerileri doğrultusunda konulmuştur. Uyku süresi, uykusuzluk semptomları ve BAG arasındaki ilişki çok değişkenli lojistik regresyon analizi kullanılarak değerlendirilmiştir.

Bulgular: UGZ [olasılık oranı (OR)=4,28, %95 güven aralığı (CI): 3,28-5.19], USG (OR=2,14, %95 CI: 1,78-3,86), SEU (OR=4,54, %95 CI: 1,09-5,63) ve gece uykusu <7 saat (OR=1,84, %95 CI: 1,08-1,89) olan sağlık çalışanlarında BAG sıklığı diğerlerine kıyasla anlamlı derecede yüksekti. Ayrıca, lojistik regresyon analizine göre, gece uykusu <7 saat ile birlikte UGZ, USG ve SEU varlığı BAG olasılığını sırasıyla 5,16 (düzeltilmiş OR=5,16), 2,15 (düzeltilmiş OR=2,15) ve 5,26 (düzeltilmiş OR=5,26) kat artırmıştı.

Sonuç: Bu çalışma, vardiyalı çalışanlarda uykusuzluk semptomlarıyla birlikte kısa gece uykusunun (7 saatten az) BAG gelişme riskini artırdığını ortaya koymuştur. Bu nedenle, BAG oluşumunu önlemek için uyku hijyenine odaklanmak, uykusuzluk için düzenli taramalar yapmak ve sağlıklı gıdalara ve fiziksel aktiviteye erişimi teşvik etmek önemlidir.

Anahtar Kelimeler: Sağlık çalışanı, bozulmuş açlık glukozu, uykusuzluk, uyku süresi

Address for Correspondence/Yazışma Adresi: Niloofar Safaei M.D., Iran University of Medical Sciences, Occupational Medicine Research Center, Department of Occupational Medicine, Tehran, Iran
E-mail: niloofarsafaei20@yahoo.com **ORCID-ID:** orcid.org/0009-0002-1226-5172
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Introduction

Impaired fasting glucose (IFG) is a condition characterized by blood glucose levels that are higher than normal but not high enough to be classified as diabetes. IFG is associated with an increased risk of cardiovascular disease and type 2 diabetes.[1,2] Prediabetes, which includes IFG, is significantly associated with several factors. These factors include advanced age, a family history of diabetes, being overweight, obese, or centrally obese, high systolic blood pressure, and elevated serum triglyceride levels.[3,4] Numerous studies have indicated that prediabetes can be influenced by various factors, including the quantity, quality, and duration of sleep. Adequate and regular sleep is crucial for the proper functioning of the body's metabolism, hormonal processes, and regulation of glucose metabolism.[5,6] Research has shown that short-term sleep restriction or sleep disturbances,[5,7] as well as chronic sleep deprivation,[5,8,9] are associated with glucose intolerance, insulin resistance, and metabolic and endocrine changes in healthy individuals. Additionally, there is a correlation between inadequate sleep (less than five hours) or excessive sleep (more than nine hours), difficulty initiating and maintaining sleep, and metabolic disorders such as type 2 diabetes and obesity.[10,11] A study conducted by Gottlieb et al.[12] demonstrated an increased prevalence of impaired glucose tolerance (IGT) and diabetes among individuals with both short and long sleep durations. The Western New York Health Study, which compared short sleep (less than 6 hours) to the usual sleep length (6-8 hours per night), found that sleeping less than 6 hours was associated with an increased frequency of IFG.[13] However, the results of these studies are inconsistent. Rafalson et al.[13] showed an association between IFG and short sleep duration, but Hung et al.[14] observed no link between IFG and disturbed sleep. Additionally, poor sleep quality and sleep fragmentation can lead to impaired glucose regulation and metabolism, increasing the risk of IFG.[7,15,16] In a study by Lou et al.[17] the frequency of IFG increased in individuals reporting less restful sleep (based on PSQI) and shorter sleep durations (less than 7 hours) compared to those with good sleep quality and a duration of 6 to 8 hours. To our knowledge, the majority of studies in this field have focused more on sleep quality, and studies exploring the relationships between insomnia symptoms, sleep duration, and IFG are scarce. This study aimed to examine the relationships between insomnia symptoms, sleeping less than 7 hours at night, and the prevalence of IFG in shift workers

Materials and Methods

This descriptive-analytical study was conducted on all healthcare personnel (n=443) at an educational hospital in Tehran from December 2022 to April 2023. The inclusion criteria comprised individuals engaged in shift work and having at least one year of work experience. Before participating in the study, each subject provided written informed consent, and the research protocol was reviewed and approved by the ethical committee of the Iran University of Medical Sciences and Health Services (approval number: IR.IUMS.FMD.REC.1401.182, date: 27.06.2022).

An occupational medicine resident conducted in-person interviews with the study's participants. The interviews covered general information such as age, gender, education level, marital status, history of underlying diseases (including hypothyroidism and diabetes), cigarette smoking, physical activity, and family history of diseases (diabetes, hypertension, cardiovascular disease, and malignancy). Additionally, occupational details were gathered, including job title, work history, employment status, possession of primary and supplemental insurance, daily and weekly working hours, shift worker status (regular or non-regular), and the number of shifts worked in a month. Participants with pre-existing conditions including diabetes, chronic obstructive pulmonary disease, neuropathy, psychosis, depression, cardiovascular disease, stroke, a history of antihypertensive treatment, or those who were pregnant were excluded from the study.

Sleep Assessment Instrument

In this study, the Insomnia Severity Index (ISI) questionnaire was employed to assess insomnia and its symptoms. The ISI questionnaire consists of seven questions, each rated on a 5-point Likert-Type Scale ranging from 0 to 4. The total score, ranging from 0 to 28, provides an evaluation of the type and severity of insomnia experienced during the preceding month. Based on the total score, the following classifications were used: a score of 0-7 indicated no clinical insomnia, 8-14 indicated subthreshold insomnia, 15-21 indicated moderate insomnia, and 22-28 indicated severe insomnia.[18] Additionally, three specific questions were used to assess insomnia symptoms, namely difficulty initiating sleep (DIS), difficulty maintaining sleep (DMS), and early morning awakening (EMA).

In the DIS question, participants were asked to indicate whether it took them an hour or more to fall asleep. For the DMS question, participants were asked if they woke up more than three times during the night. In the EMA question, participants were asked if they experienced sleep problems due to waking up too early in the morning. A 5-point Likert Scale (ranging from 0 to 4) was used to rate each question, with 0 indicating "never", 1 indicating "rare", 2 indicating "occasional", 3 indicating "usually", and 4 indicating "always". A score of 3 or 4 on each of these questions determined the occurrence of the related problem.[18]

Furthermore, participants were asked about their sleep duration on weekdays (Saturday through Wednesday) and weekends (Thursday and Friday) during the preceding seven days. To calculate the average weekly sleep length, the following formula was used: [(5 × weekday sleep duration) + (2 × weekend sleep duration)] / 7. This formula took into account the weighted average of weeknights and weekend nights.[19] Based on the reported sleep duration, participants were categorized into the following groups:

- Less than 7 hours per night, indicating short sleep
- 7 to 8 hours per night, indicating normal sleep (reference group)
- 9 hours or more per night, indicating long sleep.[20]

The STOP-BANG questionnaire was employed to assess the risk of obstructive sleep apnea (OSA). It consists of eight yes or no questions, which are as follows: 1. Frequent snoring (S), 2. Daily fatigue (T), 3. Observed apnea (O), 4. Hypertension (P), 5. Body Mass Index (BMI) >35 kg/m^2 (B), 6. Age >50 years old (A), 7. Neck circumference >40 cm (N), 8. Male gender (G). In this study, the participants were divided into two groups based on their STOP-Bang score: a low-risk group (0-2 points) and a high-risk group (3-8 points).[21] All participants underwent a 12-hour overnight fasting period, and blood samples were collected to measure fasting blood sugar (FBS) levels. "According to the current definition by the American Diabetes Association, FBS levels ≤99 mg/dL were categorized as normal, while levels ranging from 100 mg/dL to 125 mg/dL were considered indicative of IFG. Participants with blood sugar levels exceeding 126 mg/dL were excluded from the study".[22]

Statistical Analysis

The study data were entered and analyzed using SPSS version 22.0, a statistical software. Descriptive statistics, such as mean and standard deviation, were used for quantitative variables, while frequency and percentage were used for qualitative variables. The independent Student's t-test was employed to compare quantitative variables between two groups of participants. The chi-square test was used to compare qualitative variables between the two groups. To investigate the relationships between the frequency of IFG and sleep-related variables (insomnia and sleep duration), multivariable logistic regression models were utilized. The results of the multivariable analysis were presented as adjusted odds ratios (ORs) along with 95% confidence intervals (95% CIs). The models also included appropriate interaction terms to assess the combined effects of specific insomnia symptoms and sleep duration on the prevalence of IFG. All statistical tests were two-tailed, and a significance threshold of 0.05 was applied.

Results

The present study involved 410 healthcare workers, with a mean age of 40.71±1.9 years (ranging from 24 to 63 years) and a mean work experience of 14.5±1.04 years (ranging from 1 to 32 years). Among these participants, 287 (70%) were married, 256 (62.43%) were female, and 33 (8.04%) were smokers. More than half of the workforce (53.6%) possessed a bachelor's degree. The average daily working hours were 7.71±1.72 hours, and the average weekly working hours were 53.32±2.15 hours. Additionally, 160 (39.02%) participants had regular shift work. The workers had a mean BMI of 24.18±4.06 kg/m^2 (ranging from 17.35 to 33.9 kg/m^2) and a fasting blood glucose rate of 103.05±8.20 mg/dL (ranging from 85 to 126 mg/dL). Among the workers, 24.87% (n=102) had IFG.

Table 1 indicates that individuals with IFG were significantly more likely to be male (70.58% vs. 26.62%), older (42.64±3.9 vs. 38.86±2.2 years), had higher work experience (15.39±3.2 vs. 12.39±5.3 years), had a higher prevalence of cigarette smoking (12.74% vs. 6.49%), had OSA (26.47% vs. 13.96%), and experience moderate-severe insomnia (41.19% vs. 26.62%) compared to those without IFG. Moreover, subjects with IFG had a significantly higher BMI (25.12±1.16 kg/m^2) compared to those without IFG (21±2.76 kg/m^2) (Table 1).

Table 1. Baseline characteristics of study participants according to the presence or absence of impaired fasting glucose

Impaired fasting glucose				
Baseline characteristics	**Yes (n=102)**	**No (n=308)**	**p**	**OR (CI)***
Age (years) (mean ± standard deviation)	42.64±3.9	38.86±2.2	<0.001	
BMI (kg/m^2) (mean ± standard deviation)	25.12±1.16	21±2.76	<0.001	
Male gender n (%)	72 (70.58)	82 (26.62)	<0.001	6.61 (4.03-10.85)
Marital status (married) n (%)	65 (63.72)	222 (72.07)	0.055	0.68 (0.424-1.09)
Cigarette, (smoker) n (%)	13 (12.74)	20 (6.49)	0.024	2.10 (1.00-4.3)
Physical activity (regular) n (%)	41 (40.19)	217 (70.45)	0.023	0.62 (0.39- 0.99)
Work experience (year) (mean ± standard deviation)	15.39±3.2	12.39±5.3	0.01	
Type of shift (non-regular) n (%)	46 (45.09)	204 (66.23)	<0.001	0.41 (0.26-0.66)
Insomnia (moderate-sever) n (%)123	41 (41.19)	82 (26.62)	0.01	1.85 (1.15-2.96)
OSA** (high risk) n (%)	27 (26.47)	43 (13.96)	<0.001	2.21 (1.28-3.82)

*OR: Odds ratio, CI: Confidence interval, **OSA: Obstructive sleep apnea

According to the ISI questionnaire, the mean insomnia score among the participants was 11.4±5.7, ranging from 0 to 24. The distribution of insomnia severity categories was as follows:

- 45% of participants had no clinical insomnia.
- 25% of participants had subthreshold insomnia.
- 23% of participants had moderate insomnia.
- 7% of participants had severe insomnia.

In total, 123 participants (30%) had moderate to severe insomnia. Based on insomnia symptoms, 21.95% of participants had DIS, 16.34% had DMS, and 23.17% had EMA. The mean sleep duration on weeknights was 6.88±1.02 hours, on weekend nights it was 8.1±1.31 hours, and the average weekly sleep duration was 7.5±1.9 hours. Based on participants' reported sleep duration, 42.4% were classified as short sleepers, sleeping less than 7 hours per night, 51.5% were considered normal sleepers, sleeping 7-8 hours per night, and 6.1% were classified as long sleepers, sleeping 9 hours or more per night.
According to the STOP-BANG score, 340 participants (82.92%) were classified as low risk for OSA, while 70 participants (17.07%) were classified as high risk for OSA.

Comparison of the Prevalence of IFG Between Healthcare Workers with and Without Insomnia Symptoms

It was found that healthcare workers with DIS, DMS, and EMA had a significantly higher prevalence of IFG: (OR=7.38, 95% CI: 4.41-12.37), (4.09, 95% CI: 2.42-6.11), and 7.71, 95% CI: 4.63-12.81) than those without insomnia symptoms respectively.
After adjusting for potential confounding factors such as sex, age, BMI, work experience, cigarette smoking, physical activity, and sleep duration, there was still a significant association between short sleep duration and IFG (Table 2).

Comparison of the Prevalence of IFG Between Healthcare Workers with Short, Normal and Long Sleep Durations

In terms of sleep duration, healthcare workers with short sleep duration (<7 hours per night) had a significantly higher prevalence of IFG compared to those with normal sleep duration (7-8 hours per night) (OR=2.21, 95% CI: 1.38-3.54). After adjusting for potential confounding factors including sex, age, BMI, work experience, cigarette smoking, physical activity, and insomnia symptoms, there was still a significant association between short sleep duration and IFG (OR=1.84, 95% CI: 1.08-1.89). On the other hand, long sleep duration (≥9 hours per night) did not show a significant association with IFG. (Table 2 provides further details on these associations.)
Table 3 presents the results obtained from multiple logistic regression models assessing the prevalence of IFG in relation to sleep duration and insomnia symptoms. The analysis revealed that compared to the reference group (individuals with a normal

Table 2. Associations of impaired fasting glycaemia with sleep characteristics

		Impaired fasting glucose				
Individual symptoms of insomnia		**No n (%)**	**Yes n (%)**	**p**	**OR (95% CI)**	**Adjusted OR (95% CI)**
Difficulty initiating sleep	No n=320	270 (84.37%)	50 (15.62%)	<0.001	1	1
	Yes n=90	38 (42.22%)	52 (57.77%)		7.38 (4.41-12.37)	4.27 (3.28-5.19)*
Difficulty maintaining sleep	No n=333	269 (80.78%)	64 (19.21%)	<0.001	1	1
	Yes n=77	39 (50.64%)	38 (48.05%)		4.09 (2.42-6.91)	2.14 (1.78-3.86)*
Early morning awakening	No n=312	266 (85.25%)	46 (14.74%)	<0.001	1	1
	Yes 98 n=	42 (42.85%)	56 (57.14%)		7.71 (4.63-12.81)	4.54 (1.09-5.63)*
Sleep duration (hours per night)	<7 n=143	93 (65.03%)	50 (34.96%)	<0.001	2.21 (1.38-3.54)	1.84 (1.08-1.89)**
	7-8 n=241	194 (80.49%)	47 (19.50%)		1	1
	≥9 n=26	21 (80.76%)	5 (19.23 %)	0.48	0.98 (0.35-2.74)	

*Odds ratios were adjusted sex, age, BMI, work experiences, cigarette smoking, shift working, physical activity, OSA and sleep duration.
**Odds ratios were adjusted sex, age, BMI, work experiences, cigarette smoking, shift working, physical activity, OSA and insomnia symptoms.
OR: Odds ratio, CI: Confidence interval, BMI: Body max index, OSA: Obstructive sleep apnea

sleep duration and no symptoms of insomnia), individuals who had less than 7 hours of sleep per night and experienced DIS, DMS, or EMA had significantly higher prevalence of IFG, (adjusted OR=5.16, 95% CI: 3.21-6.12), (adjusted OR=2.15, 95% CI: 1.23-2.58), and (adjusted OR=5.26, 95% CI: 3.78-5.89), respectively. Using likelihood ratio tests, it was determined that short sleep duration and the presence of individual insomnia symptoms (DIS and EMA) were significant predictors of the prevalence of IFG.

Discussion

The findings indicated that healthcare workers with insomnia symptoms (DIS, DMS, and EMA) are at a higher risk of IFG compared to workers without insomnia symptoms, with OR of 4.27, 2.14, and 4.54, respectively. Additionally, workers who slept less than 7 hours per night had a significantly higher prevalence of IFG (OR=1.84) compared to those with a normal sleep duration, regardless of the presence of insomnia symptoms. Additional analysis revealed that the presence of insomnia symptoms (DIS, DMS, and EMA) combined with less than 7 hours of night sleep significantly increased the likelihood of IFG by 5.16, 2.15, and 5.26 times, respectively. The main findings of the study were that both short sleep duration and insomnia symptoms had an impact on the prevalence of IFG. Previous epidemiological studies have demonstrated a connection between sleep durations of less than five hours or more than nine hours, difficulties in initiating and maintaining sleep, and metabolic disorders such as type 2 diabetes and obesity.[10,11]

Consistent with our results, Rafalson et al.[13] reported an association between IFG and short sleep duration, while Hung et al.[14] found no link between IFG and disrupted sleep. Short sleep duration has been shown to increase appetite and calorie intake, particularly for carbohydrate-rich foods, by 14% in individuals with normal weight,[23,24] and 15% in middle-aged obese individuals.[7]

Our results indicate that healthcare workers with insomnia symptoms (DIS, DMS, and EMA) face an elevated risk of IFG compared to workers without insomnia symptoms. In a study conducted by Lou et al.[17] the frequency of IFG increased among individuals who reported less restful sleep (based on PSQI) and shorter sleep durations (less than 7 hours) compared to those who experienced a good night's sleep lasting 6-8 hours. While Lou et al.[17] examined the combined effect of sleep quality and

Table 3. Associations of impaired fasting glucose with the joint effects of short sleep duration and individual symptoms of insomnia

Impaired fasting glucose						
Sleep duration (hours per night)			**No n (%)**	**Yes n (%)**	**Adjusted OR* (95% CI)**	**p value** for interaction**
DIS	No n=195	7-8	173 (88.71%)	22 (11.28%)	1	0.03
	No n=99	<7.	76 (76.76%)	23 (23.23%)	1.14 (1.06-2.02)	
	Yes n=46	7-8	21 (7.31%)	25 (25.77%)	3.17 (2.15-4.89)	
	Yes n=44	<7	17 (38.63%)	27 (61.36%)	5.16 (3.21-6.12)	
DMS	No n=196	7-8	167 (85.20%)	29 (14.79%)	1	0.07
	No n=111	<7	81 (72.97%)	30 (27.02%)	1.07 (0.89-1.81)	
	Yes n=45	7-8	27 (60%)	18 (40%)	1.87 (0.52-1.58)	
	Yes n=32	<7	12 (37.5%)	20 (62.5%)	2.15 (1.23-2.58)	
EMA	No n=190	7-8	170 (89.47%)	20 (10.52%)	1	0.02
	No n=96	<7	75 (78.12%)	21 (21.87%)	2.14 (1.69-3.25)	
	Yes n=51	7-8	24 (47.05%)	27 (52.94%)	3.99 (2.87-3.57)	
	Yes n=47	<7	18 (38.29%)	29 (61.70%)	5.26 (3.78-5.89)	

*: Odds ratios were adjusted sex, age, BMI, work experiences, cigarette smoking, physical activity.

**: p value for interactions was based on the likelihood ratio test.

DIS: Difficulty initiating sleep, DMS: Difficulty maintaining sleep, EMA: Early morning awakening, OR: Odds ratio, CI: Confidence interval

quantity on IFG, our study focused on the impact of insomnia symptoms and sleep duration on IFG. Despite this difference in approach, we obtained similar results.

In our study, we observed that the impact of sleeping less than 7 hours per night on the prevalence of IFG (OR=1.84) was less significant compared to the effect of insomnia symptoms: DIS (OR=4.27), DMS (OR=2.14), and EMA (OR=4.54). IFG is physiologically caused by reduced liver sensitivity to insulin or impaired insulin production.[25] Several studies have indicated that poor sleep quality and sleep fragmentation can contribute to impaired glucose regulation and metabolism, thereby increasing the risk of IFG.[7,15,16]

The anorexigenic leptin levels,[26-29] tolerance to glucose, glucose effectiveness, sensitivity to insulin, and β cell function are reduced after sleep deprivation.[5,23,30,31] Following three nights of disrupted sleep with slow wave patterns, insulin sensitivity decreases by 25%,[32] while glucose tolerance decreases by 23%,[7] thereby increasing the risk of diabetes and IGT.

Additionally, in our study, 17.07% of participants had OSA, and the frequency of obstructive apnea was higher in subjects with IFG. OSA is characterized by repeated closure or narrowing of the upper airway during sleep, while insomnia is characterized by difficulty initiating or maintaining sleep, early awakening without being able to return to sleep, or a combination of these symptoms.[33]

The concept of the "sleep apnea and insomnia syndrome" was first described in 1973.[34] This clinical syndrome has garnered significant attention, leading to numerous studies, and it has been observed that insomnia and OSA often coexist. However, the extent of their coexistence varies across different studies. For instance, Smith et al.[35] found that 39% of patients with OSA also experienced insomnia, while Cronlein et al.[36] reported that 10.7% of patients diagnosed with insomnia had clinically significant OSA. Several studies have demonstrated a correlation between OSA and insulin resistance, as well as glucose intolerance.[37,38] Therefore, the increased frequency of IFG observed in individuals with insomnia may be partly attributed to the presence of OSA alongside insomnia. However, it is important to note that this factor (sleep apnea) was taken into account and adjusted for in the multivariable logistic regression analysis, and the significant association between insomnia symptoms and IFG remained.

In our study, we did not find a significant correlation between long sleep duration and the prevalence of IFG. However, our findings differ from a study conducted by Lou et al.[17], where individuals with long sleep duration were found to have a significant risk of developing IFG compared to those with high-quality sleep and normal night sleep duration of 6 to 8 hours. One possible explanation for these discrepant results is that the number of individuals with long sleep duration was very small in our study. Therefore, it is recommended to conduct larger-scale studies to further investigate the relationship between sleep duration of more than 8 hours and the prevalence of IFG, as well as its connection with insomnia.

Our research has several advantages and limitations. One of the strengths is that it investigated both sleep duration and insomnia symptoms, which sets it apart from other studies. However, there are three notable limitations to consider. Firstly, the methodology of the study relied on cross-sectional data, which means that it is not possible to establish a causal relationship between insomnia symptoms, sleep duration, and IFG. Longitudinal studies would be needed to determine the temporal sequence and potential causal links between these factors. Secondly, the information regarding sleep duration and insomnia symptoms was gathered through self-reported questions. While valid questionnaires such as the ISI are commonly used for screening sleep disorders, objective measures were not employed. Objective instruments, such as polysomnography or actigraphy, could provide more accurate and reliable data on sleep duration and sleep disturbances. Lastly, the study focused on shift workers, who are known to experience higher levels of sleep disturbances compared to the general population. This specific population may have unique characteristics that could impact the generalizability of the study's findings to other groups. Considering these limitations, it would be beneficial for future research to incorporate longitudinal designs, objective measures of sleep, and diverse populations to further investigate the relationship between sleep duration, insomnia symptoms, and IFG.

Recent research indicates that the disruption of circadian rhythm caused by shift work can increase the risk of impaired glucose and lipid metabolism, adipose tissue dysfunction, and cardiovascular and hemostatic dysfunction.[39-42] Since IFG is a risk factor for type 2 diabetes and cardiovascular disease, it is recommended to regularly screen shift workers for insomnia and IFG. In addition to addressing sleep disturbances, promoting access to healthy foods, fostering appropriate and healthy eating habits, and encouraging physical activity in the workplace are vital for the well-being of shift workers.

Conclusion

In conclusion, the current study demonstrates that healthcare workers who experience less than 7 hours of night sleep and exhibit insomnia symptoms, particularly EMA, DIS, and DMS, have a significantly higher risk of IFG by 5.16, 2.15, and 5.26 times, respectively, compared to workers with normal sleep (both in terms of quality and quantity). Considering the impact of insomnia symptoms and short sleep duration on glucose metabolism and endocrine function, it is important to prioritize sleep hygiene, make adjustments to working hours, promote access to healthy foods, and encourage regular exercise in order to prevent the occurrence or worsening of IFG. Additionally, it is recommended to conduct periodic screenings for insomnia among shift workers to prevent the development of IFG.

Ethics

Ethics Committee Approval: The research protocol was reviewed and approved by the ethical committee of the Iran University of Medical Sciences and Health Services (approval number: IR.IUMS.FMD.REC.1401.182, date: 27.06.2022).

Informed Consent: Before participating in the study, each subject provided written informed consent.

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Footnotes

Authorship Contributions

Surgical and Medical Practices: E.K.M., Concept: E.K.M., S.M., Design: E.K.M., S.M., Data Collection or Processing: O.A., N.S., Analysis or Interpretation: E.K.M., N.S., Literature Search: O.A., N.S., Writing: E.K.M., S.M., O.A., N.S.

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Predictors and Mediators of Sleep Quality After Multiple Consecutive Devastating Earthquakes in Türkiye

Türkiye'de Art Arda Yaşanan Yıkıcı Depremler Sonrası Uyku Kalitesinin Belirleyicileri ve Aracı Faktörleri

Burak Mete[1], Hakan Demirhindi[1], Fatma İrem Dağlı[1], Kübra Işık[2], Ferdi Tanır[1], Esra Doğan Mete[3]

[1]*Çukurova University Faculty of Medicine, Department of Public Health, Adana, Türkiye*
[2]*Şanlıurfa Suruç State Hospital, Clinic of Neurology, Şanlıurfa, Türkiye*
[3]*Çukurova University Faculty of Medicine, Department of Child and Adolescent Psychiatry, Adana, Türkiye*

Abstract

Objective: The aim of this study is to determine the prevalence of insomnia and the level of sleep quality in the first month of earthquakes in Kahramanmaraş and to investigate the effects of earthquake stress coping strategies on sleep quality and insomnia.

Materials and Methods: This cross-sectional study included 509 adults in Adana. Sleep problems were assessed with the Insomnia Severity Index and Pittsburgh Sleep Quality Index (PSQI), and the coping level with earthquake stress with the Coping with Earthquake Stress Scale (CESS).

Results: The mean age of the individuals was 29.42±12.62 years and 73.1% were female. After the earthquake, 64% of the participants had decreased sleep duration, 66.8% had increased night awakenings, 77.6% had difficulty falling asleep, and 7.3% started to use sleeping pills to sleep. All participants had poor sleep quality; 26.1% had moderate insomnia and 8.1% had clinical insomnia. After the earthquake, the risk of moderate and clinical insomnia was found to be increased Odds ratio (OR)=2.33 times in the 18-40 age group, OR=2.07 times in females, OR=1.88 times in those with children, and OR=2.29 times in people with previous sleep disorders. The use of the positive reappraisal strategy improved sleep quality, and each unit increase in this sub-dimension of CESS caused a 0.137-unit decrease in the PSQI score. Coping strategies contributed to the improvement of sleep quality both directly and indirectly by reducing insomnia.

Conclusion: Sleep problems were common in the subacute period after the earthquake. We recommend interventions to develop positive reappraisal strategies for groups vulnerable to sleep problems.

Keywords: Insomnia, earthquakes, sleep quality

Öz

Amaç: Bu çalışmanın amacı Kahramanmaraş merkezli depremlerin birinci ayında uykusuzluk prevalansını ve uyku kalitesi düzeyini saptamak, deprem stresi ile başetme stratejilerinin uyku kalitesi ve uykusuzluk üzerindeki etkisini araştırmaktır.

Gereç ve Yöntem: Bu kesitsel çalışma Adana'da 509 yetişkin üzerinde yürütülmüştür. Uyku sorunlarını değerlendirmek için Uykusuzluk Şiddet İndeksi ve Pittsburgh Uyku Kalitesi İndeksi (PSQI) kullanılmış ve deprem stresiyle başa çıkma düzeyi Deprem Stresiyle Başa Çıkma Ölçeği (CESS) ile değerlendirilmiştir.

Bulgular: Bireylerin yaş ortalaması 29,42±12,62 yıl olup, %73,1'i kadındır. Depremden sonra katılımcıların %64'ünün uyku süresi azalmış, %66,8'inin gece uyanmaları artmış, %77,6'sı uykuya dalmakta güçlük çekmiş ve %7,3'ü uyumak için uyku ilacı kullanmaya başlamıştır. Katılımcıların tamamının uyku kalitesi düşüktür; %26,1'inde orta derecede uykusuzluk ve %8,1'inde klinik uykusuzluk vardır. Depremden sonra orta ve klinik uykusuzluk riskinin 18-40 yaş grubunda Odds oranı (OR)=2,33 kat, kadınlarda OR=2,07 kat, çocuk sahibi olanlarda OR=1,88 kat ve daha önce uyku bozukluğu olanlarda OR=2,29 kat arttığı bulunmuştur. Olumlu yeniden değerlendirme stratejisinin kullanımı uyku kalitesini artırmış ve alt boyuttaki her bir birimlik artış PSQI puanında 0,137 birimlik düşüşe neden olmuştur. CESS, uykusuzluğu azaltarak hem doğrudan hem de dolaylı olarak uyku kalitesinin iyileşmesine katkıda bulunmuştur.

Sonuç: Depremden sonraki subakut dönemde uyku sorunları yaygındır. Uyku sorunlarına karşı savunmasız gruplar için olumlu yeniden değerlendirme stratejileri geliştirmeye yönelik müdahaleler öneriyoruz.

Anahtar Kelimeler: Uykusuzluk, deprem, uyku kalitesi

Address for Correspondence/Yazışma Adresi: Assoc. Prof. Burak Mete, Çukurova University Faculty of Medicine, Department of Public Health, Adana, Türkiye
E-mail: burakmete2008@gmail.com **ORCID-ID:** orcid.org/0000-0002-0780-6176

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Introduction

Major disasters cause many negative consequences in physical, mental, economic, social and other areas. Various problems may occur in the short, medium and long term in individuals who experience disasters such as earthquakes. One of these problems is the risk of developing insomnia and problems related to sleep quality.[1] After earthquakes, which are one of natural disasters, sleep disorders have been observed at varying rates between 10.7 and 70% among earthquake victims in addition to various psychiatric disorders including post-traumatic stress disorder (PTSD), anxiety and depression.[2-5] Recent studies have shown that impaired sleep is a basic symptom rather than a secondary finding for psychiatric disorders.[6] Findings on the relationship between sleep disorders and psychiatric symptoms have led researchers to investigate sleep disorders that occur after major disasters such as earthquakes.[7] Recognition of sleep disorders will be important in terms of prevention of psychiatric findings and diseases that may develop. The long-term persistence of sleep disorders is an important risk for many cardiovascular and metabolic diseases as well as psychological effects.[8] On 6 February 2023, two consecutive earthquakes with a magnitude of 7.7 Mw and 7.6 Mw occurred in Türkiye with the epicentre in Kahramanmaraş affecting approximately 11 cities. The earthquakes were followed by more than 38 thousand aftershocks with magnitudes up to 6.7 Mw.[9] One of the cities affected by the earthquakes was Adana, where approximately 500 people lost their lives and thousands of buildings were damaged. This study aimed to investigate the frequency of insomnia, the level of sleep quality and the factors affecting insomnia in adults living in Adana at the end of the first month after two major earthquakes.

Materials and Methods

Design and Recruitment

This study was conducted in Adana province by the researchers of Çukurova University Faculty of Medicine, Department of Public Health, Adana, Türkiye in March 2023. The study was conducted in accordance with the Declaration of Helsinki and was approved by Çukurova University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee (approval number: 36, date: 07.04.2023). The population of the cross-sectional study consisted of adults living in Adana. The minimum sample size was calculated as 503 assuming a frequency of 20.6%, a type-1 error level of 5%, a confidence interval of 95% and a design effect of 2.[10] The prepared questionnaire form included the written participant consent section where the purpose of the research was mentioned, stating that the information obtained during the research would only be used for scientific purposes, and evaluated in confidentiality within the framework of scientific ethical rules. The questionnaire form was sent to the people on the list from the social media and communication accounts of the researchers and they were asked to distribute it to other people on their own accounts. In order to prevent re-completion, the online questionnaire was allowed to be filled out and submitted once. Among people who were reached by online survey and snowball sampling method and gave consent to participate a total of 587 questionnaires were returned. After removing the questionnaires with missing data or those incorrectly completed 509 questionnaires were evaluated. The questionnaire form included sociodemographic information, questions about the earthquake-sleep relationship, the Insomnia Severity Index (ISI), the Pittsburgh Sleep Quality Index (PSQI), and the Coping Strategies with Earthquake Stress scale (CESS).

Instruments

Insomnia Severity Index (ISI)

The index was developed and tested for validity by Bastien et al.[11] The Turkish validity and reliability study of the scale was conducted by Boysan et al.[12] in 2010. The internal consistency coefficient calculated to determine the reliability of the scale was reported as 0.79. It is a five-point Likert-type scale consisting of seven items. Each item is scored between 0 and 4 and the total score varies between 0-28. The evaluation of the score obtained from the scale is as follows; 0-7 indicates "clinically insignificant insomnia", 8-14 "insomnia subthreshold", 15-21 "moderate clinical insomnia", and 22-28 "severe clinical insomnia".[12]

Pittsburgh Sleep Quality Index (PSQI)

The scale was originally developed and tested for validity by Buysse et al.[13] in 1988. The scale includes a total of 24 questions, among them, 19 are self-rated questions. Five questions are answered by the individual's spouse or roommate, but they are used for clinical information only and therefore not tabulated in the scoring of PSQI. Self-assessment questions include various items related to sleep quality. These are intended to estimate sleep duration and latency, and the frequency and severity of specific sleep-related problems. The 19 items are grouped into seven component scores, each weighted equally on a 0-3 scale. The seven component scores are then summed to yield a global PSQI score which ranges between 0-21; higher scores indicating worse sleep quality. The components are subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, sleep medication use, and daytime dysfunction. The sum of these seven component scores gives the total index score. The index does not indicate the presence or prevalence of sleep disorders. However, a PSQI total score of 5 and above indicates poor sleep quality.[13] Ağargün et al.[14] (1996) performed the Turkish validity and reliability study of the PSQI.

Coping with Earthquake Stress Scale (CESS)

The scale was created by Yondem and Eren[15] in 2008 who also performed the scale's Turkish validity and reliability study. The main motivation for the scale was the view that natural disasters were a source of situational stress where there was a threat to life, and that the scales used in the literature to assess coping could not be adapted to all stress situations, and that the functionality of coping strategies might change in different situations. How people cope with natural disasters and traumas was the subject of many studies, where commonly used stress and coping scales were utilised.[16,17] Jeavons et

al.[18] stated that there was an increase in the use of problem-focused coping strategies over time in some studies looking at posttraumatic coping strategies, but there was no change in the use of emotion-focused and especially avoidance strategies. A positive relationship was found between emotion-focused and avoidance strategies. When the literature was examined, it was emphasised that natural disasters had short and long-term psychological effects and that the effects might vary according to the severity, suddenness and unexpectedness of the disaster, and the rate of death and destruction it caused. It could be assumed that after such a disaster, not only the individuals who were primarily affected by the earthquake but also the whole society in general experienced this stress and there were efforts to cope with this situation. CESS was a result of the need to develop a scale to determine coping strategies for earthquake stress, which was a common but not frequently observed source of stress. To determine what these efforts were and through which dimensions they could be explained was important in terms of providing a valid and reliable measurement tool for the researches to be conducted to understand the coping strategies used by the individual towards natural events beyond his/her control and to reveal the different variables related to these coping strategies. The scale consists of three sub-dimensions which are positive reappraisal, seeking social support, and religious coping. The first one positive reappraisal sub-dimension aims to determine if the individual, in response to coping with earthquake stress, tries to build up coping strategies like being optimistic, thinking positively, not magnifying negativities, accepting what was lived as an experience, giving himself/herself time for thinking about the future. The strategies examined in the seeking social support sub-dimension include sharing the experiences, feelings and/or fears with friends or someone who can cope better with the problem. the religious coping sub-dimension includes strategies like entrusting him/herself to God, relaxing in prayer, believing that destiny cannot be changed and fulfilling religious duties more faithfully. In responding to the CESS, a 4-point rating scale was used, ranging from "always (4)" to "never (1)". However, item 4 (I try to keep my emotions to myself) and item 12 (I prefer not to talk about my fears and anxieties) are reversely scored since they express that the individual does not seek social support. The score ranges from 5 to 20 for both the religious coping and seeking social support sub-dimensions, each consisting of 5 items, while between 6 and 24 for the positive reappraisal sub-dimension, consisting of 6 items. The higher the score obtained for each dimension, the more the individual uses that coping strategy, and vice versa. The Cronbach's alpha (α) coefficients for the CESS were found to be α=0.85 for religious coping, α=0.69 for positive reappraisal, and α=0.74 for seeking social support.

Statistical Analysis

SPSS® 20 (IBM, USA) and JAMOVI Ver.2.3 softwares were used in the analysis of the data.[19] The assumption of normality was tested by the Kolmogorov-Smirnov test. Mann-Whitney U test was used for comparisons of two independent groups that did not comply with normal distribution, and Kruskal-Wallis test was used for comparisons of three groups. Spearman correlation analysis was preferred for ratio data that did not meet the normal distribution assumption. In further analysis, multivariate linear regression analysis to estimate the sleep quality score (ratio data that fits normal distribution), logistic regression analysis to estimate the risk of insomnia (dichotomous qualitative data), mediation analysis to evaluate the mediating effect of insomnia on the effect of coping strategies with earthquake stress on sleep quality was used. A $p<0.05$ value was considered statistically significant. Rank biserial correlation coefficient values were calculated in the effect size evaluation. Rank biserial correlation coefficients of 0.10, 0.30 and 0.50 or greater indicated small, medium and large effect sizes, respectively.

Results

The mean age of the individuals included in the study was 29.42±12.62 years (minimum=18 maximum=84) and 73.1% of the participants were female. After the earthquake, 64% of the participants reported decreased sleep duration, 66.8% increased night awakenings, 77.6% difficulty in falling asleep, and 7.3% to start using sleeping pills to sleep. All participants had poor sleep quality, 26.1% had moderate insomnia, and 8.1% had clinical insomnia. Information about the sociodemographic characteristics of the individuals and changes in sleep habits after the earthquake were given in Table 1. When the relationship between the scores obtained from the sub-dimensions of the CSES scale and the sub-dimensions related to insomnia and sleep quality was evaluated, the total CESS score and the CESS Positive reappraisal sub-dimension score were found to show a weak negative correlation with the total ISI score, total PSQI score, and PSQI components sleep latency, and daytime dysfunction, while the CESS positive reappraisal sub-dimension score with PSQI components subjective sleep quality, sleep disorder and sleep medication use (Table 2). The logistic regression model to predict the risk of moderate and clinical insomnia in individuals was found to be significant (omnibus test $p<0.001$). The accuracy rate of the model was 69.4%. The independent variables included in the model were age, sex, employment status, number of children, chronic disease status, psychiatric disease, and sleep disorder. After the earthquake, the risk of moderate and clinical insomnia increased 2.33 times in the 18-40 age group, 2.07 times in women, 1.88 times in those with children, and 2.29 times in those with previous sleep disorders (Table 3). When the scores obtained from the PSQI and ISI scales were compared according to various sociodemographic characteristics, it was found that PSQI scores were higher in females, separated/spouse deceased people, people with chronic disease, people with psychiatric disease, and people with prior sleep problems, while the scores obtained from the ISI were higher in females, separated/spouse deceased people, people with children, actively working people, people with chronic disease, people with prior sleep problems, and people who changed cities after the earthquake (Table 4). The linear regression analysis to predict the PSQI score was found to be significant (analysis of variance $p<0.001$).

The dependent variable was the total PSQI score, while the independent variables of the model were religious coping, positive reappraisal, and social support sub-dimensions of the CESS. The positive reappraisal sub-dimension contributed to the model with each unit increase in this sub-dimension causing a 0.137-unit decrease in the PSQI score (Table 5). In the mediating effect analysis of sleep quality, insomnia severity and coping strategies with earthquake stress; it was found that the direct effect of coping strategies with earthquake stress on sleep quality was not significant, the mediated effect of insomnia was significant and had a negative effect. It caused an indirect increase in sleep quality by reducing insomnia. Coping strategies with earthquake stress had 64.5% of their total effect on sleep quality through indirect effect by reducing the severity of insomnia (Figure 1).

Table 1. Distribution of sociodemographic characteristics and sleep problems

Features	n (%)
Sex	
Female	372 (73.1)
Male	137 (26.9)
Age	
18-40	407 (80.0)
41 and above	102 (20.0)
Marital status	
Married	156 (30.6)
Single	341 (67.0)
Separated/spouse deceased	12 (2.4)
Having children	
No	358 (70.3)
Yes	151 (29.7)
Actively working	
Yes	230 (45.2)
No	279 (54.8)
Sleep duration after the earthquake	
No change	143 (28.1)
Increased	40 (7.9)
Decreased	326 (64.0)
More frequent night awakenings after the earthquake	
Yes	340 (66.8)
No	169 (33.2)
Having trouble falling asleep after the earthquake	
Yes	395 (77.6)
No	114 (22.4)
Starting to use any medication to sleep after the earthquake	
Yes	37 (7.3)
No	472 (92.7)
Insomnia Severity Index	
Clinically insignificant insomnia	137 (26.9)
Lower threshold insomnia	198 (38.9)
Moderately severe clinical insomnia	133 (26.1)
Severe clinical insomnia	41 (8.1)
Pittsburgh Sleep Quality Index	
Normal sleep quality	0
Poor sleep quality	509 (100.0)
Total	509 (100.0)

Discussion

Earthquakes are disasters leading to catastrophic social and economic effects. In addition to physical injuries and deaths, they may lead to behavioural and psychological problems, and sleep problems are among these problems. In this study, sleep problems (sleep quality and insomnia) were investigated in the first month after the earthquake in Adana province, which was affected by two earthquakes with a magnitude of 7.8 Mw and 7.7 Mw, the epicentre of which was Kahramanmaraş in Türkiye on 6 February 2023.[9] According to the results of our study, all of the participants had poor sleep quality (PSQI >5), 26.1% had moderate insomnia and 8.1% had clinical insomnia. After the earthquake, the risk of moderate and clinical insomnia increased 2.33 times in the 18-40 age group, 2.07 times in females, 1.88 times in those having children, and 2.29 times in people with previous sleep disorders. It was found that sleep quality score after the earthquake was higher in females, separated/spouse deceased, people with chronic diseases, people with psychiatric diseases, and people with sleep problems before the earthquake, insomnia was higher in women, divorced/separated people, people with children, working people, people with chronic diseases, people with sleep problems and people who changed cities after the earthquake. In a study conducted by Bavafa et al.[10] after the Ezgeleh earthquake (7.3 Mw) in Iran, the frequency of poor sleep quality was found to be 20.61%. Sleep quality was found to be related to depression, anxiety and severity of stress. Sleep initiation time was found to have a positive relationship with stress. In the study conducted by Khazaie et al.[20] sleep quality and severity of insomnia were found to be associated with some personality characteristics, psychological distress, experiential avoidance and dysfunctional beliefs and attitudes related to sleep. In another study conducted by Khazaie et al.[21] 10 days after the Kermanshah earthquake, it was found that factors such as dysfunctional beliefs and attitudes related to sleep, experiential avoidance, neurotic personality traits and emotion regulation problems associated with poor sleep quality and insomnia were effective. In our study, when coping strategies with earthquake stress were evaluated, a weak negative correlation was found between the positive reappraisal dimension and the total scores of the ISI and PSQI, sleep latency, sleep disturbance, sleep medication use, and daytime dysfunction. It was found that sleep quality was better in individuals with positive reappraisal and each unit increase in the positive reappraisal dimension caused a 0.137-unit decrease in the PSQI score. In the study conducted by Li et al.[22] in Japan, financial difficulties

Table 2. Correlation between insomnia, sleep quality and coping strategies					
		Coping with Earthquake Stress Scale (CESS) scores			
		Total	Religious coping sub-dimension	Positive reappraisal sub-dimension	Seeking social support sub-dimension
ISI total score	r	-0.114**	-0.035	-0.162***	-0.010
PSQI total score	r	-0.094*	0.004	-0.164***	-0.011
Subjective sleep quality (PSQI)	r	-0.057	0.024	-0.131**	0.022
Sleep latency (PSQI)	r	-0.096*	-0.074	-0.131**	0.035
Sleep duration (PSQI)	r	0.040	0.030	0.075	-0.045
Sleep activity (PSQI)	r	0.026	0.016	-0.014	0.030
Sleep disorder (PSQI)	r	-0.066	0.042	-0.160***	-0.008
Sleep medication use (PSQI)	r	-0.059	-0.011	-0.117**	0.015
Daytime dysfunction (PSQI)	r	-0.145***	-0.073	-0.140**	-0.040
*p<0.05, **p<0.01, ***p<0.001. ISI: Insomnia Severity Index, PSQI: Pittsburgh Sleep Quality Index					

Table 3. Logistic regression analysis for predicting insomnia risk					
	B	p	OR	95% CI OR	
				Lower	Upper
Age (risk group: 18-40 years)	0.849	0.009*	2.338	1.239	4.411
Sex (risk group: female)	0.727	0.002*	2.070	1.305	3.283
Working (risk group: not working)	-0.304	0.179	0.738	0.474	1.149
Child (risk group: present)	0.635	0.027*	1.888	1.075	3.316
Chronic disease (risk group: present)	0.507	0.082	1.661	0.937	2.943
Psychiatric illness (risk group: present)	0.212	0.553	1.236	0.614	2.488
Sleep disturbance	0.828	0.017*	2.290	1.162	4.512
Constant	-1.521	<0.001	0.219		
*Significant factors; OR: Odds ratio, CI: Confidence interval					

after the earthquake were found to be associated with short sleep duration and insufficient sleep. Two dimensions of social support was measured at baseline: instrumental and emotional support. Instrumental support was assessed by asking the question, "Do you have someone who looks after you when you are sick and confined to a bed for a few days?" Emotional support was assessed by asking if the respondent had someone who listened to his/her concerns and complaints. It was found that instrumental support decreased sleep problems and emotional support increased sleep quality.[22] In our study, no significant relationship was found between social support and insomnia and sleep quality. In the study conducted by Fan et al.[23] the frequency of sleep disorders was reported as 38.3% at 12 months and 37.5% at 24 months after the earthquake. Both at 12 and 24 months, sleep disturbance and short sleep duration were found to be associated with increased depression and PTSD symptoms.[23] In the study conducted by Geng et al.[24] 12 months after the earthquake, it was found that 48.90% of the participants slept less than 7 hours, 27.68% had difficulty falling asleep, 8.82% had problems staying asleep, 22.60% had poor sleep quality, and 40.01% had problems with daytime functioning. Sleep problems assessed by the PSQI general scale remained high until 18 and 30 months after the earthquake, and the prevalence was reported as between 28.79% and 30.18%. It was found that lack of social support, depression, anxiety and unfavourable living conditions increased the risk of sleep problems.[24] In the cohort study conducted by Chen et al.[25] post-earthquake sleep change patterns were examined in people exposed to the Wenchuan earthquake in China and it was investigated whether certain sleep-related change patterns could [predict mental health problems (PTSD), anxiety and depression] 10 years after the Wenchuan earthquake. Four different sleep problem patterns were identified and it was found that individuals with constant-high and increasing sleep patterns were more likely to experience PTSD, anxiety and depression 10 years later.[25] The systematic review conducted by Cox et al.[26] reported that there was a relationship between objective and subjective sleep disturbance and PTSD in studies conducted in different groups and sleep disturbance was found to be a predictor for PTSD. Continued sleep disturbance results in PTSD. It has been reported that sleep disturbance may be more than just an epiphenomenon of PTSD. In the study conducted by Tempesta et al.[27] the effect of earthquake on sleep quality in the long term was investigated. In the comparison of the participants before and after the earthquake, it was found that there was a significant deterioration in sleep

Table 4. Comparison of factors on Pittsburgh Sleep Quality Index (PSQI) and Insomnia Severity Index (ISI) scores				
	PSQI scores		ISI scores	
	Median (IQR)	p (effect size)	Median (IQR)	p (effect size)
Sex				
Female	14 (4)*	<0.001 (0.284)	12 (9.25)*	0.024 (0.130)
Male	13 (4)		11 (8)	
Age				
18-40	14 (3)	0.557 (0.037)	12 (9)	0.960 (0.003)
41 and above	13 (4)		12 (8)	
Marital status				
Married	14 (3)	0.021 (0.015)	13 (9)	0.012 (0.017)
Single	14 (3)		11 (10)	
Separated/spouse deceased	16 (2.75)*		14.5 (10.8)*	
Having children				
Yes	14 (3.50)	0.645 (0.025)	13 (10)*	0.020 (0.129)
No	14 (3.75)		12 (9)	
Actively working				
Yes	14 (3)	0.604 (0.026)	13 (8)*	<0.001 (0.180)
No	14 (4)		11 (11)	
Medication use due to a non-sleep-related chronic disease				
Yes	14 (4)*	0.005 (0.189)	14 (8)*	0.002 (0.216)
No	14 (3)		11 (9)	
Mental (psychiatric) illness diagnosed before the earthquake				
Yes	16 (4.5)*	0.001 (0.359)	13 (9)	0.151 (0.132)
No	14 (3)		12 (9)	
Sleep-related illness diagnosed before the earthquake				
Yes	15 (3.75)*	0.002 (0.286)	15 (10.3)*	0.001 (0.297)
No	14 (3)		12 (9)	
Experienced the earthquake in a disaster province and travelled to a province outside the disaster provinces to stay?				
Yes	14 (4)	0.293 (0.059)	12 (9)*	0.025 (0.128)
No	14 (3)		12 (9)	
*Significant values, IQR: Inter-quartile range, PSQI, Pittsburgh Sleep Quality Index, ISI: Insomnia Severity Index Score				

Table 5. Multiple linear regression analysis for the prediction of PSQI score according to CESS sub-dimensions					
CESS sub-dimensions	Unstandardised coefficients		p	Collinearity statistics	
	B	Std. Error		Tolerance	VIF
(Constant)	15.358	0.679	<0.001		
Religious coping (CESS)	0.043	0.031	0.168	0.901	1.110
Positive reappraisal (CESS)	-0.137	0.031	<0.001	0.879	1.138
Seeking social support (CESS)	0.027	0.034	0.423	0.956	1.046
Regression equation (estimated PSQI) = 15.35-0.137 x (positive reappraisal score), PSQI: Pittsburgh Sleep Quality Index, CESS: Coping with Earthquake Stress scale, Std.: Standard, VIF: Variance Inflation Factor					

quality after exposure to trauma. In addition, two years after the earthquake, it was found that PSQI scores were higher in those exposed to the earthquake compared to those living in the surrounding areas, and sleep quality impairment was higher in people living within 70 km from the epicentre of the earthquake. It has been reported that proximity to the epicentre increases the risk of sleep disorders. In the study by Geng et al.[28] approximately 47% of the participants reported difficulty in initiating or maintaining sleep after the earthquake. Sleep disturbances were more common when accompanied by PTSD and depressive symptoms. In longitudinal analyses, depression and PTSD predicted sleep disturbances, while sleep

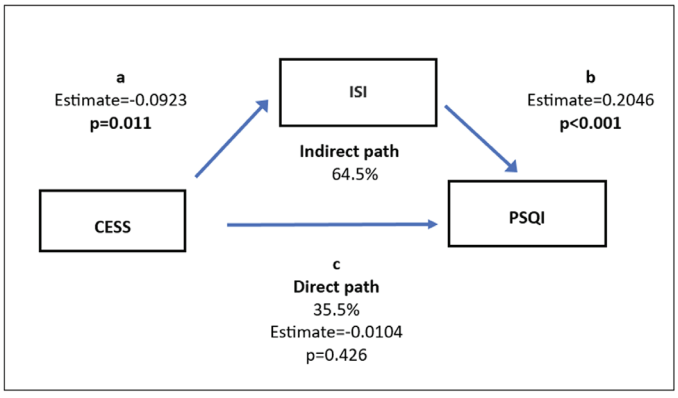

Figure 1. Conceptual diagram of path estimates of mediation between CESS, ISI and PSQI
CESS: Coping with Earthquake Stress Scale; PSQI: Pittsburgh Sleep Quality Index, ISI: Insomnia Severity Index

disturbances predicted depression over time. There was a bidirectional and interdependent relationship between sleep disorders, depression and PTSD.[28] In our study, sleep problems in the subacute period after the earthquake were determined and it was found that the rates of poor sleep quality were higher compared to the literature. This difference in the results may be related to the time when the studies were conducted; in the literature, mostly late-term problems and their results were evaluated. In the study conducted by Ma and Lin[29] media exposure in the post-disaster period was found to be associated with poor sleep quality. Our study was conducted in the subacute period of the earthquake, and the presence of intense media exposure during the study period and the high number of felt aftershocks might have increased sleep problems. The prevalence and incidence of sleep-related problems vary depending on the period of natural disasters and the specific situation. Approximately one-third of the adult population has difficulty sleeping or symptoms of insomnia.[30] The prevalence of insomnia is estimated to be 10% severe enough to cause daytime sleepiness and is higher in women than in men (17.6% and 10.1%, respectively).[31] Additionally, insomnia has been found to be a persistent disorder (lasting more than five years) and affects more than 40% of patients with severe insomnia symptoms at at presentation.[31] In our study, the frequency of moderate and severe insomnia was found to be approximately 35%, and the frequency of poor sleep quality was 100%. Compared to normal times, sleep problems in the general population appear to increase after the earthquake.

Study Limitations

The research was conducted using objective and validated measurement instruments. However, some limitations can be mentioned as the research was single-centred, it was conducted online and the invitations to participate were communicated via social media accounts of the researchers and consecutively of the participants and declaration-based receipt of psychiatric disease information.

Conclusion

Sleep problems were common in the subacute period after the earthquake. Predictors for insomnia and poor sleep quality were being young, being a female, having children, having a sleep disorder before the earthquake, being separated/having a deceased spouse, having a chronic disease, having a psychiatric disease, and changing cities after the earthquake. Detection of sleep problems and intervention in vulnerable groups (women, children, separated people, people with psychiatric illness, and people with chronic illness) in the early period will be important in terms of preventing the emergence of further problems. It was seen that sleep problems that developed after the earthquake were associated with stress in the early period and difficulties in living conditions and psychiatric disorders in the late period. Early detection of sleep problems as both causes and consequences of psychiatric disorders will be very preventive. Longitudinal studies are needed to see the long-term effects of the earthquake on vulnerable groups. We recommend planning interventions that will develop a positive reappraisal strategy in these groups.

Ethics

Ethics Committee Approval: The study was conducted in accordance with the Declaration of Helsinki and was approved by Çukurova University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee (approval number: 36, date: 07.04.2023).
Informed Consent: The participants' approval section was included in the prepared questionnaire form.

Footnotes

Authorship Contributions

Concept: B.M., H.D., F.İ.D., K.I., F.T., E.D.M., Design: B.M., H.D., F.İ.D., K.I., F.T., E.D.M., Data Collection or Processing: B.M., F.İ.D., E.D.M., Analysis or Interpretation: B.M., H.D., F.İ.D., K.I., F.T., E.D.M., Literature Search: B.M., H.D., F.İ.D., K.I., F.T., E.D.M., Writing: B.M., H.D., F.İ.D., K.I., F.T., E.D.M.
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A Mediational Evaluation of Smartphone Addiction Effect on Insomnia and Sleepiness in Adolescents and Young Adults

Ergenlerde ve Genç Yetişkinlerde Akıllı Telefon Bağımlılığının Uykusuzluk ve Uykululuk Üzerindeki Etkisinin Aracı Olarak Değerlendirilmesi

Fatma Atun Ütük[1], Onur Yücel[2], Masoumeh Asadi[3], Mert Yücel[4], Dilara Yanık[5], Hakan Demirhindi[6], Burak Mete[6], Esra Doğan Mete[7]

[1]*Mersin University Faculty of Medicine, Department of Family Medicine, Mersin, Türkiye*
[2]*Çukurova University Faculty of Medicine, Department of Pediatrics, Adana, Türkiye*
[3]*Atatürk University Research Hospital, Department of Gynecology and Obstetrics, Erzurum, Türkiye*
[4]*İslahiye State Hospital, Clinic of Emergency Medicine, Gaziantep, Türkiye*
[5]*Çukurova University Faculty of Medicine, Department of Chest Surgery, Adana, Türkiye*
[6]*Çukurova University Faculty of Medicine, Department of Public Health, Adana, Türkiye*
[7]*Çukurova University Faculty of Medicine, Department of Child and Adolescent Psychiatry, Adana, Türkiye*

Abstract

Objective: Good sleep quality is an important factor for a healthy life. The aim of this study was to investigate the factors affecting insomnia and daytime sleepiness in adolescents and young adults.

Materials and Methods: This cross-sectional study was conducted on 394 adolescents and young adults aged between 15 to 30 years. Our questionnaire consisted of a sociodemographic section, questions about factors affecting sleep quality, Smartphone addiction scale-short form, Epworth Sleepiness Scale, and Insomnia Severity Index Scale.

Results: The mean age of the 394 participants was 20±3.65 years. Risk factors for insomnia in adolescents and young adults were found to be smoking, caffeine consumption between the hours of 18:00-24:00, pre-sleep eating habits, and possible smartphone addiction. Risk factors for daytime sleepiness included being female, daytime sleeping habits, lack of regular physical activity habits, and possible smartphone addiction. The rates of sleepiness and insomnia were higher in both those under the age of 18 and those with possible smartphone addiction. A weak positive correlation was found between smartphone addiction, daytime sleepiness, and insomnia. Smartphone addiction increased the risk of daytime sleepiness by Odds ratio (OR)=2.652 times and moderate-clinical insomnia severity by OR=2.102 times, while lack of physical activity habit increased daytime sleepiness by OR=1.801 times. Smartphone addiction was found to be a partial mediator of sleepiness.

Öz

Amaç: Uyku kalitesinin iyi olması sağlıklı bir yaşam için önemli bir faktördür. Bu çalışmanın adölesan ve geç yetişkinlerde uykusuzluk ve gündüz uykululuğu üzerindeki etkili olan faktörlerin incelenmesidir.

Gereç ve Yöntem: Bu kesitsel tipteki çalışma 15-30 yaş aralığındaki 394 adölesan ve genç yetişkin üzerinde yapılmıştır. Anket formu; sosyodemografik bölüm, uyku kalitesini etkileyen faktörlerle ilgili sorular, akıllı telefon bağımlılığı ölçeği-kısa form, Epworth Uykululuk Ölçeği ve Uykusuzluk Şiddeti Endeks Ölçeği'nden oluşmaktadır.

Bulgular: Çalışmaya dahil edilen 394 kişinin yaş ortalaması 20±3,65 dir. Adölesan ve genç erişkinlerde uykusuzluk için risk faktörleri; sigara kullanmak, kafein tüketim zamanının 18:00-24:00 saatleri arasında olması, uyku öncesi yeme alışkanlığı ve muhtemel akıllı telefon bağımlılığıdır. Gündüz uykululuğu için risk faktörleri kadın olmak, gündüz uyuma alışkanlığı, düzenli fiziksel aktivite alışkanlığı yokluğu ve muhtemel akıllı telefon bağımlılığıdır. Hem 18 yaşın altındakilerde hem de olası akıllı telefon bağımlılığı olanlarda uykululuk ve uykusuzluk oranlarının daha yüksek olduğu tespit edilmiştir. Akıllı telefon bağımlılığı ile gündüz uykululuğu ve uykusuzluk arasında pozitif yönde zayıf korelasyon olduğu bulunmuştur. Akıllı telefon bağımlılığının gündüz uykuluğu riskini Odds oranı (OR)=2,652 kat, orta-klinik düzeyde uykusuzluk şiddetini OR=2,102 kat, fiziksel aktivite alışkanlığı olmamasının gündüz uykuluğunu OR=1,801 kat artırdığı bulunmuştur. Akıllı telefon bağımlılığının uykululuk üzerinde kısmi mediatör olduğu bulunmuştur.

Address for Correspondence/Yazışma Adresi: Fatma Atun Ütük, MD, Mersin University Faculty of Medicine, Department of Family Medicine, Mersin, Türkiye
E-mail: f.atunutuk@gmail.com **ORCID-ID:** orcid.org/0000-0001-8804-1058
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Conclusion: Smartphone addiction is directly and indirectly associated with sleep problems in adolescents and young adults.
Keywords: Sleep, adolescent, technology addiction

Sonuç: Adölesan ve genç yetişkinlerde akıllı telefon bağımlılığının direkt ve indirekt etkiyle uyku sorunları ile ilişkilidir.
Anahtar Kelimeler: Uyku, adölesan, teknoloji bağımlılığı

Introduction

Sleep is the reversible and partial loss of the organism's communication with the environment. On average, humans spend one-third of their lives sleeping. Sleep is not only a component of daily life; but also a vital necessity that forms the basis of a healthy life in which the body renews itself.[1] Sleep quality has been found to be affected by many factors including diet, physical activity, genetics and environmental factors.[2] Quality sleep holds significant importance for health, and the enduring consequences of inadequate sleep are linked to various severe health conditions such as diabetes, cardiovascular disease, depression, anxiety, heart attack, obesity, and stroke.[3] Additionally, sleep disorders heighten the susceptibility to infectious diseases.[4] An important limitation of research on the relationship between sleep and health is the lack of a clear definition of "good-quality sleep".[5] Sleep quality is usually defined by the individuals themselves. Since everyone has different lifestyles, habits and needs, what makes sleep "good quality" varies greatly.[6] Sleep has a great impact on the health and well-being of children and adolescents. While proper nutrition, physical activity and healthy social relationships improve sleep quality, stress, or irregular sleep-wake patterns, stimulants such as caffeine, nicotine and alcohol have been found to reduce sleep quality in various studies.[7] It has also been shown that nighttime use of screen-based media devices, especially cell phones or television, is associated with negative sleep outcomes such as insufficient sleep duration and poor sleep quality in adolescents.[8] It has been observed that young people have a trend of spending more time daily on online activities using various technological devices (smartphones, tablets, laptops and computers) for various educational and entertainment purposes and this habit may turn into a health risk factor. Some of the problems that occur as a result of problematic technology/internet use are shortened and disorganised sleep, and problems with initiating and ending sleep.[9] Since there is a significant increase in the occurrence of sleep disorders today, it is of great importance to understand the factors affecting sleep quality. The aim of this study was to investigate the effect of factors such as caffeine consumption, smartphone addiction and physical activity on insomnia and daytime sleepiness in adolescents and young adults.

Materials and Methods

This cross-sectional study was conducted in Adana, Türkiye between December 2022 and February 2023 by researchers from Çukurova University Faculty of Medicine Department of Public Health. The population of the study consisted of adolescents and young adults aged 15-30 years living in Adana. The sample size was calculated as 384 with Epi-Info™ ver.7 software[10] with a reference frequency of 50%, a type 1 error of 5% and a confidence interval of 95%, and a design effect of 1. The total number of people reached was 394. Adolescents and young adults living in Adana were reached by convenience sampling method and invited to fill out an online questionnaire prepared with Google™ forms. The online questionnaire was disseminated by Çukurova University Faculty of Medicine intern physicians using the telephone interview technique and telephone messaging application tools after explaining the purpose of the study. Ethical approval was obtained from Çukurova University Faculty of Medicine Non-Interventional Clinical Researches Ethics Committee (approval number: 35, date: 02.12.2022). In the prepared questionnaire form, the purpose of the research was mentioned, stating that the information obtained would be kept confidential and used anonymously for scientific purposes only. The participants who gave consent were allowed to fill in the electronic questionnaire form consisting of sociodemographic information, questions about factors affecting sleep quality, and three scales: Smartphone Addiction Scale-Short form, Epworth Sleepiness Scale and Insomnia Severity Index Scale. Caffeine consumption was classified as ≤200 mg/day; 200.1-400 mg/day and ≥400.1 mg/day.[11]

Smartphone Addiction Scale-Short Form

The Smartphone Addiction Scale-Short Form was developed by Kwon et al.[12] to measure the risk of smartphone addiction in adolescents and its Turkish validity and reliability study was conducted by Noyan et al.[13] in 2015 The scale consists of 10 items and is evaluated on a six-point Likert scale (scored between 1 and 6). The total score varies between 10 and 60. The higher the score obtained from the test, the higher the risk for addiction is predicted. The scale has one factor and no subscales. The cut-off scores were 31 for men and 33 for women referencing the Korean sample by Kwon et al.[12] The internal consistency coefficient (Cronbach's alpha) of the scale calculated to determine the reliability of the scale is 0.867.[13]

Epworth Sleepiness Scale

The Epworth Sleepiness Scale, developed by Johns[14], underwent a Turkish validity and reliability study conducted by Izci et al.[15] This scale was utilized to gauge individuals' levels of sleepiness and displayed a Cronbach's alpha coefficient of 0.86, indicating strong internal consistency. As a straightforward, self-report-based tool, its purpose is to evaluate the likelihood of experiencing sleepiness across eight different daily life scenarios, such as reading in a seated position, watching television, being in public, traveling in a car, napping in the afternoon, engaging in conversation, remaining quietly after lunch without consuming alcohol, and being in a stationary car amidst traffic for a few minutes. With a cut-off score set at >10, it exhibits both high sensitivity and specificity in detecting abnormal daytime sleepiness.

Insomnia Severity Index Scale

The Insomnia Severity Index Scale, developed by Bastien et al.[16] and validated for Turkish use by Boysan et al.[17] in 2010, assesses the severity of insomnia. With a Cronbach's alpha coefficient of 0.79, it demonstrates good internal consistency. This scale comprises seven items on a five-point Likert-type scale, where each item ranges from 0 to 4. The total score spans from 0 to 28, with classifications as follows: 0-7 signifies clinically insignificant insomnia, 8-14 suggests subthreshold insomnia, 15-21 indicates clinically moderate insomnia, and 22-28 represents clinically severe insomnia.

Statistical Analysis

SPSS 20 (IBM-U.S.A.) software was used for data analysis. Qualitative data were given as frequency and percentage; while quantitative data as median and interquartile range. Kolmogorov-Smirnov test was used to test the normality. The data were further analysed using the Mann-Whitney U test, Kruskal-Wallis test, One-Way ANOVA test, chi-square test, logistic regression analysis, and mediation analysis with a $p<0.05$ being considered statistically significant.

Results

The mean age of the 394 participants was 20±3.65 years and <18 years %21.8, among them male-to-female ratio was 38.3% to 61.7%, 95.2% were single, 19.3% smoked cigarettes, 25.1% drank alcohol, 44.2% had high school diploma or lower, 55.8% had bachelor or higher education diploma, 12.4% had chronic physical/mental illness, 11.4% was regular medication user, and 21.6% were active-workers. Regarding the characteristics related to sleep routines, 22.8% of the participants reported having children in their sleeping/living environment, 34.3% having daytime sleeping habits, 32.5% having pre-sleep eating habits, 92.4% having pre-sleep screen exposure, 29.2% using blue screen filters, and 39.6% to have regular physical activity habits. When the characteristics related to caffeine consumption were analysed, 79.7% of them reported that they consume less than 200 mg of caffeine daily, 32.2% consume caffeine-containing food/beverage 1-4 days a week, 42.9% of the participants consume caffeine between 12:00-18:00 hours and 32.5% between 18:00-24:00 hours (Table 1).

It was found that Insomnia Severity Index Scale scores were statistically significantly higher in smokers ($p=0.002$), those consuming caffeine between 18.00-24.00 hours ($p=0.017$), those with pre-sleep eating habits ($p<0.001$), and those with possible smartphone addiction ($p<0.001$). The scores obtained from the Epworth Sleepiness Scale were found to be statistically significantly higher in women ($p=0.020$), people with daytime sleeping habits ($p<0.001$), people who did not engage in regular physical activity ($p<0.001$) and people with possible smartphone addiction ($p<0.001$) (Table 2). In cases where the rates of sleepiness and insomnia are higher in both those under the age of 18 and those who have a possible smartphone addiction. A confounding effect of age was observed in this relationship. Age causes smartphone addiction and its effect on sleepiness to be

Table 1. Participants' sociodemographic characteristics, sleep and daily habits

Characteristics	**Mean ± Standard deviation (Min.-Max.)**
Age	20±3.65 (15-35)
	Frequency (%)
Age	
<18 years	86 (21.8)
≥18 years	308 (78.2)
Sex (n=394)	
Male	151 (38.3)
Female	243 (61.7)
Marital status (n=394)	
Single	375 (95.2)
Married	19 (4.8)
Smoking (n=394)	
Yes	76 (19.3)
No	318 (80.7)
Alcohol consumption (n=394)	
Yes	99 (25.1)
No	295 (74.9)
Monthly income of the family (n=329)	
Income more than expenditure	62 (15.7)
Income equal to expenditure	187 (47.5)
Income less than expenditure	80 (20.3)
Education status	
Diploma of high school and lower	174 (44.2)
Diploma of under- and post-graduate	220 (55.8)
Chronic disease status	
Yes	49 (12.4)
No	345 (87.6)
Regular medication use (n=394)	
Yes	45 (11.4)
No	349 (88.6)
Employment status (n=394)	
Active worker	85 (21.6)
Not active worker	309 (78.4)
Presence of children in sleeping/living area (n=394)	
Yes	90 (22.8)
No	304 (77.2)
Daytime sleep	
Yes	135 (34.3)
No	259 (65.7)
Pre-sleep eating habit (n=394)	
Yes	128 (32.5)
No	266 (67.5)
Screen exposure before sleep	
Yes	364 (92.4)
No	30 (7.6)

Table 1. Continued	
Characteristics	**Mean ± Standard deviation (Min.-Max.)**
Blue screen filter (n=394)	
Yes	115 (29.2)
No	279 (70.8)
Regular physical activity (n=394)	
Yes	156 (39.6)
No	238 (60.4)
Amount of caffeine consumption	
0-200 mg/day	298 (79.7)
200.1-400 mg/day	62 (16.6)
400.1 mg/day and more	14 (3.7)
Caffeine consumption	
Never/rare	60 (15.2)
1-4 days a week	127 (32.2)
5-7 days a week	207 (52.5)
Time of caffeine consumption	
06:00-12:00	88 (22.3)
12:00-18:00	169 (42.9)
18:00-24:00	128 (32.5)
24:00-06:00	9 (2.3)
n: Number of partecipants, Min.-Max.: Minimum-maximum	

0.7% less, and its effect on insomnia to be 0.9% less. (Table 3). Logistic regression analysis to predict the likelihood of daytime sleepiness and insomnia severity was found to be significant (omnibus test p<0.001). Two models were created; daytime sleepiness was the dependent variable in the first model and insomnia severity in the second model. The independent variables of both models were possible smartphone addiction, sex, smoking, alcohol use, pre-sleep screen exposure, blue screen filter use, pre-sleep eating habits, regular physical activity habits, chronic disease comorbidity and regular medication use. Among the variables included in the model, possible smartphone addiction (p<0.001) and lack of regular physical activity (p=0.009) were found to be statistically significant predictors of daytime sleepiness; while possible smartphone addiction was found to be a significant (p=0.014) predictor of insomnia severity. The probability of daytime sleepiness was found to be 2.652 times higher in those with smartphone addiction and 1.801 times higher in those who did not engage in regular physical activity. The risk of moderate-to-clinical insomnia increased 2.102-fold in those with possible smartphone addiction (Table 4). When the partial correlations (controlling for age) between the scores of the Smartphone Addiction Scale, Epworth Sleepiness Scale and Insomnia Severity Index Scale were analysed, it was found that there was a weak positive correlation between smartphone addiction and sleepiness and insomnia (Table 5). In the mediation analysis evaluating the relationship between insomnia, sleepiness and smartphone addiction; smartphone addiction was found to be a direct and indirect predictor of sleepiness. While 86.6% of the effect of smartphone addiction on sleepiness was direct, 13.4% was indirect. Insomnia is an important mediator of sleepiness. Smartphone addiction led to increased insomnia and increased insomnia led to increased sleepiness (Figure 1).

Discussion

Sleep is an important part of health and normal development. Daily activities, individual factors and changes in the environment may affect sleep. In studies conducted so far, it has been found that there are many factors affecting sleep quality.[18] In this study in which we examined the factors affecting sleep quality in adolescents and young adults, the risk factors for insomnia were smoking, caffeine consumption time between 18:00-24:00 hours, pre-sleep eating habits and possible smartphone addiction, while the risk factors for daytime sleepiness were being female, daytime sleeping habit, lack of regular physical activity habit and possible smartphone addiction. It was found in cases where the rates of sleepiness and insomnia are higher in both those under the age of 18 and those who have a possible smartphone addiction, while smartphone addiction increased the risk of daytime sleepiness by 2.652 times, and moderate-to-clinical insomnia severity by 2.102 times. The lack of physical activity habits increased daytime sleepiness by 1.801 times. Smartphone addiction was found to have a direct effect on sleepiness and an indirect effect through increasing insomnia. A weak positive correlation between smartphone addiction and sleepiness or insomnia was also found.

The results of a meta-analysis revealed that smokers have a 1.47 times higher likelihood of encountering sleep-related issues compared to non-smokers.[19] Nicotine, by stimulating cholinergic neurons in the basal forebrain, heightens arousal and alertness. Various forms of nicotine intake-such as patches, pills, or cigarettes-might contribute to sleep disturbances. Regardless of the form, nicotine consumption diminishes total sleep duration, prolongs the time taken to fall asleep, hampers deep and rapid eye movement (REM) sleep stages, and elevates the likelihood of early morning awakening. Consequently,

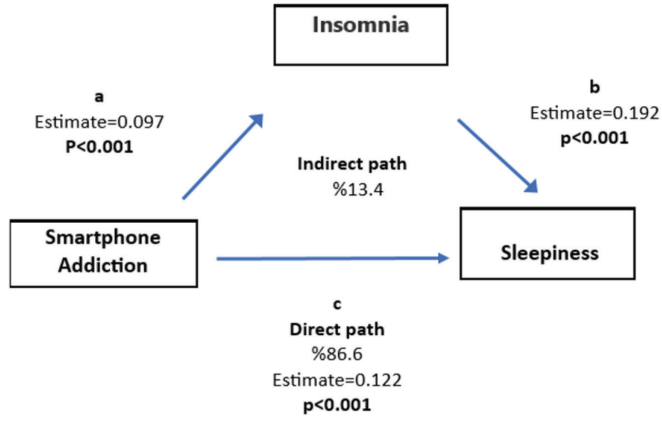

Figure 1. Mediation analaysis path diagram between smartphone addiction and sleepiness with insomnia mediation

Table 2. Association of participants' sociodemographic characteristics and habits with insomnia severity (by Insomnia Severity Index Scale) and daytime sleepiness (by Epworth Sleepiness Scale)

Characteristics		Insomnia Severity Index Scale Scores	p	Epworth Sleepiness Scale Scores	p
		Median (IQR)		Median (IQR)	
Age	<18 years	11 (7)	0.530	10 (7)	0.563
	≥18 years	10 (6)		9 (8)	
Sex	Female	11 (6)	0.250	10 (8)	**0.020***
	Male	9 (6)		8 (8)	
Smoker	Yes	12.5 (7.75)	**0.002***	9 (7.5)	0.682
	No	10 (5)		10 (7.25)	
Alcohol comsumer	Yes	10 (5)	0.957	8 (9)	0.204
	No	10 (6)		10 (7)	
Chronic disease comorbidity	Yes	11 (6.5)	0.990	10 (9)	0.676
	No	10 (6)		9 (7.5)	
Regular medication use	Yes	12 (6)	0.330	10 (9)	0.366
	No	10 (5.5)		9 (8)	
Caffeine consumption	Rare	9 (4.75)	0.169	9 (7)	0.278
	1-4 days a week	10 (6)		9 (8)	
	5-7 days a week	11 (6)		10 (7)	
Time of caffeine consumption	06.00-12.00	10 (6)	**0.017***	10 (8.75)	0.921
	12:00-18:00	10 (5)*		9 (8)	
	18:00-24:00	12 (8)*		9 (7.75)	
	24:00-06:00	11 (12)		9 (8.5)	
Bed partner	Yes	10 (5)	0.872	10 (9)	0.582
	No	10 (6)		9 (7)	
The child where he/she sleeps	Yes	11 (6)	0.519	9 (7.25)	0.818
	No	10 (5.75)		9.5 (7)	
Screen exposure before sleep	Yes	10 (6)	0.433	9 (7)	0.129
	No	9 (5.25)		8 (9.25)	
Blue screen filter use	Yes	10 (6)	0.495	9 (10)	0.986
	No	10 (6)		9 (7)	
Daytime sleeping habits	Yes	10 (6)	0.702	11 (7)	**<0.001***
	No	10 (6)		8 (8)	
Pre-sleep eating habits	Yes	12 (7)	**<0.001***	10 (8)	0.131
	No	9.5 (5.25)		9 (8)	
Regular physical activity	Yes	10 (6.75)	0.806	8 (7)	**<0.001***
	No	10 (6)		11 (7)	
Possible smartphone addiction	Yes	12 (7)	**<0.001***	12 (8.75)	**<0.001***
	No	9 (6)		8 (8)	

*Statistically significant differences,
IQR=Interquartile range

avoiding nicotine is advised to uphold quality sleep.[20] In our study, we similarly observed that smoking escalated the severity of insomnia.

In a systematic review conducted, the impact of smartphone addiction on sleep quality was examined. The study revealed that smartphone addiction leads to poor sleep quality, and this in turn negatively affects the individual's daily life.[21] In a study conducted at a university in Türkiye with university students, more than half of the participants were found to have poor sleep quality, with a smartphone addiction frequency of 34.6%. It was also found that university students with smartphone addiction have a statistically significantly higher risk of having poor sleep quality compared to other students.[22] A large population study in the United Kingdom

Table 3. Association between possible smartphone addiction and daytime sleepiness and insomnia severity

Age			Possible smartphone addiction		p*	p**	Crude OR	Adjusted OR	Counfounding effect
			Yes	No					
			n (%)	n (%)					
<18	Sleepiness	High	18 (41.9)	25 (58.5)	<0.038	<0.001	2.70	2.72	-0.7%
		Low	8 (20.5)	31 (79.5)					
≥18	Sleepiness	High	66 (45.2)	80 (54.8)	<0.001				
		Low	36 (23.4)	118 (76.6)					
<18	Insomnia severity	High	24 (39.3)	37 (60.7)	0.001	0.005	2.23	2.21	-0.9%
		Low	2 (9.5)	19 (90.5)					
≥18	Insomnia severity	High	86 (36.6)	149 (75.4)	0.049				
		Low	16 (24.6)	49 (75.4)					

*Chi-square test, **Cochran's and Mantel-Haenszel test, OR: Odds ratio

Table 4. Logistic regression analysis predicting daytime sleepiness and insomnia severity

Models (Dependent variables)	Model 1 (Sleepiness estimate)			Model 2 (Insomnia estimate)		
Characteristics (Independent variables)	B	p	OR (95% CI)	B (SE)	p	OR (95% CI)
Age ≥18 years (ref.)/<18 years	0.000	0.990	1.000 (0.941-1.062)	-0.050	0.155	0.951 (0.887-1.019)
Possible smartphone addiction None (ref.)/Present	0.975	<0.001*	2.652 (1.675-4.199)	0.743	0.014*	2.102 (1.165-3.792)
Sex Male (ref.)/Female	0.173	0.464	1.189 (0.749-1.887)	0.492	0.072	1.636 (0.957-2.798)
Smoker No (ref.)/Yes	0.205	0.501	1.227 (0.676-2.230)	-0.651	0.093	0.522 (0.244-1.115)
Alcohol user No (ref.)/Yes	0.292	0.305	1.340 (0.766-2.342)	0.350	0.289	1.419 (0.743-2.711)
Screen exposure before sleep No (ref.)/Yes	-0.268	0.514	0.765 (0.342-1.712)	-0.268	0.588	0.765 (0.290-2.016)
Pre-sleep eating habits No (ref.)/Yes	-0.213	0.367	0.808 (0.508-1.284)	-0.204	0.477	0.816 (0.466-1.430)
Regular physical activity habits No (ref.)/Yes	0.589	0.009*	1.801 (1.157-2.806)	0.108	0.684	1.113 (0.663-1.870)
Chronic disease comorbidity No (ref.)/Available	0.211	0.616	1.234 (0.543-2.808)	0.114	0.831	1.121 (0.394-3.189)
Regular medication use No (ref.)/Available	0.207	0.645	1.231 (0.510-2.972)	1.096	0.099	2.993 (0.813-11.024)
	Chi-square (omnibus): 10.236; p<0.001; -2 log likelihood=495.852; Nagelkerke R^2=0.112; n=382			Chi-square (omnibus): 11.577; p=0.006; -2 log likelihood=383.013; Nagelkerke R^2=0.095; n=382		

*Statistically significant differences, SE: Standard error, OR: Odds ratio, CI: Confidence interval

Table 5. Partial Correlations between smartphone addiction and insomnia, sleepiness

		Smartphone Addiction Scale Scores	Epworth Sleepiness Scale Scores	Insomnia Severity Index Scale Scores
Smartphone Addiction Scores	r	1.000	0.331*	0.247*
	p		<0.001	<0.001
Epworth Sleepiness Scale	r		1.000	0.242*
	p			<0.001
Insomnia Severity Index Scale	r			1.000
	p			.

*Statistically significant differences, controlling for "age"

examining the relationship between smartphone addiction and poor sleep quality found that approximately 61.6% of participants reported poor sleep, and 68.7% of those with smartphone addiction had poor sleep quality.[23] Commonly consumed stimulants like caffeine, prevalent in coffee, tea, chocolate, energy drinks, and sodas, are widely used even by children and adolescents.[24] Having four cups of brewed coffee (equivalent to 400 mg caffeine) up to 6 hours before bedtime notably disrupts sleep quality.[25] Even consuming caffeine in the morning can shift the REM phase of sleep to earlier nighttime hours.[25] In a study involving 309 children aged 8 to 12, the impact of sleep quality, caffeine intake, and daytime behaviors was explored. Caffeine consumption was linked to poorer sleep quality, increased morning fatigue, and disrupted sleep routines. Among children, the primary sources of caffeine were reported to be coffee and tea (41%) and carbonated drinks (40%).[26] Notably, our study observed higher insomnia severity among individuals consuming caffeinated beverages between 6:00 PM and midnight. Intake during these hours could delay the onset of sleep.

Research exploring the link between physical activity and sleep quality has presented varied findings. Some studies suggest that individuals engaged in physical activity experience better sleep quality compared to those who are less active.[27,28] However, other research indicates that moderate physical activity doesn't notably enhance sleep duration, habitual sleep efficiency, or reduce sleep disturbances.[28] A meta-analysis revealed that the overall impact of physical activity on sleep quality wasn't substantial. It did indicate that physical activity significantly influenced the sleep quality of children, middle-aged, and elderly individuals, but didn't notably affect the sleep quality of young people. Additionally, moderate to low-intensity physical activity was linked to improved sleep quality, whereas high-intensity physical activity didn't demonstrate a significant effect.[29] Interestingly, our study revealed that lower physical activity levels increased the likelihood of daytime sleepiness. This association could potentially be attributed to improved physical resilience in individuals who engaged in regular activity, leading to them feeling more energized the following day after exercising. Although delays in sleep patterns were expected to occur as part of the physiological impact of adolescent development and the resulting changes in the circadian regulation of sleep, lifestyle changes resulting from increased access and use of screen-based media devices were shown to contribute greatly to adolescents' poor sleep hygiene.[30] In a study among 323 university students, high levels of smartphone addiction were associated with poorer sleep quality.[31] In a study examining the relationship between smartphone use and sleep quality based on 4-month sleep data collected from 75 participants' sleep trackers and smartphone usage data collected from their personal devices; smartphone use in bed was shown to increase sleep latency and increase mean heart rate. These results suggested that smartphone use in bed worsened both rest quality and sleep quality. Smartphone use may also lead to the shortening of total sleep time by increasing awake time during the night.[32] In a cross-sectional study conducted among 9846 adolescents in Norway, 90% of the participants reported using digital devices in the last hour before lights out. This was found to be associated with delayed sleep onset and shorter sleep duration.[33]

Study Limitations

The limitations of our study include the fact that the population of the study consists only of adolescents and young adults living in Adana, the use of non-probability sampling method, the use of online surveys and the fact that the data are based on self-reports. Due to the use of non-probability sampling method, the representativeness of the sample was low and there was a selection bias. Using an online survey may have caused information bias in participants' understanding and interpretation of the questions.

Conclusion

According to the results of our study, in adolescents and young adults, possible smartphone addiction, smoking, caffeine consumption between 18:00-24:00, and pre-sleep eating habits were associated with insomnia, while possible smartphone addiction, being female, daytime sleeping habits, and lack of regular physical activity habits were associated with daytime sleepiness. Smartphone addiction was an important risk factor for both conditions. We recommend that adolescents and young adults should be educated about the importance of sleep in terms of health, and efforts should be made to increase awareness of smartphone, cigarette and caffeine addiction and physical activity. More emphasis should be placed on measures that can be taken and activities that can be performed for each condition that worsens sleep quality.

Ethics

Ethics Committee Approval: Ethical approval was obtained from Çukurova University Faculty of Medicine Non-Interventional Clinical Researches Ethics Committee (approval number: 35, date: 02.12.2022).

Informed Consent: The participants who gave consent were allowed to fill in the electronic questionnaire form consisting of sociodemographic information, questions about factors affecting sleep quality, and three scales.

Footnotes

Authorship Contributions

Concept: F.A.Ü., O.Y., M.A., M.Y., D.Y., E.D.M., Design: F.A.Ü., O.Y., M.A., M.Y., D.Y., E.D.M., Data Collection or Processing: F.A.Ü., O.Y., M.A., M.Y., D.Y., E.D.M., Analysis or Interpretation: F.A.Ü., O.Y., M.A., M.Y., D.Y., H.D., B.M., E.D.M., Literature Search: F.A.Ü., O.Y., M.A., M.Y., D.Y., H.D., B.M., E.D.M., Writing: F.A.Ü., O.Y., M.A., M.Y., D.Y., H.D., B.M., E.D.M.

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HLA Subtype Distribution in Central Disorders of Hypersomnolence and Relationship of HLA Typing with Clinical and Electrophysiological Findings in Patients with Excessive Daytime Sleepiness

Hipersomnolansın Santral Bozukluklarında HLA Alttiplerinin Dağılımı ve Gündüz Aşırı Uykululuk Yakınması Olan Hastalarda HLA Tiplendirmesinin Klinik ve Elektrofizyolojik Bulgularla İlişkisi

Merve Aktan Süzgün, Büşra Zeybek*, Utku Oğan Akyıldız*, Erkan Yılmaz**, Derya Karadeniz, Gülçin Benbir Şenel

İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Department of Neurology, Sleep and Disorders Unit, İstanbul, Türkiye
**Adnan Menderes University Faculty of Medicine, Department of Neurology, Aydın, Türkiye*
***İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Department of Organ Transplantation, HLA Laboratory, İstanbul, Türkiye*

Abstract

Objective: Human leukocyte antigens (HLA antigens) provides important data on differential diagnosis of central disorders of hypersomnolence (CDH). While the relation of narcolepsy type-1 (NT1) with autoimmunity has been well-characterized by HLAs, the literature on other types of CDH is insufficient. This study aims to reveal HLA antigens subtypes in the whole spectrum of CDH, and explore their association with objective sleep measures.

Materials and Methods: Patients who complained of excessive daytime sleepiness and underwent HLA antigens typing were analyzed. Demographics, anthropometrics, sleep-related complaints, polysomnography, and multiple sleep latency test parameters were documented. The frequency of HLA antigens phenotypes was compared between CDH subtypes, and it was analyzed for sleep-related clinical and electrophysiological features.

Results: Eighty-two participants were included [median age: 37.0 (17.0-66.0), 62.5% female], of whom 80 reached a final diagnosis of hypersomnolence (31 narcolepsy, 25 non-narcolepsy CDH and 24 non-central hypersomnia). The most common HLA antigens subtype in the whole population was DQB1*03 (95.1%). DQB1*06 was more frequent in NT1 compared to other groups (p<0.001), while DQB1*02 was more commonly seen in non-narcolepsy cases (p<0.001). The clinical and polysomnographic features that were specific to narcolepsy were more frequent in the presence of DQB1*06 and, in the absence of DQB1*02 and DQB1*05.

Öz

Amaç: İnsan lökosit antijeni (HLA) hipersomnolansın santral bozukluklarının tanısal değerlendirilmesinde önemli veriler sunmaktadır. Narkolepsi tip 1 (NT1) ile otoimmünite ilişkisi HLA tiplendirmesi üzerinden halihazırda gösterilmişken, hipersomnolansın santral bozukluklarının diğer türleriyle ilgili veriler sınırlıdır. Bu çalışmanın amacı, hipersomnolansın santral bozuklukları spektrumundaki HLA alt tiplerini ve bu alt tiplerin objektif uyku parametreleriyle ilişkisini araştırmaktır.

Gereç ve Yöntem: Çalışmaya gündüz aşırı gündüz uykululuk şikayetiyle uyku laboratuvarına başvuran ve HLA tiplendirmesi yapılan hastalar dahil edilmiştir. Hastaların demografik bilgileri, antropometrik verileri, uyku yakınmaları, polisomnografi ve çoklu uyku latans testi parametreleri kaydedilmiştir. HLA alt tiplerinin sıklığı farklı hipersomni alt grupları arasında karşılaştırılmış ve hastaların klinik ve elektrofizyolojik verileriyle birlikte analiz edilmiştir.

Bulgular: Çalışmaya 82 katılımcı dahil edilmiş [ortanca yaş: 37,0 (17,0-66,0), %62,5 kadın], bu hastalardan 80'i nihai tanı alabilmiştir (31 narkolepsi, 25 narkolepsi-dışı santral hipersomni ve 24 santral-olmayan hipersomni). Tüm çalışma popülasyonunda en yaygın HLA alt tipi DQB1*03 olarak saptanmıştır (%95,1). NT1 olgularında diğer gruplara kıyasla DQB1*06 anlamlı olarak daha sık görülürken (p<0,001), DQB1*02 ise narkolepsi-dışı hipersomnilerde daha yaygındır (p<0,001). Narkolepsiye özgü klinik ve polisomnografik özellikler DQB1*06'nın varlığında ve DQB1*02 ile DQB1*05'in yokluğunda daha sık pozitif bulunmuştur.

Address for Correspondence/Yazışma Adresi: Merve Aktan Süzgün MD, İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Department of Neurology, Sleep and Disorders Unit, İstanbul, Türkiye
E-mail: aktansuzgunmerve@gmail.com **ORCID-ID:** orcid.org/0000-0002-0332-8453
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Conclusion: This study not only showed the power of DQB1*06 to differentiate NT1 from non-NT1, in line with existing literature; also revealed importance of DQB1*03 as a potent common marker of hypersomnolence and DQB1*02 as more frequent in non-narcolepsy CDH. These observations will enable more comprehensive analyses as the study population increases and diversifies.

Keywords: Disorders of excessive somnolence, human leukocyte antigen, HLA antigens, autoimmunity

Sonuç: Bu çalışma mevcut literatür verileriyle uyumlu olarak DQB1*06'nın NT1 olgularını, NT1-dışı hipersomnilerden ayırt etme gücünü göstermiştir. Ayrıca hipersomni için güçlü bir ortak belirteç olarak DQB1*03'ün ve narkolepsi-dışı hipersomnilerde daha sık görülen DQB1*02'nin tanısal önemini ortaya koymuştur. Bu gözlemler, çalışma popülasyonu ve çeşitliliği arttıkça daha kapsamlı analizlere olanak tanıyacaktır.

Anahtar Kelimeler: Aşırı uyku halinin bozuklukları, insan lökositantijeni (HLA) antijenleri, otoimmunite

Introduction

Central disorders of hypersomnolence (CDH) are a group of sleep disorders characterised by excessive daytime sleepiness (EDS), which refers to being sleepy during the day when one should remain awake and alert, and/or hypersomnia, which refers to increased sleep duration at night.[1] An estimated 5% of the general population suffers from EDS and/or hypersomnolence, and in about 1-2% of the population, EDS/hypersomnolence is due to central causes, so-called CDH.[2] In the latest version of the International Classification of Sleep Disorders published in 2023 (ICSD-3-TR), CDH is categorized under eight subheadings.[3] These are narcolepsy type-1 (NT1), narcolepsy type-2 (NT2), idiopathic hypersomnia (IH), Kleine-Levin syndrome, hypersomnia due to a medical disorder, hypersomnia due to a medication or substance, hypersomnia due to a mental disorder and insufficient sleep syndrome.[3] The diagnostic tools specified in the diagnostic criteria for differentiating the subtypes of CDH from each other and from other sleep disorders are mainly based on clinical history/anamnesis, full-night polysomnography (PSG) and multiple sleep latency test (MSLT), and for selected cases as an optional tool, the measurement of hypocretin level in cerebrospinal fluid. However, in clinical practice, various other diagnostic instruments, e.g. subjective sleep assessment scales, ambulatory sleep monitoring, and human leukocyte antigens (HLA antigens) typing are frequently used in the differential diagnosis processes.[4]

The close association of the HLA antigens system, which comprises a gene complex responsible for encoding cell surface proteins that regulate immune system functions,[5] with the pathogenesis of NT1 has already been shown through large-scale population studies.[6,7] Among HLA antigens class II genes, DRB1*15:01, DQA1*01:02 and DQB1*06:02 are the most common disease-associated haplotypes in narcolepsy.[8] More than 85% of patients with NT1 have HLA antigens DQB1*0602, often in combination with HLA antigens DRB1*1501, while only around 40% of the patients having narcolepsy without cataplexy have HLA antigens DQB1*0602 suggesting a strong genetic susceptibility for autoimmunity against hypocretin-producing neurons in NT1, whereas an increased pathogenetic heterogeneity in NT2.[9] Demonstration of these HLA antigens subtypes not only provides support for confirming the diagnosis of NT1 but may also predict the severity of clinical symptoms; for example, DQB1*0602 positivity has already been shown to be associated with increased frequency of naps and risk of accidents due to daytime sleepiness in NT1.[10] Therefore, HLA antigens typing has important implications in the clinical practice of narcolepsy. However, HLA antigens subtypes that may be used in the differential diagnosis of hypersomnolence subtypes apart from NT1, including all central and non-central causes of hypersomnolence, have not yet been demonstrated. This study aimed to document the relationships between HLA antigens class II genes and both the type of hypersomnolence diagnoses and the sleep-related clinical and electrophysiological features in a wide spectrum of patients presenting with EDS and/or hypersomnia. Based on the hypothesis that there are specific HLA antigens patterns encompassing different types of hypersomnolence, this study will provide a perspective on the associations between HLA antigens subtypes and various phenotypes of hypersomnolence with their specific clinical and electrophysiological findings.

Materials and Methods

This study was conducted with a retrospective design in the sleep and disorders units of İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine and Aydın Adnan Menderes University, Faculty of Medicine, after the approval of the Ethics Committee of the İstanbul University-Cerrahpaşa (approval number: 15.11.2023-837477, date: 15.11.2023).

Participants

Among the patients who applied to the sleep clinic with complaints of EDS and/or hypersomnia in the last two years and who underwent PSG and MSLT examinations due to these complaints, those whose HLA antigens typing data could be accessed were retrospectively included in the study. Patients with systemic or neurologic diseases or comorbid sleep disorders that may cause EDS and/or hypersomnia were excluded from the study. Informed consent had been obtained from all the study participants to get an allowance to investigate past medical records.

Diagnostic Work-up for EDS/Hypersomnolence

After the recording of routine demographic and anthropometric parameters, baseline Epworth Sleepiness scale scores[11] of all study participants at the time of the hypersomnolence diagnosis were documented. Also, the presence of narcolepsy-specific clinical complaints, e.g. cataplexy, hypnogogic/hypnapompic hallucinations and sleep paralysis and a history of REM (rapid eye movements) sleep behaviour disorder (RBD) attacks, were noted. All participants were evaluated with a full-night video-PSG at Sleep Laboratory [American Academy of Sleep Medicine (AASM) type 1] and MSLT after the PSG night. The recording and scoring of sleep and associated events were performed

according to the on-time AASM Manual for the Scoring of Sleep and Associated Events.[12,13] The following parameters were evaluated in full-night PSG: Total sleep time (minutes), sleep efficiency (percent), wakefulness after sleep onset (WASO, minutes), sleep and REM-sleep latency (minutes), distribution of sleep stages N1, N2, N3 and REM (percent), apnea-hypopnea index (AHI/hour), periodic limb movements index (/hour), REM sleep without atonia (RWA, present/absent), sleep onset REM (SOREM, present/absent); whereas sleep latency and number of SOREMs were documented from MSLT recordings. According to the results of subjective and objective sleep assessment, and in line with the diagnostic criteria in the 3rd edition-text revision of the International classification of sleep disorders,[3] the study participants were grouped as (1) NT1, (2) NT2, (3) IH, (4) other (5) CDH residual hypersomnia after positive airway pressure therapy in obstructive sleep apnea (RH) and (6) non-central disorders of hypersomnolence (non-CDH), which was characterised by the presence of subjective sleepiness, but lack of any objective evidence of CDH or insufficient fulfil of CDH diagnostic criteria.

HLA Antigens Typing

The isolation of the DNA from blood samples was conducted using BioRobot EZ1 and an EZ-DNA extraction kit (Qiagen-Germany). HLA antigens typing at 2 digits of HLA-A, HLA-B, HLA-C and HLA-DQ alleles was determined with Luminex 100/200 Instrument that uses sequence-specific oligonucleotide probes bound to color-coded microbeads for identification of HLA antigens alleles (Luminex Corp., USA). LIFECODES SSO Typing kits were used for the HLA antigens typing (Lifecodes, Immucor, Germany). These tests are reverse sequence-specific oligonucleotide DNA typing assays in which SSO (Sequence-Specific Oligonucleotide) probes and color-coded microspheres are used in order to identify HLA antigens alleles. Polymerase chain reaction mixture included 15 µL of the Lifecodes Master Mix (Immucor), 200 ng of genomic DNA, and 2.5 U Taq polymerase for a 50 µL final volume. The patterns were compared with the common and well-documented HLA antigens alleles Probe Hit Tables (IMGT/HLA antigens Sequence Database Release 3.11.0) by using the MatchIT DNA program (Immucor). Further details regarding the molecular cycles and sample processing were presented in a previous article; see Kocak et al.[14]

Statistical Analysis

IBM SPSS Statistics Data Editor 26.0 and RStudio IDE 2022.07.0 were used for the statistical analysis and data visualization. Categorical data was shown as n (%), whereas continuous data was shown as median (minimum-maximum). After determining the non-parametric distribution of the dataset by the Shapiro-Wilk test, the chi-square test was used for the categorical data, and the Mann-Whitney-U test and Kruskal-Wallis tests were used for the continuous data to perform group comparisons. Post-hoc analysis was performed using a pairwise Z-test for categorical data and a Dunn test for continuous data. A p-value equal to or lower than 0.05 was accepted as statistically significant. Based on the sample size calculation with G*power 3.1.9.7 with reference to the study by Han et al.[15] comparing the incidence of DQB1*0602 carriage in NT1 and NT2 cases, when type I error (α)=0.05, power (1-β)=0.95, effect size d=0.66 and the alternative hypothesis is two-way, it was planned to include at least 75 participants to reach a significant difference between the groups and a total of 82 participants were included. Firstly, the HLA antigens phenotype distribution among the main groups and subgroups of hypersomnolence diagnosis were compared. Then, the objective sleep assessment parameters were compared among the HLA antigens positive vs negative groups for certain and most frequent HLA antigens phenotypes, overall, to reveal the relationship between HLA antigens phenotypes and different types of hypersomnolence both regarding the final diagnoses and their objective sleep characteristics.

Results

Eighty-two participants were included to the study, with the median age of 37.0 (17.0-66.0) and a female dominance 62.5%, of which 80 reached a final diagnosis of hypersomnolence. The general diagnosis distribution was 31 patients with narcolepsy, 25 patients with non-narcolepsy CDH and 24 patients with non-CDH. More specifically, NT1 group composed of 25 patients, NT2 group 6 patients, IH group 14 patients, other CDH group 3 patients, RH group 6 patients and non-CDH 24 patients. In the whole group, the median sleep latency in nighttime sleep was 8.4 minutes with 25.3% SOREM, whereas the median sleep latency in MSLT was 6.8 minutes with a median of 0.5 SOREM count. The most common HLA antigens subtype in the whole population was DQB1*03 (95.1%), followed by DQB1*05 (76.5%) and DQA1*01 (73.3%), see Table 1. The most common HLA antigens subtype, DQB1*03, was also the most evenly distributed allel among different types of hypersomnolence diagnosis (92.0% in narcolepsy, 95.0% in non-narcolepsy CDH and 100% in non-CDH group), suggests

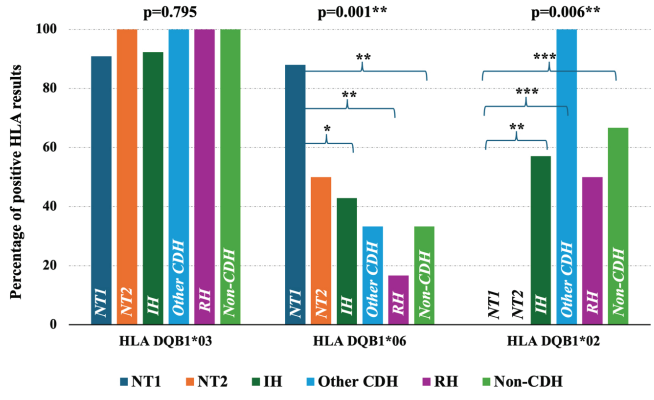

Figure 1. The percentage distribution of HLA DQB1*03, HLA DQB1*06 and HLA DQB1*02 positive patients, respectively, categorized by different types of hypersomnolence.
CDH: Central disorders of hypersomnolence, IH: Idiopathic hypersomnia, NT1: Narcolepsy type-1, NT2: Narcolepsy type-2, RH: Residual hypersomnia

Table 1. The comparison of different HLA phenotypes among (1) general groups, and (2) subgroups of hypersomnolence diagnosis

HLA Subtypes and general distribution			Hypersomnolence groups					Hypersomnolence subgroups						
HLA phenotypes positivity	n of HLA results	n of positive HLA results	Overall (n=80)	Narcolepsy (n=31)	Non-narcolep y CDH (n=25)	Non-CDH hypersomnia (n=24)	Test statistics	p	NT1 (n=25)	NT2 (n=6)	IH (n=14)	Other CDH (n=3)	RH (n=6)	Non-CDH (n=24)	Test statistics	p
DQB1*03 (%)	61	58	95.1	92.0	95.0	100.0	1.336	0.513	90.9	100.0	92.3	100.0	100.0	100.0	2.378	0.795
DQB1*05 (%)	34	26	76.5	60.0	90.9	83.3	3.507	0.173	57.1	100.0	83.3	100.0	100.0	83.3	4.825	0.438
DQA1*01 (%)	15	11	73.3	72.7	66.7	100.0	0.434	0.805	72.7	0	50.0	0	100.0	100.0	1.286	0.732
DRB1*04 (%)	13	7	53.8	63.6	0	0	2.758	0.252	63.6	0	0	0	0	0	2.758	0.252
DQA1*03 (%)	15	8	53.3	63.6	33.3	0	2.094	0.351	63.6	0	0	0	100.0	0	4.773	0.189
DQB1*06 (%)	78	41	52.6	**80.6a**	**34.8b**	**33.3b**	**17.191**	**<0.001*** **	**88.0a**	**50.0a,b**	**42.9b**	**33.3a,b**	**16.7b**	**33.3b**	**20.240**	**0.001****
DRB1*15 (%)	12	6	50.0	40.0	100.0	100.0	2.400	0.301	40.0	0	100.0	0	0	100.0	2.400	0.301
DQA1*05 (%)	15	6	40.0	36.4	33.3	100.0	1.616	0.446	36.4	0	50.0	0	0	100.0	2.311	0.510
DRB1*11 (%)	13	5	38.5	36.4	0	100.0	2.245	0.325	36.4	0	0	0	0	38.5	2.245	0.325
DQB1*02 (%)	38	14	36.8	**0a**	**60.0b**	**66.7b**	**15.459**	**<0.001*** **	**0a**	**0a,b**	**57.1b**	**100.0b**	**50.0a,b**	**66.7b**	**16.248**	**0.006****
DRB1*01 (%)	13	4	30.8	36.4	0	0	1.051	0.591	36.4	0	0	0	0	0	1.051	0.591
DRB1*14 (%)	13	2	15.4	18.2	0	0	0.430	0.807	18.2	0	0	0	0	0	0.430	0.807
DRB1*16 (%)	13	1	7.7	0	100.0	0			0	0	100.0	0	0	0		
DQA1*02 (%)	15	1	6.7	0	33.3	0			0	0	50.0	0	0	0		
DQB1*04 (%)	16	1	6.3	0	0	50.0			0	0	0	0	0	50.0		
DQB1*08 (%)	21	0	0.0	0	0	0			0	0	0	0	0	0		

The values that were designated with different letter in each row were significantly different from each other in pairwise group comparison. Chi-square test was used for categorical group comparisons of percentages. Significant results was demonstrated in bold. p<0.05*, p<0.01**, p<0.001***,

CDH: Central disorders of hypersomnolence, HLA: Human leukocyte antigen, IH: Idiopathic hypersomnia, NT1: Narcolepsy type-1, NT2: Narcolepsy type-2, RH: Residual hypersomnia

being a common marker of hypersomnolence. DQB1*06 was significantly more frequent in NT1 compared to IH, RH and non-CDH groups (p=0.001), whereas the presence of DQB1*02 subtype in IH, other-CDH and non-CDH groups, compared to NT1 was statistically significant (p=0.006), see Figure 1. In other words, the high frequency of DQB1*6 and the absence of DQB1*02 in narcolepsy cases were significantly different from non-narcolepsy CDH and non-CDH groups (p<0.001). Regarding the relationship between subjective or objective sleep assessment parameters and HLA antigens subtype distribution, the most prominent finding was that clinical and polysomnographical features which were known to be specific for narcolepsy were more frequent in presence of DQB1*06 and, in absence of DQB1*05 and DQB1*02. REM latency in nighttime PSG was shorter in DQB1*06 positive subjects compared to negative ones (p=0.002) and longer in DQB1*05 positive subjects compared to negative ones (p=0.017). The percent of positive SOREM in nighttime sleep was higher in DQB1*06 positive subjects compared to negative ones and in DQB1*05 and DQB1*02 negative subjects compared to positive ones (p=0.001). The same group differences were also observed for the SOREM count in MSLT (Table 2). Sleep latency in MSLT was significantly shorter DQB1*06 positive subjects compared to negative ones (p=0.007) and longer in DQB1*02 positive subjects compared to negative ones (p=0.002). The clinical parameters, that were questioned specifically as the narcolepsy-specific complaints like cataplexy, sleep paralysis and hypnogogic/hypnapompic hallucinations were more frequent in DQB1*06 positive and DQB1*02-DQB1*05 negative subjects. The comparison analysis, conducted for the positivity vs. negativity of other HLA-DQ and HLA-DR phenotypes listed in Table 1, in relation to subjective or objective sleep assessment parameters did not reveal any significant difference.

Discussion

This study demonstrated the reliability of DQB1*06 to differentiate narcolepsy, more specifically NT1, from other types of hypersomnolences in line with existing literature. Moreover, it revealed a subtype as DQB1*03, which was similarly distributed in different types of hypersomnolence as a potent common marker of EDS/hypersomnia. Last but not least, DQB1*02 and DQB1*05 subtypes

Table 2. The comparison of demographical and sleep-related features among different HLA phenotypes (HLA DQB1*06, *05 and *02) in all study population

			HLA DQB1*06				HLA DQB1*05				HLA DQB1*02			
	Overall (n=82)	**Test type**	**HLA DQB1*06 (+), n=41**	**HLA DQB1*06 (-), n=37**	**Test statistics**	**p**	**HLA DQB1*05 (+), n=26**	**HLA DQB1*05 (-), n=8**	**Test statistics**	**p**	**HLA DQB1*02 (+), n=14**	**HLA DQB1*02 (-), n=24**	**Test statistics**	**p**
Age, years	37.0 (17.0-66.0)	Mann-Whitney-U	37.0 (18.0-57.0)	37.0 (17.0-66.0)	802.0	0.981	39.0 (17.0-57.0)	38.0 (22.0-50.0)	118.0	0.591	35.0 (18.0-52.0)	36.0 (20.0-57.0)	191.0	0.501
Gender, female, %	62.5	Chi-square	68.3	56.4	0.750	0.386	61.5	62.5	0.002	0.961	28.6a	66.7b	5.147	0.023*
Body-mass index, kg/m^2	27.3 (15.6-47.6)	Mann-Whitney-U	27.8 (15.6-44.1)	26.7 (17.5-47.6)	883.0	0.422	27.0 (17.5-39.5)	29.7 (22.3-44.1)	83.0	0.413	27.7 (22.8-36.0)	27.7 (19.4-44.1)	174.0	0.870
Total sleep time, minutes	420.5 (261.0-552.0)	Mann-Whitney-U	435.7 (299.5-545.5)	412.0 (261.0-552.0)	894.5	0.261	429.0 (329.5-545.5)	433.5 (315.0-506.0)	107.5	0.889	410.5 (327.0-541.0)	434.0 (299.5-509.0)	132.5	0.287
Sleep latency, minutes	8.4 (0-240.0)	Mann-Whitney-U	6.9 (0-240.0)	10.4 (0.2-90.0)	649.0	0.199	7.5 (0.2-86.0)	8.9 (0-59.3)	104.5	1.000	17.5 (4.4)	11.0 (0-240.0)	203.5	0.287
REM latency, minutes	88.7 (0-469.3)	Mann-Whitney-U	67.0 (0-322.0)	115.9 (1.3-469.3)	444.5	0.002**	101.9 (0-285.0)	8.7 (2.0-119.3)	162.0	0.017*	83.5 (3.0-278.5)	61.5 (0-391.0)	209.0	0.223
WASO, minutes	61.1 (6.1-479.1)	Mann-Whitney-U	62.9 (6.1-479.1)	59.5 (54.2-97.8)	713.0	0.511	52.6 (16.1-136.5)	52.8 (6.1-84.0)	117.0	0.618	64.7 (14.8-158.7)	60.7 (6.1-479.1)	201.0	0.330
Sleep efficiency, %	88.2 (46.6-97.8)	Mann-Whitney-U	88.2 (46.6-96.5)	87.8 (54.2-97.8)	860.0	0.433	89.2 (72.3-96.5)	89.9 (70.3-96.4)	101.5	0.921	87.4 (70.6-95.7)	89.0 (46.6-96.5)	143.5	0.463
RWA, yes, %	31.6	Chi-square	40.0	23.1	1.891	0.169	30.8	37.5	0.125	0.724	21.4	25.0	0.062	0.803
RBD, yes, %	17.5	Chi-square	19.5	15.4	0.037	0.848	11.5	37.5	2.506	0.113	14.3	16.7	0.038	0.846
SOREM in nighttime sleep, yes, %	25.3	Chi-square	42.5a	7.7b	13.272	0.001**	23.1a	87.5b	11.115	0.001**	0.0	54.2	11.527	0.001**
Sleep latency in MSLT, minutes	6.8 (0.5-19.4)	Mann-Whitney-U	4.7 (0.5-17.6)	8.2 (0.7-19.4)	464.0	0.007**	5.2 (0.8-19.4)	2.8 (0.8-12.0)	122.5	0.254	10.1 (1.1-15.9)	4.4 (0.8-14.4)	248.0	0.002**
SOREM count in MSLT, n	0.5 (0-5.0)	Mann-Whitney-U	2.0 (0-5.0)	0 (0-5.0)	1084.5	<0.001***	0.5 (0-4.0)	3.0 (0-5.0)	42.5	0.018*	0 (0-4.0)	2.0 (0-5.0)	62.0	0.002**
Cataplexy, yes, %	30.5	Chi-square	53.7a	7.7b	17.576	<0.001***	30.8a	75.0b	4.941	0.026*	0.0	54.2	11.527	0.001**
Sleep paralysis, yes, %	46.3	Chi-square	61.0a	30.8b	7.336	0.007**	46.2a	87.5b	4.242	0.039*	35.7	66.7	3.426	0.064
Hallucinations, yes, %	37.5	Chi-square	51.2a	23.1b	6.754	0.009**	50.0	75.0	1.551	0.213	28.6	62.5	4.071	0.044*

The values that were designated with different letter in each row were significantly different from each other in pairwise group comparison. Chi-square was used for categorical variables, Mann-Whitney-U was used for continous variables. Significant results was demonstrated in bold. p<0.05*, p<0.01**, p<0.001***,

HLA: Human leukocyte antigen, MSLT: Multiple sleep latency test, RBD: REM sleep behaviour disorder, RWA: REM sleep without atonia, SOREM: Sleep onset REM, WASO: Wakefullness after sleep onset

were found to be less associated with narcolepsy and its clinical or polysomnographical features, rather more related other-CDH and non-CDH groups. The autoimmune nature of NT1 was well documented in the literature[16] via (1) the hypocretinergic / orexinergic neural loss due to a predominantly T-cell mediated inflammatory infiltration, (2) consequently decreased hypocretin/orexin levels in cerebrospinal fluid, (3) significant temporal and causal association with certain pre-morbid infections or vaccinations,[17,18] especially documented during H1N1 pandemic and H1N1 vaccination, and (4) HLADQB1*0602 phenotype positivity up to 98% of NT1, including both idiopathic[19] and vaccine-triggered cases,[20] which is also an important data about the genetic predisposition of NT1.[21] Despite a large body of evidence for immune and genetic background of NT1, the similar pathogenetic mechanisms could not be shown in NT2 or IH so far. Although it is known that HLADQB1*0602 positivity can be detected up to 40-60% of patients with NT2 and also 5-30% of normal healthy population, some authors claim that it may be a clue for conversion to NT1 in initially diagnosed as NT2 or IH.[22] The unresolved problem is whether this must be regarded as a disease progression, that suggest a continuous pathological spectrum from NT2-IH to NT1, or just as an initial misdiagnosis due to the partial lack of characteristic symptoms of NT1, like cataplexy. The roots of this question extend to the absence of established immune or genetic mechanisms related to the hypersomnolence subtypes apart from NT1. A recent study performed by Gool et al.[23] investigated the potential immunological triggers for NT2 and IH in a large cohort, and it was revealed that infection and/or vaccination were reported before the development of NT2 and IH in 36/71 individuals (50.7%) and infections were mainly caused by Ebstein-Barr virus, followed by other respiratory infections. On the other hand, the well-defined infectious triggers of NT1, flu and influenza vaccination were uncommon in NT2 and IH.[23] Surprisingly, 80% of patients with NT2 in this cohort were HLA antigens DQB1*0602 positive.[23] When this evidence about the possible immunological triggers and genetic predisposition in NT2 and IH was taken into account with the data presented in this article about the shared HLA antigens phenotypes among non-NT1 hypersomnolence subtypes, revealing the need to extend this work in broader analyses of HLA antigens system and its interrelationship with the systemic immunological markers.

Study Limitations

This study has certain limitations. (1) The interpretation of the DQB1*03 subtype as a common marker of hypersomnolence with similar distribution among different types of diagnosis needs to be grounded by the healthy population carrier frequencies. (2) To manage the discrimination of different CDH categories from each other by HLA antigens typing, the study population must be larger enough to subcategorise each CDH defined in ICSD-3-TR. (3) More comprehensive implications of HLA antigens typing on the differential diagnosis of EDS/hypersomnolence require the analysis of each of the class I (A, B, C) and class II alleles of HLA antigens (DR, DQ, DP) in all study subjects, that was not possible within the scope of this study. (4) The lack of cerebrospinal fluid hypocretin measurement and the sub-analysis of HLADQB1*06 positive subjects for the presence/absence of DQB1*0602 was also a limitation for the diagnostic certainty and confirmation of NT1 cases.

Conclusion

By revealing the role of DQB1*06 in differentiating narcolepsy type 1 (NT1) from non-NT1, this study aligns with existing research and emphasizes its diagnostic significance. Moreover, DQB1*03 has been identified as a prominent common marker for hypersomnolence, while DQB1*02 is more frequently associated with non-narcolepsy CDH.

Ethics

Ethics Committee Approval: This study was conducted with a retrospective design in the sleep and disorders units of İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine and Aydın Adnan Menderes University, Faculty of Medicine, after the approval of the Ethics Committee of the İstanbul University-Cerrahpaşa (approval number: 15.11.2023-837477, date: 15.11.2023).
Informed Consent: Informed consent had been obtained from all the study participants to get an allowance to investigate past medical records.

Footnotes

Authorship Contributions

Surgical and Medical Practices: M.A.S., B.Z., U.O.A., D.K., G.B.Ş., Concept: M.A.S., G.B.Ş., Design: M.A.S., G.B.Ş., Data Collection or Processing: M.A.S., B.Z., E.Y., G.B.Ş., Analysis or Interpretation: M.A.S., U.O.A., D.K., G.B.Ş., Literature Search: M.A.S., E.Y., Writing: M.A.S.
Conflict of Interest: Gülçin Benbir Şenel, MD, is the editor of the Journal of Turkish Sleep Medicine. She had no involvement in the peer-review process of this article and had no access to information regarding its peer review. The other authors have no conflicts of interest to disclose.
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Do Chronotype and Insomnia in Medical Students Give Information About Attention Deficit Disorder with Hyperactivity Disorder?

Tıp Fakültesi Öğrencilerinde Kronotip ve İnsomnia, Dikkat Eksikliği Hiperaktivite Bozukluğu Hakkında Bilgi Verir Mi?

Hanife Kocakaya, Hayriye Mihrimah Öztürk

Kırıkkale University Faculty of Medicine, Department of Psychiatry, Kırıkkale, Türkiye

Abstract

Objective: Many people with attention deficit disorder with hyperactivity (ADHD) still receive inadequate identification and treatment today. In this context, given the challenging, competitive nature of medical education based on social and experiential learning, being diagnosed with ADHD may cause difficulties. This study aims to evaluate the associations among sleep problems, individual chronotypes, and symptoms of ADHD in medical students.

Materials and Methods: In this cross-sectional study, 453 university students were included. Sociodemographic data form, Adult ADHD Self-Report Scale (ASRS), Munich Chronotype Questionnaire, Insomnia Severity Index, and Depression-Anxiety-Stress Scale were administered to the participants.

Results: Of the 388 participants who met the inclusion criteria, 222 were female (57.3%), and the mean age of the participants was 20.80±1.89 years. The participants' mean total ASRS score was 29.11±10.08, and 39 (11%) were at high risk for ADHD. We found that 30 (76%) of the 39 participants at high risk for ADHD were intermediate type, eight (20.5%) were evening types, and one (2.5%) was morning type. The findings showed that 34 (87.2%) of the people at high risk for ADHD reported having insomnia. The independent predictors of the ASRS score were insomnia severity, self-injury, depression and anxiety score (p=0.004, p=0.020, p=0.001, p=0.021).

Conclusion: Our study found that individuals with a high risk for ADHD revealed specific differences in their circadian rhythm as well as higher levels of insomnia, depression, anxiety, and stress. It was observed that the severity of insomnia, self-induced harm, depression and anxiety scores affected the ASRS score.

Keywords: Attention deficit disorder with hyperactivity, insomnia, chronotype, depression, anxiety

Öz

Amaç: Günümüzde dikkat eksikliği hiperaktivite bozukluğu (DEHB) olan pek çok kişiye hala yeterince tanı konamamakta ve tedavi verilememektedir. Bu bağlamda tıp eğitiminin sosyal ve deneyimsel öğrenmeye dayanan zorlu, rekabetçi doğası düşünüldüğünde DEHB tanılı olmak zorlanmalara sebep olabilir. Bu çalışmada tıp fakültesi öğrencilerinde uyku sorunları ve bireysel kronotipler ile DEHB belirtileri arasındaki ilişkilerin değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntem: Kesitsel tipte tasarlanmış bu araştırmaya, 453 üniversite öğrencisi dahil edilmiştir. Katılımcılara sosyodemografik veri formu, Erişkin DEHB Kendi Bildirim Ölçeği (KBÖ), Münih Kronotip Anketi, Uykusuzluk Şiddeti İndeksi ve Depresyon-Anksiyete-Stres Ölçeği uygulandı.

Bulgular: Çalışmamıza dahil edilme kriterlerini karşılayan 388 katılımcıdan, 222'si kadın (%57,3) olup, katılımcıların yaş ortalaması 20,80±1,89'du. Katılımcıların toplam DEHB-KBÖ puan ortalaması 29,11±10,08 olup, katılımcılardan 39'unun (%11) DEHB açısından yüksek risk altında olduğu saptanmıştır. DEHB açısından yüksek riskli olan 39 katılımcıdan 30'unun (%76) aratip, 8'inin (%20,5) akşamcıl tip, 1'inin (%2,5) ise sabahçıl tip olduğu görülmüştür. DEHB açısından yüksek riskli bireylerden 34'ünün (%87,2) uykusuzluk yaşadığı saptandı. KBÖ puanı bağımsız için yordayıcının ise; uykusuzluk şiddeti, kendini yaralama, depresyon ve anksiyete puanı (p=0,004, p=0,02, p=0,001, p=0,021) olduğu görüldü.

Sonuç: Çalışmamızda, DEHB açısından yüksek riskli olan bireylerin sirkadiyen ritim açısından farklılık gösterdikleri, daha fazla uyku sorunu, anksiyete, depresyon ve stres yaşadıkları görülmüştür. KBÖ puanı üzerinde etkili olan faktörün ise uykusuzluk şiddeti, kendini yaralama depresyon ve anksiyete skorları olduğu görülmüştür.

Anahtar Kelimeler: Dikkat eksikliği hiperaktivite bozukluğu, uykusuzluk, kronotip, depresyon, anksiyete

Address for Correspondence/Yazışma Adresi: Hanife Kocakaya, MD, Assoc. Prof., Kırıkkale University Faculty of Medicine, Department of Psychiatry, Kırıkkale, Türkiye
E-mail: drhanifekocakaya@gmail.com **ORCID-ID:** orcid.org/0000-0002-5907-3808

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Introduction

Attention deficit disorder with hyperactivity (ADHD) is a neurodevelopmental condition that typically starts in childhood and is characterized by difficulties in paying attention, excessive levels of activity, and impulsive behavior.[1] Although ADHD symptoms are known to decline with age, 4-60% of adults with ADHD still experience symptoms that impair their social interactions, academic achievement, and interpersonal connections.[2] The estimated cross-country prevalence rate in adults is 2.8 percent.[3] Moreover, individuals with ADHD demonstrate a susceptibility to other psychiatric disorders. Major depressive disorder, anxiety disorders, alcohol-substance use disorders, and sleep disorders are some of them.[4,5]

Sleep is a basic, multifunctional requirement regulated by endogenous circadian rhythms and homeostatic processes. The main regulators of circadian rhythm are the Suprachiasmatic Nucleus and the hormone melatonin.[6] Humans are divided into different chronotypes, such as morningness (30%), intermediate type (IT) (60%), and eveningness (10%), in terms of temporal differences in circadian rhythm, especially in the sleep-wake cycle, body temperature cycle, and secretion time differences of some hormones. Accordingly, individuals with the morning type (MT) sleep in the early hours, wake up in the early hours and show the best performance in their mental and physical activities in the morning hours. The evening type (ET) is characterized by a tendency to sleep later, difficulty rising in the morning, and the most optimal performance in intellectual and physical endeavors during the afternoon and evening.[7] Studies have shown that people with ADHD frequently experience sleep issues, such as trouble falling asleep, excessively early morning awakenings, and not feeling sufficiently rested despite sleeping. It has also been reported that the evening chronotype is more common in ADHD than in the normal population and that the ET is more associated with attention, sleep problems, and disruptive behaviors.[8] Snitselaar et al.[9] found that prolonged sleep latency, trouble maintaining sleep, waking up late in the morning, and circadian rhythm disturbances were frequently observed in adults diagnosed with ADHD. On the other hand, there are research findings on the relationship between attention deficit symptoms and sleep disorder symptoms in community-based samples. In a study conducted with university students, a significant relationship was found between attention deficit and hyperactivity symptoms, insomnia, and feeling sleepy during the day.[10] Despite substantial information on ADHD clinical signs, neurobiology, the load of sickness, and effective therapy, many people with ADHD are still having trouble with diagnosis and treatment.[11] In this context, considering the challenging, competitive nature of medical education based on social and experiential learning, being diagnosed with ADHD may cause difficulties.[12] Thus, it might be helpful to find medical students who are at risk for ADHD. This study aimed to evaluate the associations among sleep problems, individual chronotypes, and symptoms of ADHD in medical students.

Materials and Methods

Ethics Approval

The Non-interventional Research Ethics Committee of the Kırıkkale University Faculty of Medicine acknowledged this study (approval number: 2022.12.15 date: 21.12.2022).

Study Design, Setting, and Participants

The Department of Mental Health and Diseases at Kırıkkale University Faculty of Medicine conducted this cross-sectional and descriptive study. This study included 453 students who were actively studying in the 3rd, 4th, and 5th grades of the faculty of medicine in the 2022-2023 academic year. In this study, no sample selection was made, and volunteers who completed and approved the survey form were included. However, this study excluded two students with bipolar disorder and 61 students who used antidepressant medications for any reason. This study included 388 of the remaining 390 students who completely completed the study questionnaires. Sociodemographic data form, Adult ADHD Disorder Self-Report Scale (ASRS), munich chronotype questionnaire, Insomnia Severity Index (ISI), and Depression-Anxiety-Stress Scale-21 (DASS-21) were applied to the participants. All cases were evaluated according to DSM-5 diagnostic criteria during clinical interview and diagnosis. Following the clinical interview and ASRS application, the patients were divided into groups as "highly probable ADHD," "probable ADHD", and "non-ADHD" according to the scale scores and their clinical findings were compared.

Survey

The researchers developed the sociodemographic data form to record sociodemographic and clinical characteristics.

Adult ADHD Self-report Scale (ASRS): This scale is designed to screen adults for ADHD. The scale consists of two subscales, part A (attention deficit) and part B (hyperactivity/impulsivity). The scale is a five-point Likert-type Rating Scale scored between 0-4. Our country has conducted validity and reliability studies. People who score 24 points or higher on the scale are considered to have "highly probable ADHD", those who score 17-23 points are considered to have "probable ADHD," and those who score 0-16 points do not have ADHD.[13]

The Munich Chronotype Questionnaire (MCTQ): The scale uses three basic parameters to independently assess sleep time during work and free days; (1) the mid-point between the start and finish times of sleep on work days (mid-sleep on work days: MSW), (2) the midpoint of the start and finish times of sleep on free days (mid-sleep on free days: MSF), (3) the mid-point of the start and finish times of sleep on free days with a correction to account for sleep dept on work days (sleep corrected mid-sleep on free-days: MSFsc). When sleep time on work or school days is greater than or equal to sleep time on holidays, we use MSF. When working days are fewer than holidays, MSFsc is applied. Those with MSFsc or MSF values lower than 2.17 are classified as MT; those between 2.17 and 7.25 are IT; and those higher than 7.25 are ET.[14,15]

Insomnia Severity Index: The self-assess scale was created specifically to measure subjective sleep quality and insomnia.

The scale items, which comprise seven questions, are assigned scores ranging from 0 to 4. If the total score ranges between 15 and 21, it suggests the existence of moderate insomnia. A study on Turkish reliability and validity was carried out.[16,17]

Depression-Anxiety-Stress Scale (DASS-21): The scale, abbreviated DAS-42, is used to measure anxiety, depression and stress. An individual's score of 5 points and above from the depression sub-dimension, 4 points and above from anxiety, and 8 points and above from stress indicates that he/she has an illness.[18] Sarıçam[19] conducted a validity and reliability study for Türkiye. This scale is a 4-point Likert-type scale and consists of seven questions each measuring "depression, stress and anxiety dimensions".

Statistical Analysis

The software "SPSS for Windows v22.0 (SPSS Inc., Chicago, IL, USA)" was preferred for the statistical calculation. Scale data were presented as "mean values (X) and standard deviation (SD)", while nominal variables were presented as "percentages (%)". Normality and homogeneity were observed independently with the "Kolmogorov-Smirnov" or "Shapiro Wilk" tests. After the participants were divided into two groups according to gender, the data were compared using the chi-square test and the independent sample t-test. Then, we used ANOVA and the Tukey multiple comparisons test to compare the demographic data and clinical findings. The relationship between measurement scales was assessed using Pearson's correlation test. The participants were divided into three groups according to the ASRS test scores, and reveal the predictive markers based on the literature information on the clinical features of ADHD. Then, a linear regression analysis was performed. Elimination was performed using the enter method after the variables were inserted into the analysis. Statistical significance was set at $p<0.05$ and $p<0.001$.

Results

This study was introduced to 453 students who were actively studying in the 3rd, 4th, and 5th grades of the Faculty of Medicine. However, this study only included 388 participants after excluding two students with bipolar disorder, two students who did not complete the scales and sixty-one students who used antidepressant drugs for any reason. The 388 students who met the inclusion criteria were between 19 and 25 years (minimum-maximum); 222 were female (57.3%), and the mean age was 20.80±1.89 years. The economic status of the sample was high at 65.3%, low at 6.2%. Parents' education level was 56.4% university and upper. Twenty-six participans (6.7%) had a history of self mutilation (Table 1 displays the initial characteristics and scores of the participants). The ASRS total mean score was 29.11±10.08. ISI mean score was 9.61±5.03. DASS-21 total mean score was 20.96±10.93, depression subscale mean score was 7.45±4.38, anxiety subscale mean score was 7.03±3.31 and stress subscale mean score was 6.44±4.32. According to MCTQ, participants' MSF was 5:53, MSW was 4:44 and MSFsc was 5.22 minutes. Male participants' MSW and MSF values were significantly lower than females (p=0.014). In the subscale of hyperactivity-ımpulsivity scores, female participants had higher scores than male participants (p=0.042). Using the ASRS cutoff points of both subscales, 44% of (n=174) participants were classified as a non-ADHD group, 45% (n=175) were classified as probable ADHD group, and 11% of (n=39) students were classified as highly likely ADHD group. The ADHD group had highest mean scores on the DASS-21 and ISI scales although non-ADHD group had significantly lower mean scores in DASS-21 and ISI scales ($p<0.001$). MSW and MSF times were later in the ADHD group than the probable ADHD and non-ADHD groups (sleep characteristics and DASS-21 scores of ADHD groups were shown in Table 2). ASRS scores were significantly, positively and moderately correlated with DASS-21 and low with ISI scores. There was a positive and weak correlation between ASRS, MSF and MSW (correlation coefficient: 0-0.29, little if any correlation, 0.30-0.49 low correlation, 0.50-0.69 moderate correlation, Pearson correlation analysis is shown in Table 3). Linear regression analysis was performed to test the possible effect of independent variables on ADHD diagnosed using ASRS. The selection of the independent variables that were thought to be effective in the diagnosis of ADHD was based on the literature information on the clinical features of ADHD. The effects of independent variables (age, gender, DASS-Depression, DASS-Anxiety, self-injury, ISI score and MSFsc) on ADHD were evaluated by linear regression analysis. Linear regression analysis revealed that ISI scores (B=0.020, Beta=0.158, t=2.905, p=0.004), self-injury scores (B=0.288, Beta=0.110, t=2.339, p=0.020), depression scores (B=0.034, Beta=0.230, t=3.331, p=0.001) and anxiety scores (B=0.031, Beta=0.159, t=2.319, p=0.021) were independent predictors of ASRS (Table 4).

Discussion

This study aims to evaluate the associations among sleep problems, individual chronotypes, and symptoms of ADHD in medical students. As a result, persons at high risk for ADHD had different circadian rhythms and experienced increased sleep problems, depression, anxiety, and stress. It was observed that the factors affecting the ASRS score were insomnia severity, self-injury and depression scores. Although ADHD is recognized as a neurodiversity characterized by lifelong differences, it can cause restlessness, sleep problems, occupational failure, and functional disorders due to its ability to affect executive functions.[11] In this context, considering the challenging, competitive nature of medical education based on social and experiential learning, being diagnosed with ADHD may cause difficulties. Therefore, it may be beneficial to identify individuals at risk for ADHD among medical students.[12] In this context, 39 (11%) of the 388 participants included in our study were found to be at high risk for ADHD. The prevalence of ADHD among medical students has been reported in the literature to range from 5.5 to 23.7%, depending on the society and measurement used.[20,21] According to two studies evaluating medical students in their final year that were conducted in our country, the prevalence was 15.5% and 17.2%, respectively.[22,23] Our results are consistent with the current literature. Chronotype refers to a person's diurnal preference and describes individual differences in activity and

alertness throughout the day. There are three basic chronotypes: morning, evening, and intermediate, in which the person feels most energetic and effective.[6,7] Among the 388 participants in our study, 37 (9.6%) were morning, 323 (83.2%) were intermediate and 28 (7.2%) were evening. As a result, the intermediate chronotype was the most prevalent in our sample. This study coincides with the findings of previous research on the chronotype characteristics of Turkish undergraduates, which reveal that the middle type is the most prevalent and the ET is the least common.[24,25] Growing data indicates a relationship between ADHD and circadian phase delay.[26] In our study, we found that 30 (76%) of the 39 participants at high risk for ADHD were IT, 8 (20.5%) were ET, and 1 (2.5%) were MT. The prevalence of eveningism was significantly higher in ADHD patients than in non-ADHD patients and healthy controls, according to a study of adult patients who were admitted to a psychiatric clinic for the first time and healthy controls.[27] In a study of college students based on individual chronotypes, attention deficit and impulsivity, 44 (17.25%) were classified as ET, 54 (21.17%) as MT, and 157 (61.56%) as intermediate.[24] Furthermore, our study revealed a positive correlation between the ASRS score and MSF and MSW. It was also reported that chronotypes were correlated with ASRS mean scores in the study by Yılbaş and Günel Karadeniz[24] One of the most prevalent sleep problems is insomnia, and medical students are especially sensitive to them.[28] An insomnia prevalence of 139 (64.2%) was found among the participants in our study. Recent systematic reviews of 250 studies found that 41.16 percent of college students suffered from sleep disorders.[28] Individuals with ADHD are also at risk for sleep disorders. There have been suggestions that a reciprocal connection exists between ADHD and sleep disorders and that sleep problems could be an early predictor of ADHD.[29] The hypothalamic-pituitary-adrenal axis can be responsible for that, and changes in cortisol levels have been linked to irregular sleep patterns.[12] Insomnia was identified in 34 (87.2%) of the individuals at high risk for ADHD in our study. Also, it was revealed that the high-risk group in terms of ADHD had higher insomnia severity than the other groups experiencing moderate insomnia. Our study found that the severity of sleeplessness increased as ASRS scores increased. Sleep disorders may appear in up to 83% of individuals with ADHD who have greater primary sleep problems, longer sleep onset latency, and insomnia, according to recent studies.[30] Comorbidity rates in ADHD patients have been reported to be 60-80%. A population

Table 1. Baseline characteristics of participants

	Mean ± SD/N (%)			p
	Total (n=388)	Female (n=222)	Male (n=166)	
Age	20.80±1.89	20.85±1.86	20.86±1.93	0.959
Income				
High	254 (65.3%)	145 (65.3%)	108 (65.1%)	0.951
Medium	111 (28.5%)	64 (28.8%)	47 (28.3%)	
Low	24 (6.2%)	13 (5.9%)	11 (6.6%)	
Parental education				
Non	10 (2.6%)	4 (1.8%)	6 (3.6%)	0.378
Primary	69 (17.8%)	42 (18.9%)	27 (16.3%)	
High school	90 (23.2%)	53 (23.9%)	37 (22.3%)	
University	187 (48.2%)	101 (45.5%)	86 (51.8%)	
Msc/PHD	32 (8.2%)	22 (9.9%)	10 (6.0%)	
Presence of family history of psychiatric disorders	52 (13.4%)	33 (14.9%)	19 (11.4%)	0.328
Self mutilation history	26 (6.7%)	14 (6.3%)	12 (7.2%)	0.719
DASS-21	20.96±10.93	21.22±11.23	20.61±10.55	0.595
Depression	7.45±4.38	7.56±4.40	7.30±4.36	0.558
Anxiety	7.03±3.31	6.95±3.36	7.13±3.22	0.597
Stress	6.44±4.32	6.65±4.43	6.16±4.15	0.270
ASRS total				
Inattention	29.11±10.08	29.70±9.41	28.33±10.89	0.192
Hyperactivity-Impulsivity	13.81±5.51 15.31±5.89	13.87±5.18 15.84±5.45	13.74±5.91 14.61±6.37	0.829 0.042
ISI	9.61±5.03	9.69±4.99	9.51±5.10	0.725
MSW (hour: minute)	4:44	4:35	4:55	0.054
MSF (hour: minute)	5:53	5:43	6:08	0.014*

*p<0.05,

DASS-21: Depression-Anxiety-Stress Scale, ASRS: Adult Attention Deficit Hyperactivity Disorder Self-Report Scale, ISI: Insomnia Severity Index, MSW: Mid-sleep on work days, MSF: Mid-sleep on freedays, SD: Standard deviation

analysis in twenty countries revealed that having three or more problems increased the likelihood of having ADHD by tenfold.[3] Our study found that the high-risk group for ADHD had much greater levels of depression, anxiety, and stress than the probable and non-risk groups. Anxiety, depression, and stress levels increased as the ASRS score increased. In a study, 5693 medical students were evaluated in terms of ADHD symptoms, depression, suicidal behaviours and anxiety. Consequently, it was found that anxiety and depression levels were considerably greater for students with high ASRS scores.[21] A study assessing the prevalence of ADHD and related conditions in medical students found that those with ADHD scored higher on anxiety and depression scales than people in general.[23] The presence of anxiety and depression concomitant with ADHD has been shown in other studies.[30] ADHD is undertreated because it is not adequately recognized and may persist for a lifetime. This

Table 2. Sleep features and DASS-21 scores of ADHD groups

	Highly likely ADHD (n=39)	Likely ADHD (n=175)	Non-ADHD (n=174)	p
MSW (hour:minute)	5:24	4:46	4:32	<0.001**
MSF (hour:minute)	6:48	5:54	5:40	<0.001**
MSFsc (hour:minute)	6.01	5.18	5.16	0.026*
DASS-21 (mean ± SD)	32.91±10.41	23.24±10.31	16.12±8.75	<0.001**
Depression	11.48±4.55	8.38±4.15	5.59±2.91	<0.001**
Anxiety	10.35±3.31	7.59±3.01	5.76±2.91	<0.001**
Stress	10.76±3.85	7.27±4.29	4.46±3.44	<0.001**
ISI (mean ± SD)	15.26±5.27	10.11±4.77	8.08±4.51	<0.001**

p<0.005*, p<0.001**,

DASS-21: Depression-Anxiety-Stress Scale, ASRS: Adult Attention Deficit Hyperactivity Disorder Self-Report Scale, ISI: Insomnia Severity Index, MSW: Mid-sleep on work days, MSF: Mid-sleep on freedays, SD: Standard deviation

Table 3. Evaluation of the relationships between the scales by pearson correlation analysis

		MSF	MSW	$ASRS_{total}$	ISI	$DASS_{total}$
MSF	Pearson correlation	1	0.677**	0.170	0.261	0.147
	Sig. (2-tailed)		<0.001	<0.001	<0.001	0.002
MSW	Pearson correlation	0.677**	1	0.146	0.260	0.157
	Sig. (2-tailed)	<0.001		0.003	<0.001	0.001
$ASRS_{total}$	Pearson correlation	0.170	0.146	1	0.365*	0.514**
	Sig. (2-tailed)	<0.001	0.003		<0.001	<0.001
ISI	Pearson correlation	0.261	0.260	0.365*	1	**0.483***
	Sig. (2-tailed)	<0.001	<0.001	<0.001		<0.001
$DASS_{total}$	Pearson correlation	0.147	0.157	0.514**	0.483*	1
	Sig. (2-tailed)	0.002	0.001	<0.001	<0.001	

p<0.005, p<0.001,

DASS-21: Depression-Anxiety-Stress Scale, ASRS: Adult Attention Deficit Hyperactivity Disorder Self-Report Scale, ISI: Insomnia Severity Index, MSW: Mid-sleep on work days, MSF: Mid-sleep on freedays, *Low correlation, **Moderate correlation

Table 4. Predictors of ADHD by linear regression analysis

Variable		B	S.E	Beta	t	p	95% CI
MSFsc		4.053	0.000	0.035	0.709	0.479	0.000-0.000
ISI		0.020	0.007	0.158	2.905	**0.004**	0.007-0.034
DASS-21	**Depression**	0.034	0.010	0.230	3.331	**0.001**	0.014-0.054
	Anxiety	0.031	0.013	0.159	2.319	**0.021**	0.0-0.057
Age		-0.003	0.016	-0.009	-0.185	0.853	-0.035-0.029
Sex		0.034	0.061	0.026	0.557	0.578	-0.086-0.154
Self-injury		0.288	0.123	0.110	2.339	**0.020**	0.046-0.530

p<0.005, p<0.00,

DASS-21: Depression-Anxiety-Stress Scale, ISI: Insomnia Severity Index, MSF: Mid-sleep on freedays, CI: Confidence interval

condition causes difficulties in many aspects of their lives (e.g., academic and social) and comorbid conditions.[11] In this context, the factors that may be associated with the ASRS score were evaluated in linear regression analysis in our study. This analysis revealed that ISI, self-injury, depression and anxiety score were independent predictors of ASRS. These findings suggest that students with insomnia, self-harm, anxiety, and depression may have a higher likelihood of having ADHD. However, no association was observed between ASRS and chronotype. This may be explained by the fact that sleep problems are specific to ADHD, and symptoms of insomnia are a component of ADHD's presentation. ADHD symptoms, such as inattention, difficulty planning, or nocturnal activity, can directly lead to poor sleep hygiene and insomnia. In ADHD, insomnia is frequently associated with depressive symptoms.[9,31] A longitudinal study revealed a strong correlation between symptoms of sleeplessness at age 18 and ADHD persistence throughout early adulthood.[32]

Study Limitations

Among the study's strengths is that it has a larger sample size than comparable studies and that its participant group is homogeneous. A limitation of this study is that the participants were not given a structured interview, and all of the assessments were based on their subjective ideas.

Conclusion

Our study found that individuals with a high risk for ADHD revealed specific differences in their circadian rhythm as well as higher levels of insomnia, depression, anxiety, and stress. It was observed that the severity of insomnia, self-induced harm, and depression scores affected the ASRS score. Many individuals with ADHD are still undiagnosed and undertreated. In this context, considering the challenging, competitive nature of medical education based on social and experiential learning, being diagnosed with ADHD may cause difficulties. Our study aimed to increase awareness of ADHD among medical students and identify individuals at risk. In this context, the ASRS may be a reliable aid for clinicians diagnosing ADHD in adults, but a clinical interview should be supplemented.

Ethics

Ethics Committee Approval: The Non-interventional Research Ethics Committee of the Kırıkkale University Faculty of Medicine acknowledged this study (approval number: 2022.12.15 date: 21.12.2022).

Informed Consent: The individuals who volunteered to participate in our investigation were provided with comprehensive information regarding this study, and their approval was obtained.

Footnotes

Authorship Contributions

Concept: H.K., Design: H.K., H.M.Ö., Data Collection or Processing: H.K., H.M.Ö., Analysis or Interpretation: H.M.Ö., Literature Search: H.K., H.M.Ö., Writing: H.K.

Conflict of Interest: No conflict of interest was declared by the authors.

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Sleep and Quality of Life of Turkish University Students During the COVID-19 Pandemic

COVID-19 Salgını Sırasında Türk Üniversite Öğrencilerinin Uyku ve Yaşam Kalitesi

Sema Tan[1], Pauline A Hendriksen[1], Hilal Bardakçı[2], Nilay Aksoy[3], Joris C Verster[1,4,5]

[1]*Utrecht University, Utrecht Institute for Pharmaceutical Sciences (UIPS), Division of Pharmacology, Utrecht, The Netherlands*
[2]*Acıbadem Mehmet Ali Aydınlar University Faculty of Pharmacy, Department of Pharmacognosy, İstanbul, Türkiye*
[3]*Altınbaş University School of Pharmacy, Department of Clinical Pharmacy, İstanbul, Türkiye*
[4]*Swinburne University School of Health Sciences, Centre for Mental Health and Brain Sciences, Melbourne, Australia*
[5]*TU Dresden Faculty of Medicine, Cognitive Neurophysiology, Department of Child and Adolescent Psychiatry, Dresden, Germany*

Abstract

Objective: In Türkiye, the Coronavirus disease-2019 (COVID-19) pandemic came with restrictions to reduce and control the spreading of the virus. A lockdown and switch to online education was one of these restrictions. The aim of this study was to evaluate the influence of these restrictions on insomnia complaints and daytime functioning.

Materials and Methods: Health science students in Türkiye aged 18-30 were asked to participate in an online survey. The survey contained questions about sleep time, sleep quality, insomnia complaints, quality of life (QoL), and daytime functioning. In total 302 students (70.8% female) participated in the study. Assessments were made for the periods (1) [before the COVID-19 pandemic (BP), 1 January 2020-10 March 2020], (2) the first no lockdown period (11 March 2020-28 April 2021), (3) lockdown (29 April 2021-17 May 2021), (4) the second no lockdown (NL2) period (18 May 2021-31 December 2021), and (5) the third no lockdown period (1 January 2022-December 2022).

Results: Total sleep time significantly increased during lockdown and NL2 compared to BP. However, sleep satisfaction, sleep quality, insomnia, daytime fatigue and QoL worsened significantly during lockdown and NL2 compared to BP. After lockdown, restrictions were gradually lifted, and assessments returned to BP levels.

Conclusion: The COVID-19 pandemic had a negative effect on sleep quality and increased insomnia complaints which in turn negatively interfered with daytime functioning and QoL.

Keywords: Sleep, sleep wake disorder, reproducibility of results

Öz

Amaç: Koronavirüs hastalığı-2019 (COVID-19) Türkiye'de virüsün yayılmasını azaltmak ve kontrol altına almak amacıyla kısıtlamalarla geldi. Sokağa çıkma yasağı ve çevrimiçi eğitime geçiş bu kısıtlamalardan bazılarıydı. Bu çalışmanın amacı Türkiye'deki COVID-19 kısıtlamaların uykusuzluk şikayetleri ve gündüz işleyişi üzerindeki etkisini değerlendirmektir.

Gereç ve Yöntem: Türkiye'deki 18-30 yaş arası sağlık bilimleri öğrencilerinden çevrimiçi bir ankete katılmaları istendi. Ankette uyku süresi, uyku kalitesi, uykusuzluk şikayetleri, yaşam kalitesi ve gündüz işleyişine ilişkin sorular yer aldı. Değerlendirmeler (1) [COVID-19 salgını öncesi (CÖ), 1 Ocak 2020-10 Mart 2020], (2) ilk sokağa çıkma yasağı öncesi, (11 Mart 2020-28 Nisan 2021), (3) Sokağa çıkma yasağı dönemi, (29 Nisan 2021-17 Mayıs 2021), (4) ikinci sokağa çıkma yasağı öncesi (YÖ2), (18 Mayıs 2021-31 Aralık 2021) ve (5) (üçüncü sokağa çıkma yasağı öncesi, (1 Ocak 2022-Aralık 2022).

Bulgular: Toplam uyku süresi sokağa çıkma yasağı dönemi ve YÖ2 sırasında CÖ'ye kıyasla önemli ölçüde arttı. Ancak uyku memnuniyeti, uyku kalitesi, uykusuzluk, gündüz yorgunluğu ve yaşam kalitesi sokağa çıkma yasağı dönemi ve YÖ2 sırasında CÖ'ye göre anlamlı derecede kötüleşti. Sokağa çıkma yasağından sonra kısıtlamalar kademeli olarak kaldırıldı ve değerlendirmeler CÖ seviyelerine geri döndü.

Sonuç: Çalışma sonucunda COVID-19 salgınının uyku kalitesini, uykusuzluk şikâyetlerini, gündüz işleyişini ve yaşam kalitesini olumsuz yönde etkilediği tespit edilmiştir.

Anahtar Kelimeler: Uyku, insomnia, gündüz işleyişi, yorgunluk, yaşam kalitesi, COVID-19, öğrenciler

Address for Correspondence/Yazışma Adresi: Joris C Verster, Assoc. Prof. Utrecht University, Utrecht Institute for Pharmaceutical Sciences (UIPS), Division of Pharmacology, Utrecht, The Netherlands
E-mail: j.c.versterster@uu.nl **ORCID-ID:** orcid.org/0000-0002-6455-2096
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Introduction

The Severe acute respiratory syndrome-Coronavirus-2 (SARS-CoV-2) was discovered in Wuhan, China in January 2020. Since then, this virus started spreading over the world and the World Health Organization declared it a pandemic on the 12th of March 2020.[1] To reduce and control the spreading of the coronavirus, countries all over the world implemented restrictions and lockdowns. However, there was great variability between and within countries regarding the stringency of the measures taken to prevent the spread of SARS-CoV-2.[2-4] Whereas some countries enforced strict lockdown periods of long duration for the general population (e.g., Australia), other countries (e.g., Sweden and Türkiye) remained relative open societies with fewer restrictions that were limited to hygiene measures and social distancing, or short-term curfews (i.e., partial lockdowns) for specific populations only.[2-4] Research revealed that lockdown measures such as the closure of social venues and stay at home orders in particular had a significant negative impact on young adults.[5,6] In addition, in many countries during the Coronavirus disease-2019 (COVID-19) pandemic there was a switch from classroom to virtual education.[7] The corresponding reduction in social interactions during the lockdown periods was reflected in significantly poorer mood (e.g., stress, anxiety, and loneliness) and a poorer quality of life (QoL).[8-10] For part of these young adults, the lockdown periods were associated with poorer health outcomes and increased health risk behaviors, such as reduced immune fitness[8], a reduction in physical activity,[11-14] and increased alcohol consumption and smoking.[15,16] The COVID-19 pandemic also had a significant impact on sleep. Several studies reported increased sleep problems during the lockdown periods, including disturbed sleep patterns and poorer sleep quality compared to before the COVID-19 pandemic.[17-25] These effects on sleep were reflected in increased daytime fatigue and impaired daytime daily functioning during the lockdown periods. The negative lockdown effects on mood seem related to these reported sleep problems. For example, it was found that psychosocial stress, anxiety, and loneliness during lockdowns was associated with altered sleep behaviors and poorer sleep quality.[18-20] Of note, part of the population also benefited from the lockdown periods.[26] That is, studying from home and being more flexible in daytime planning (e.g., no travel time and the possibility of having naps) resulted in an improvement of sleep.[18,19] The COVID-19 pandemic in Türkiye was characterized by relatively mild interventions to combat the spread of the SARS-CoV-2 virus. For the current study, the Turkish COVID-19 pandemic was divided into five-time periods[26,27]: (1) [before the COVID-19 pandemic (BP), 1 January 2020-10 March 2020], (2) the first no lockdown period (q1, 11 March 2020-28 April 2021), (3) lockdown (29 April 2021-17 May 2021), (4) the second no lockdown period (NL2, 18 May 2021-31 December 2021), and (5) the third no lockdown period (NL3, 1 January 2022-December 2022). The first COVID-19 case in Türkiye was detected on March 11th, 2020. The NL1 comprised the change from face-to-face education to online education. During this period, partial lockdowns were installed for elderly and those below 20 years old, for limited time periods, and depending on the specific risk assessment of Turkish provinces which was re-assessed every two weeks. Shopping malls, market-places, restaurants and other social venues were only closed during the first two months of NL1. A quick rise was seen in SARS-CoV-2 infections during April 2021, and a full lockdown was installed from the 29th of April 2021 until the 17th of May 2021. In addition to stay-at-home orders, public venues were closed, except for supermarkets and pharmacies. The lockdown period was followed by two no lockdown periods, NL2 and NL3. NL2 started as a partial lockdown (evening and night), and from June 2021 social venues re-opened, taking into account hygiene measures and social distancing. During NL3 there were no COVID-19 restrictions. The time periods and associated measures are described in greater detail elsewhere.[26,27] Of note, in previous Turkish research, sleep quality assessments were usually made for the overall COVID-19 pandemic, without differentiating between lockdown and no lockdown periods. In addition, the assessments did not specifically look into insomnia complaints. In contrast, in the current study separate assessments for insomnia complaints were made for both lockdown and no-lockdown periods. Thus, the current study aimed to further evaluate the impact of the COVID-19 pandemic and associated lockdown period in Türkiye on insomnia and QoL among health science students. It was expected that the lockdown period was associated with increased insomnia complaints and poorer QoL.

Materials and Methods

Turkish university students of health science faculties, 18 to 30 years old, were invited via social media (WhatsApp groups and Instagram) to participate in an online survey. The study was approved by the Science-Geo Ethics Review Board (S-G ERB) of Utrecht University (approval number: S-23525c, date: 10.05.2023). Informed consent was obtained electronically, and students were free to discontinue the survey whenever they desired. The survey was developed and completed via Google Forms and conducted in English language. A detailed description of the survey and methodology has been published elsewhere.[28] The survey comprised questions on sleep and QoL. These questions were answered for the periods BP, NL1, lockdown, NL2, and NL3. The survey collected demographic information on age, sex, university, faculty, and which class students followed (year 1 to 5). Total sleep time (in hours) was assessed and sleep quality were assessed using a scale ranging from 0 (very poor) to 10 (excellent).[29] The Insomnia Severity Index (ISI-2) was used to assess insomnia.[30] The ISI-2 comprises two items. The first item assessed the participants' satisfaction with their sleep pattern, the second item assessed to what extent sleep interfered with their daily functioning. The ISI-2 items are scored on 5-point Likert scales (score 0 to 4). The sum score of the two items is the insomnia score, ranging from 0 (no insomnia) to 8 (severe insomnia). Previous research reported that the ISI-2 has a Cronbach's alpha >0.8.[31,32] Daytime fatigue

was measured using a single-item scale, ranging from 0 (absent) to 10 (extreme).[33,34] QoL was measured using a single-item scale, ranging from 0 (very poor) to 10 (excellent).[35]

Statistical Analysis

The statistical analyses were conducted with SPSS (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 29.0. Armonk, NY, USA: IBM Corp.). Study out-comes for the different time periods were compared with the Related-Samples Friedman's Two-Way Analysis of Variance by Ranks. Differences of the periods from BP were considered significant, after Bonferroni's correction for multiple comparisons, if $p<0.0125$. The study outcomes of males and females were compared for each time period with the Independent Samples Mann-Whitney U test, applying a Bonferroni's correction for multiple comparisons ($p<0.0125$ for significance). To evaluate if the possible impact of age, the lockdown effect (difference score, lockdown minus BP) was correlated with age. In addition to age, the lockdown effect was also correlated to academic level (class level 1 to 5). Spearman's correlations were considered significant if $p<0.05$.

Results

N=307 students participated in the study. Three students were excluded from the analysis due to missing data. Two other participants were excluded because their age was outside the inclusion criteria. Data of n=302 students (n=214 females and n=88 males) were analyzed. Their mean standard deviation age was 22.1 (1.9) years old. The students originated from 17 different universities (n=9 from İstanbul and n=8 from other cities). They were students of the faculties of pharmacy (n=172), medicine (n=53), dentistry (n=76), and biochemistry and molecular biology (n=1). The majority of students followed class 2 (20.20%), class 3 (28.81%), and class 4 (33.11%), and to a lesser extent class 5 (10.93%), and class 1 (6.95%). Table 1 and Figure 1 summarize the study outcomes. Compared to BP, total sleep time was significantly increased during lockdown ($p<0.001$) and NL2 ($p=0.010$). Compared to BP, sleep quality was significantly poorer during lockdown ($p<0.001$) and NL2 ($p<0.001$). The reduction in sleep quality for NL1 and NL3 did not reach statistical significance (both $p=0.019$). Compared to BP, satisfaction with sleep was significantly reduced during lockdown ($p<0.001$) and NL2 ($p<0.001$). Compared to BP, the interference of sleep with daytime functioning was significantly greater during lockdown ($p<0.001$). Compared to BP, the ISI-2 insomnia score was significantly higher during lockdown ($p<0.001$) and NL2 ($p<0.001$). Compared to BP, daytime fatigue was significantly greater during NL1 ($p=0.007$), lockdown ($p<0.001$) and NL2 ($p<0.001$). Compared to BP, QoL was significantly poorer during NL1 ($p<0.001$), L1 ($p<0.001$), and NL2 ($p<0.001$) (Figure 2). To evaluate possible sex differences, the study outcomes of males and females were compared for each time period, applying a Bonferroni's correction for multiple com-parisons $p<0.0125$ for significance. No significant sex differences were found. To evaluate the possible impact of age, the lockdown effect (difference score, lockdown minus BP) was correlated with age. In addition to age, the lockdown effect was also correlated to academic level (class level 1 to 5). Except for a significant correlation between age and daytime sleepiness ($r=0.137$, $p=0.017$), none of the difference scores correlated significantly with age or class.

Discussion

This study aimed to assess the influence of the COVID-19 lockdown period on insomnia complaints and QoL among students in Türkiye. Total sleep time, sleep quality, satisfaction with sleep, interference of sleep with daytime functioning, insomnia ratings, daytime fatigue, and QoL of these students differed statistically significant in the lockdown period and NL2 from BP. In addition to this, daytime functioning and QoL in NL1 also differ significantly from BP. The total sleep time seemed to increase after BP with a highest amount during lockdown. The satisfaction with sleep, sleep quality, interference of sleep with daytime functioning, insomnia ratings, daytime fatigue and QoL worsened after BP and was at its worst during the lockdown period after which it started to improve again. Several previous studies on sleep during the COVID-19 pandemic have been conducted among Turkish students. For example, a survey study among Turkish medical students found that significantly poorer sleep quality during the COVID-19 pandemic was reported by 53.4% of students.[36] In another study among Turkish medical students poorer sleep was reported by 81 of

Table 1. Study outcomes

	BP	NL1	Lockdown	NL2	NL3
Total sleep time (hours)	7.4 (1.5)	7.6 (1.4)	8.0 (1.6)*	7.7 (1.4)*	7.4 (1.3)
Sleep quality	6.1 (2.7)	5.8 (2.7)	5.3 (2.7)*	5.5 (2.6)*	5.8 (2.6)
Satisfaction with sleep	1.5 (0.9)	1.7 (1.0)	2.0 (1.0)*	1.9 (1.0)*	1.7 (1.0)
Interference of sleep with daytime functioning	1.8 (1.1)	1.9 (1.1)	2.0 (1.1)*	1.9 (1.1)	1.7 (1.1)
ISI-2	3.3 (1.7)	3.6 (1.6)	4.0 (1.6)*	3.8 (1.5)*	3.4 (1.6)
Daytime fatigue	3.0 (2.8)	3.6 (2.9)*	4.3 (2.9)*	3.8 (2.8)*	3.1 (2.9)
Quality of life	5.7 (2.9)	4.8 (2.6)*	4.1 (2.6)*	4.9 (2.6)*	5.9 (4.2)

Mean and standard deviation (between brackets) for each time period. Data was compared to BP with the Related-Samples Friedman's Two-Way Analysis of Variance by Ranks. Differences from BP were considered significant, after Bonferroni's correction for multiple comparisons, if $p<0.0125$ (indicated by *).
BP: Before the COVID-19 pandemic, NL1: First no lockdown period, NL2: Second no lockdown period, NL3: Third no lockdown period, ISI-2: 2-Item Insomnia Severity Index

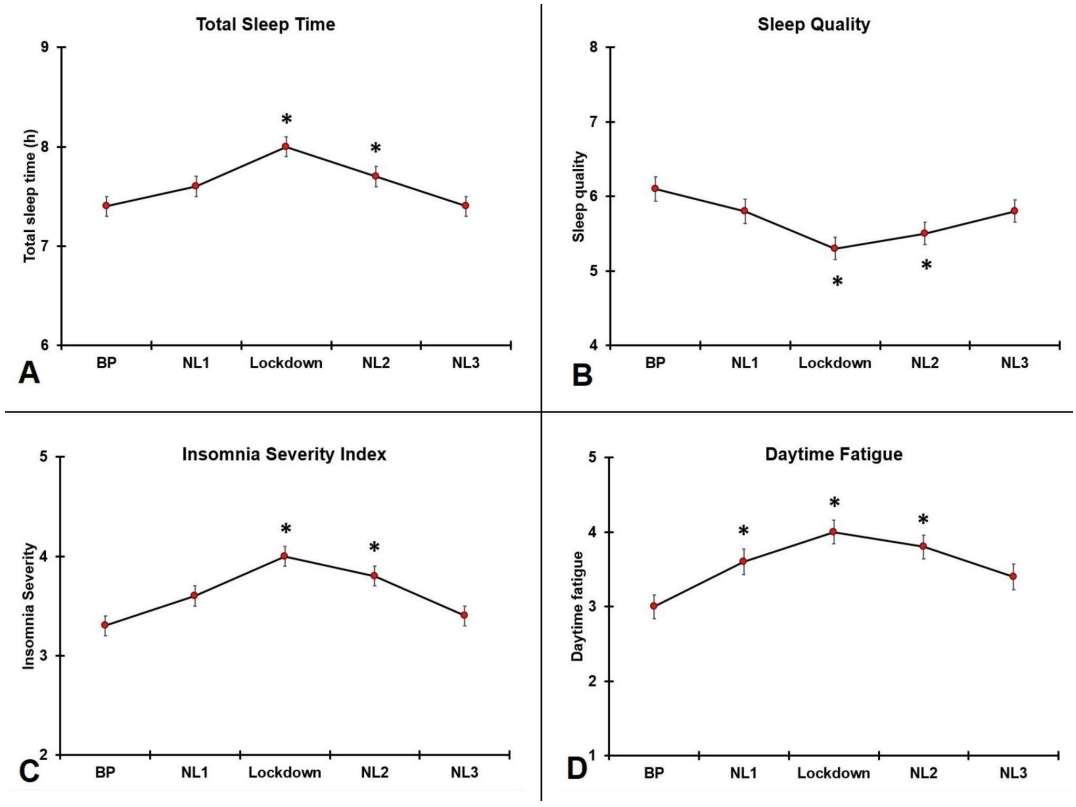

Figure 1. Sleep and daytime fatigue during the COVID-19 pandemic
Shown are (A) total sleep time, (B) sleep quality, (C) insomnia severity index, and (D) daytime fatigue. Differences from BP are considered significant, after Bonferroni's correction for multiple comparisons, if p<0.0125 (indicated by*)

BP: Before the COVID-19 pandemic, NL1: First no lockdown period, NL2: Second no lockdown period, NL3: Third no lockdown period

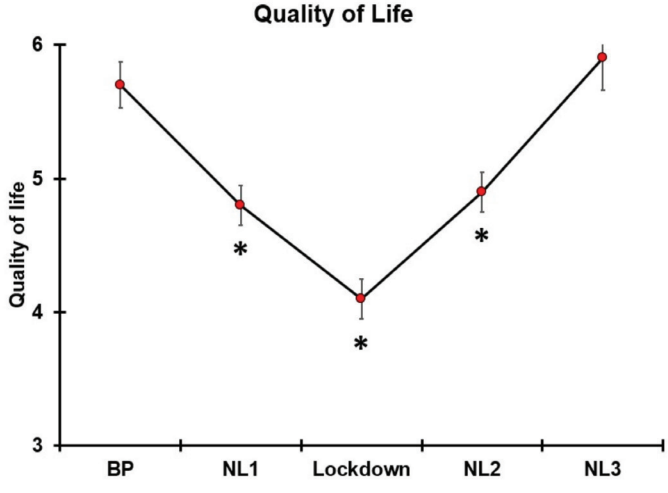

Figure 2. Quality of life during the COVID-19 pandemic
Differences from BP are considered significant, after Bonferroni's correction for multiple comparisons, if p<0.0125 (indicated by*)

BP: Before the COVID-19 pandemic, NL1: First no lockdown period, NL2: Second no lockdown period, NL3: Third no lockdown period

275 students, including increased sleep onset latency and more frequent nightly awakenings.[37] However, a study among n=699 Turkish dental students found that sleep quality during the COVID-19 pandemic was affected by only 2% of students.[38] Several factors may have impacted sleep. A study by Duygulu et al.[39] among n=1920 Turkish university students revealed that 82.3% of students were anxious about getting infected with SARS-CoV-2. The feeling of being unable to cope with the pandemic was significantly associated with experiencing sleep problems. Another survey revealed that 51.8% of n=1222 Turkish nursing students had sleep problems, and that their sleep quality correlated significantly with fear of COVID-19 and anxiety.[40] A survey among n=1065 Turkish university students revealed that poor sleep quality during the COVID-19 pandemic was associated with increased levels of depression, anxiety, stress, and eating disorders.[41] Taken together, these studies suggested that sleep of Turkish students was significantly affected during the COVID-19 pandemic. Taken together, the outcome of this study corresponds with results of earlier studies among Turkish students which also reported poorer sleep during the COVID-19 pandemic. The study adds that the insomnia complaints were most pronounced during the lockdown period, and also negatively impacted daytime functioning and QoL.

Study Limitations

There are several limitations that may have influenced the study outcomes. Firstly, recall bias may have played a role, since the data was collected retrospectively. Secondly, the data were all self-reported and therefore reflect the perceptions of the participants instead of objective assessments of sleep. Third, only a relatively small sample of students completed the survey. It is therefore unclear to what extend the results can be extrapolated to all Turkish students. Finally, the study did not assess whether or not students have been infected by SARS-CoV-2 during the COVID-19 pandemic. Other health issues and use of medicines which could have influenced sleep and academic functioning were also not considered in this survey. These could have had a significant impact on sleep assessments. Future research can take these issues into account.

Conclusion

In conclusion, this study confirmed that sleep was significantly affected during the COVID-19 pandemic in Türkiye. The study adds that insomnia complaints of Turkish students were most profound during the lockdown period. Poorer sleep significantly negatively interfered with daytime functioning and was associated with a poorer QoL. In case of future pandemics, it is important that policymakers take these negative consequences on students' health into account when considering a lockdown to combat the spread of a virus.

Ethics

Ethics Committee Approval: The study was approved by the Science-Geo Ethics Review Board (S-G ERB) of Utrecht University (approval number: S-23525c, date: 10.05.2023).
Informed Consent: Informed consent was obtained electronically, and students were free to discontinue the survey whenever they desired.

Footnotes

Authorship Contributions

Concept: S.T., P.A.H., H.B., N.A., J.C.V., Design: S.T., P.A.H., H.B., N.A., J.C.V., Data Collection or Processing: S.T., Analysis or Interpretation: J.C.V., Literature Search: S.T., J.C.V., Writing: S.T., P.A.H., H.B., N.A., J.C.V.
Conflict of Interest: Over the past 36 months, J.V. has acted as a consultant/expert advisor to Eisai, KNMP, Med Solutions, Mozand, Red Bull, Sen-Jam Pharmaceutical, and Toast!. J.V. has received travel support from Sen-Jam Pharmaceutical and owns stock from Sen-Jam Pharmaceutical. No conflict of interest was declared by the other authors.
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Development and Investigation into the Psychometric Properties of the Troy Sleep Scale

Troya Uyku Ölçeği'nin Geliştirilmesi ve Psikometrik Özelliklerinin İncelenmesi

Erhan Akıncı[1], Nurullah Bolat[2], Şükrü Alperen Korkmaz[3], Çetin Toraman[4]

[1]*Acıbadem Ataşehir Hospital, Clinic of Psychiatry, İstanbul, Türkiye*
[2]*Çanakkale Onsekiz Mart University Faculty of Medicine, Department of Child and Adolescent Psychiatry, Çanakkale, Türkiye*
[3]*Çanakkale Onsekiz Mart University Faculty of Medicine, Department Psychiatry, Çanakkale, Türkiye*
[4]*Çanakkale Onsekiz Mart University Faculty of Medicine, Department of Medical Education, Çanakkale, Türkiye*

Abstract

Objective: A unique and comprehensive self-report scale to help assess sleep in Turkish is needed. This study aimed to develop the Troy Sleep Scale (TSS) and perform validity and reliability analyses.

Materials and Methods: The study was conducted with 494 medical students and residents. The psychometric properties of the devised scale were evaluated through exploratory and confirmatory factor analyses, Cronbach's alpha and McDonald's omega reliability evaluations, and item analyses based on both classical test theory and item response theory (IRT). The reliability assessment of the TSS was carried out through test-retest, and criterion-referenced validity was employed to provide additional validation.

Results: The TSS consists of 11 items with a 3-factor structure with eigenvalues greater than 2. The factors provided information about (I) dysfunction due to sleep problems, (II) affective symptoms due to sleep problems, and (III) sleep quality. The reliability levels of all three sub-factors and overall scale scores were 0.82 and above. The test-retest reliability level had a correlation value of >0.80. The item analyses conducted in line with the IRT proved that the scale items provided a high level of information and functioned together with the answer set. The correlation between the TSS and the Pittsburgh Sleep Quality Index was analyzed for criterion-referenced validity, yielding a correlation of 0.73.

Conclusion: The psychometric properties of the TSS indicated that it was valid and reliable, making it suitable for use as a screening test for individuals with sleep-related complaints.

Keywords: Sleep, sleep wake disorders, reliability, reproducibility of results

Öz

Amaç: Türkçe'de uykuyu değerlendirmeye yardımcı olacak özgün ve kapsamlı bir öz bildirim ölçeğine ihtiyaç vardır. Bu çalışmanın amacı, Troya Uyku Ölçeğini (TUÖ) geliştirmek, geçerlilik ve güvenilirlik analizlerini yapmaktır.

Gereç ve Yöntem: Çalışma 494 tıp öğrencisi ve asistan hekim ile yürütülmüştür. Geliştirilen ölçeğin psikometrik özellikleri, açımlayıcı ve doğrulayıcı faktör analizleri, Cronbach alfa ve McDonald's omega güvenilirlik değerlendirmeleri ve hem klasik test teorisi hem de madde tepki teorisine (MTK) dayalı madde analizleri ile değerlendirilmiştir. TUÖ'nin güvenilirlik değerlendirmesi test-tekrar test yoluyla gerçekleştirilmiş ve ek doğrulama sağlamak için ölçüt referanslı geçerlilik kullanılmıştır.

Bulgular: TUÖ, özdeğeri 2'den büyük üç faktörlü bir yapıya sahip 11 maddeden oluşmaktadır. Faktörler, (I) uyku sorunlarına bağlı işlev bozukluğu, (II) uyku sorunlarına bağlı duygudurumu belirtileri ve (III) uyku kalitesi hakkında bilgi sunmaktadır. Her üç alt faktörün ve genel ölçek puanlarının güvenilirlik düzeyleri 0,82 ve üzerindedir. Test-tekrar test güvenirlik düzeyi >0,80 korelasyon değerine sahiptir. MTK doğrultusunda yapılan madde analizleri, ölçek maddelerinin yüksek düzeyde bilgi sağladığını ve cevap seti ile birlikte işlev gördüğünü kanıtlamıştır. TUÖ ile Pittsburgh Uyku Kalitesi İndeksi arasındaki korelasyon, ölçüt referanslı geçerlilik için analiz edilmiş ve 0,73'lük bir korelasyon elde edilmiştir.

Sonuç: TUÖ'nün psikometrik özellikleri, geçerli ve güvenilir olduğunu ve uyku ile ilgili yakınmaları olan bireyler için bir tarama testi olarak kullanılmaya uygun olduğunu göstermiştir.

Anahtar Kelimeler: Uyku, uyku bozukluğu, ölçek geliştirme, Türkçe ölçek, geçerlik, güvenirlik

Address for Correspondence/Yazışma Adresi: Erhan Akıncı, M.D., Assoc. Prof., Private Physician, Psychiatry Specialist, İstanbul, Türkiye
E-mail: drerhanakinci@yahoo.com **ORCID-ID:** orcid.org/0000-0003-3331-8165
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Introduction

Sleep is a fundamental requirement for human life. Regular and consistent sleep is crucial for maintaining overall health and well-being. Sleep is a dynamic process involving intricate neurochemical activity characterized by periodic transitions between different sleep stages. The structure and duration of sleep are influenced by various factors such as age and genetic predisposition.[1] Insomnia, a common symptom, often disappears when the underlying cause is addressed. Chronic insomnia is believed to affect approximately 10% of the population.[2,3] Insomnia is generally defined as the inability to initiate and maintain sleep which impairs sleep quality and integrity despite favorable conditions.[4] The negative impact of poor sleep quality is evident during the day, causing disability, impairment of cognitive and emotional functions, and behavioral problems. Sleep deprivation and fatigue often lead to daytime sleepiness, mood disturbances, attention and memory impairment, and an increased likelihood of accidents and errors.[5] Sleep problems are a common health problem in university students, insomnia is seen at a higher rate than in the general population in systemic reviews (18.5% vs. 7.5%), and sleep problems cause medical problems and stress in students and negatively affect their academic performance.[6-9] According to subjective experiences, sleep quality can be defined as satisfaction with the previous night's sleep and satisfactory wakefulness the next day. However, when subjective sleep experiences and evaluations cannot be measured or expressed numerically, they only have descriptive features. Scientific research can be conducted using numerical data obtained with valid and reliable measurement tools, and measurements made with sensitive measurement tools make the research valuable. For this purpose, scales facilitate the measurement of variable characteristics and determine the quality of the results.[10] Objective measurements such as polysomnography and actigraphy are costly and challenging for patients with sleep-related complaints.[11] Self-report methods, such as sleep diaries, sleep recording, and sleep scales, are commonly used to assess sleep quality, although they do not offer information about sleep structure. These methods attempt to gauge both the quantitative and qualitative aspects of sleep. The components and importance of sleep quality differ among individuals. Therefore, a self-report-based assessment is necessary to measure sleep quality.[12] In addition, self-report scales have many advantages, such as being inexpensive, practical, and quick to administer. Many scales have been developed to assess sleep problems and are used in Türkiye (see review).[13] Most scales for sleep problems originate from abroad, and Turkish validity and reliability studies have been conducted.[14-19] In Türkiye, there is a need for a local and comprehensive self-report scale to help distinguish individuals with sleep problems from healthy individuals and to determine sleep problems qualitatively and quantitatively. Therefore, this study aimed to develop a comprehensive and reliable self-report scale, the Troy Sleep Scale (TSS), to assess adult sleep quality.

Materials and Methods

Participants

The study was conducted between January 2022 and August 2022 with students studying at the Çanakkale Onsekiz Mart University Faculty of Medicine during the 2021-2022 academic year. The data were obtained from 494 medical students. The mean age of the students was 21.4±3.0 years. Of the participating students, 181 (36.6%) were male and 313 (63.4%) were female. Eighty-seven (17.6%) were class 1.144 (29.1%) were class 2.63 (12.8%) were class 3.40 (8.1%) were class 4.94 (19%) were class 5.35 (7.1%) were class 6 (intern doctors), and 31 (6.3%) were residents. Data from 494 medical students were randomly divided into two groups. Hair et al.[20] stated that exploratory factor analysis (EFA) results should be validated in a split sample from the original dataset or a separate sample obtained with a new application. The larger group comprised approximately 59% of the data (n=289) and was utilized for EFA, Cronbach's alpha, and McDonald's reliability coefficient calculations. The remaining 197 medical students' data were employed for confirmatory factor analysis (CFA). All 494 students' data were utilized for item response theory (IRT).

Process

Drafting of the Troy Sleep Scale

The TSS draft form was prepared as follows: (I) The scale aimed to evaluate adult sleep. (II) It was decided to use 5-degree Likert-type items (never, rarely, sometimes, most of the time, and always) as the answer set for the scale. Studies show that the options for the 5-point Likert structure work well.[21] (III) A literature review was conducted on scales assessing sleep, and candidate items were created by reviewing the relevant scales. (IV) The candidate item pool was presented to four expert psychiatrists working on sleep and one expert academician for measurement and evaluation. The experts kept items deemed appropriate on the trial form and removed those deemed inappropriate. While there were 29 items in the item pool, 23 remained after expert evaluation. (V) For Turkish language comprehensibility and plain expression, the opinion of an expert in Turkish was considered. The Turkish language expert evaluated the remaining 23 items and suggested ensuring more straightforward expressions. The items were revised in line with the recommendations of the linguist. Following the abovementioned process, a draft trial form consisting of 23 Likert-type items with a 5-point response set was obtained. Ten students participated in a pilot study using the draft form. This pilot study evaluated whether the scale items and expressions were understandable for the target group. The pilot study showed that the items and expressions were understandable.

Several scales have been developed to evaluate sleep quality, with the Pittsburgh Sleep Quality Index (PSQI) being the most commonly used.[22] The PSQI, which comprises 19 questions and seven dimensions, assesses subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbance, sleep medication use, and daytime dysfunction. A validity and

reliability study of the PSQI was conducted by Ağargün et al.[14] in Türkiye, highlighting potential limitations of the scale, such as subjective interpretations affecting scores for dimensions like sleep duration, latency, and efficiency. In this study, the PSQI was administered to all participants.

After the Development of the Draft Scale

The research was completed as follows. The approval of Çanakkale Onsekiz Mart University Clinical Research Ethics Committee (approval number: 2021-07, date: 20.10.2021) was obtained. Before the study, a consent form was obtained from all participants, indicating their agreement to participate. A draft form of the TSS was also prepared, and a trial application was carried out to obtain validity and reliability evidence of the scale. The trial applications were conducted face-to-face. To assess the validity of the TSS, item-total correlations were examined based on the classical test theory (CTT), which constructs validity within the scope of factor analysis and CFA. The scale's validity was further assessed through item discrimination and difficulty levels, item characteristic curves, and item and test information functions based on the IRT. The scale's reliability was examined using Cronbach's alpha internal consistency coefficient, McDonald's composite reliability coefficient, and marginal reliability coefficients.

Statistical Analysis

Data File Preparation Phase

The study involved analyzing forms completed by participants. It was observed that all data were present on the participant's forms. The data were subsequently transferred to JAMOVI and R statistical software. The "mvn" package of R was utilized to examine the multivariate normal distribution of the 23 items using the "henze-zirkler," "mardia," and "doornik-hansen" methods.[23] The Kaiser-Meyer-Olkin (KMO) test and Bartlett's test of sphericity were employed to analyze the data. The KMO value was interpreted based on the reference values provided. Specifically, values above 0.89 (0.90 to 1.00) were considered "excellent," values between 0.80 and 0.89 were deemed "good," values between 0.70 and 0.79 were labeled "acceptable," values between 0.60 and 0.69 were categorized as "moderate," values between 0.50 and 0.59 were classified as "low level," and values below 0.50 were deemed "unacceptable".[24] In Bartlett's test of sphericity, the hypothesis H_0 was evaluated to determine whether the correlation matrix was a unit matrix, indicating the absence of relationships between the items.

Factor Identification with Exploratory Factor Analysis (EFA)

Factor analyses were performed utilizing the principal axis factoring (PAF) methodology. PAF analyzes the shared variance among the measures instead of the error sources unique to each one. PAF, commonly used in social and behavioral science research, models the shared variance in a series of X-measures.[25] In determining the number of EFA factors, the reference value of "eigenvalue" was accepted as "1". A meaningful discussion in EFA involves assessing the extent to which the total variance (variability) of the characteristic being measured through the scale is explained. The structure obtained from factor analysis is based on Hair et al.[20] who states that in social sciences, where information is generally less precise, a solution that explains 60% of the total variance is acceptable. Warner[25] suggests that the acceptable limits are between 40% and 70%. In interpreting the factor structure, the minimum values for factor loading should be between ± 0.30 and ± 0.40. A factor-loading value of ± 0.50 is important, while ± 0.70 and above is indicative of a well-defined structure.[20]

Determination of Reliability

Cronbach's alpha, McDonald's omega, and marginal reliability coefficients were used to determine the scale's reliability. A test-retest application was performed to determine the reliability level. Sixty-six participants were administered the scale again one month later. The level of consistency was examined using a correlation analysis between the scores of the first and last applications. The test-retest administration assessed the consistency of the measurement tool, whether it gave stable results over time, and provided evidence of reliability. Adequate reliability should be 0.70 and above, according to Nunnally and Bernstein[26].

Confirmatory Factor Analysis (CFA)

In CFA analysis, the degree of model fit is important. By looking at the fit values, the suitability of the model can be determined. The literature suggests that reference values for fit indexes determined for CFA are acceptable for 0.05< root mean square error of approximation (RMSEA) ≤0.08 and excellent for 0>RMSEA≤0.05; a good fit for a Tucker-Lewis Index (TLI) is 0.95 and above; and an acceptable fit for a Comparative Fit Index (CFI) is 2< X^2/standard deviation (SD)≤ 5 and a good fit is 0>X^2/SD≤ 2.[27-34]

Data Analyses with Item Response Theory (IRT)

IRT-based measurement tools offer several advantages, including the independence of item parameters and group characteristics. Additionally, IRT allows for unique standard error estimates for each participant. In IRT analyses, item parameters are independent of the participant group, and group characteristics are independent of the item sample.[16] Furthermore, standard errors can be estimated separately by analyzing the test results for each respondent. In this context, a standard framework for evaluating their ability according to IRT can be revealed, even if the respondents are tested with different questions.[35] The validity and reliability analyses using the IRT should include an examination of the unidimensionality and local independence assumptions.[36] Unidimensionality requires that only one characteristic is assessed (the relevant items of the measurement tool are only for one characteristic), which affects the performance of individuals on the measurement tool.[37] An item correlation matrix or EFA can be used to assess unidimensionality. This study used EFA to analyze unidimensionality, as explained in detail in the results section. According to the EFA results, the TSS had three subdimensions. In this case, each factor was accepted as unidimensional separately, and IRT analyses were performed accordingly. The

assumption of local independence was tested using the Q3 statistic[38], and IRT calibrations were performed using the "Mirt v.1.30" package within the R v.4.1.2 program.[39] In the IRT, the discrimination value of an ideal scale item (i.e., "a" parameter) should be between 0.5 and 2. The parameter is generally within the acceptable range of 0.75 to 2.50 in the literature.[40] The ideal (medium difficulty level) limits for item difficulty levels (i.e., "b" parameter) are accepted between -1.00 and 1.00.[41] In aptitude or achievement tests, items with difficulty levels lower than -1.00 are considered easy, while items with difficulty levels higher than 1.00 are considered difficult.[42] The item information function is a graphical representation that illustrates the range of the trait (the trait being measured on the scale) in which the item best distinguishes individuals taking the measurement tool.[43]

Results

Classical Test Theory Validity Evidence of the Troy Sleep Scale

Construct Validity (EFA)

The normal distribution of the 23 items on the scale was analyzed. Multivariate normal distribution examination revealed a multivariate normal distribution ($p>0.05$). The KMO value was calculated as 0.89. Bartlett's sphericity test value was calculated as 2040, and the result was significant ($df=55$, $p<0.05$). As explained in the data analysis section, these results demonstrate that the data are suitable for factor analysis. PAF was adopted for the EFA. According to the data of the 23 items in the EFA data file, item-total correlation values and factor analysis input loadings were analyzed. Twelve items (3, 4, 6, 7, 8, 10, 11, 12, 17, 18, 19, and 20) with initial, extraction, and item-total correlation values below 0.30 were identified. These items were removed from the scale. The results are presented in Table 1. The initial, extraction, and corrected item-total correlation values of the remaining 11 items on the TSS were between 0.45 and 0.79. As explained in the data analysis section, these values are within the ranges recommended in the literature for EFA. Eigenvalue and scree plot analyses were performed to determine the number of factors the TSS showed with the remaining 11 items. According to the eigenvalue data, these three factors had values greater than 1. The eigenvalue of the first factor was 2.66, and the explained variance was 24.2%. The eigenvalue of the second factor was 2.38, and the variance explained by it was 21.7%. The eigenvalue of the third factor was 2.24, and the explained variance was 20.4%. Together, the three factors explain 66.2% of sleep features. As described in the Data Analysis section, this value has been accepted in the literature. The scree plot obtained from the TSS confirmed a three-factor structure (Figure 1). The scree plot shows that the TSS had three factors, all of which had eigenvalues greater than 1. Based on these results, the scale was determined to have a three-factor structure. Axis rotation was performed to determine the factors in which the 11 items of the TSS were located. As three factors were determined to be related, oblimin rotation was performed. The items for these factors are listed in Table 2. Four items were grouped under factor 1, three under factor 2, and four under factor 3. After the rotation process, the factor load values ranged from 0.44 to 0.97. The items under these factors were analyzed, and the factors were named. Factor 1 consisted of the 9th, 14th, 15th, and 16th items and was

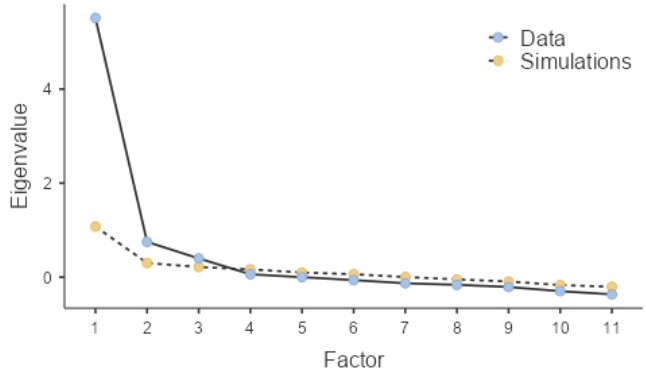

Figure 1. Scree plot obtained from Troy Sleep Scale data in exploratory factor analysis

Table 1. EFA initial loadings and item-total correlations

Item	Initial	Extraction	Corrected item-total correlation
1	0.68	0.77	0.71
2	0.58	0.58	0.58
5	0.49	0.50	0.46
9	0.46	0.45	0.63
13	0.50	0.52	0.65
14	0.63	0.64	0.76
15	0.72	0.61	0.74
16	0.76	0.70	0.79
21	0.63	0.66	0.66
22	0.68	0.68	0.68
23	0.62	0.65	0.69

EFA: Exploratory factor analysis

named Dysfunction Due to Sleep Disorder (DSD) (minimum 4, maximum 20 points). Factor 2 consisted of items 21, 22, and 23 and was labeled Affective Symptoms Due to Sleep Disorder (ASD) (minimum 3, maximum 15 points). Factor 3 consisted of items 1, 2, 5, and 13 and was called sleep quality (SQ) (minimum 4, maximum 20 points). No reverse-scored items were used for these factors.

Construct Validity (CFA)

The analyses revealed a 3-factor structure for the TSS, which consisted of 11 Likert-type items. The accuracy of this structure was analyzed using CFA. The diagram obtained from the analysis of the CFA data file is shown in Figure 2. When the diagram obtained from the CFA was examined, the 5th item under the 3rd factor had the lowest correlation (0.52). The highest correlation value was the 22nd item under the 2nd factor. As a result of the CFA, the fit indices were calculated as X^2/sd=1.98, CFI=0.98, TLI=0.97, SRMR=0.04, and RMSEA=0.06. In the DFA analysis, a covariance link was established by modifying the error terms of items 1-2 and 15-16. In this case, a correlation between the error terms of items 1 and 2 as well as 15 and 16 was accepted. Creating a covariance modification between the unknown parts of these items also showed that there were some semantic links between the items.

Reliability of Troy Sleep Scale

The reliability of the TSS was analyzed using Cronbach's alpha, McDonald's omega, and the marginal reliability coefficients. The 11 items were subjected to reliability analyses as a single-factor scale with three separate factors. Cronbach's alpha reliability value of the first factor was 0.89, McDonald's omega reliability value was 0.89, and the marginal reliability value was 0.88. The Cronbach's alpha reliability value of the second factor was 0.88, the McDonald's omega reliability value was 0.89, and the marginal reliability value was 0.86. The Cronbach's alpha reliability value of the third factor was 0.82, McDonald's omega reliability value was 0.83, and the marginal reliability value was 0.89. The Cronbach's alpha reliability value of the TSS was 0.91 and the McDonald's omega reliability value was 0.92. The values obtained from the analyses of the reliability levels of the scale are 0.70 and above and had sufficient reliability.[15] A test-retest procedure was performed to determine the reliability level. Sixty-six participants were administered the scale again one month later. The level of consistency was examined by

Table 2. Factors and items in the factors after oblimin rotation

Items		Factors		
		1	2	3
15	The sleep problem I experience at night prevents me from doing my work during the day.	0.972		
16	My night-time sleep problems impair my daytime functioning.	0.811		
9	I cannot focus on my work during the day due to insomnia at night.	0.525		
14	I suffer from forgetfulness during the day due to sleep problems at night.	0.519		
22	I am constantly nervous and irritable due to sleep problems.		0.967	
21	My tolerance for people is decreasing due to sleep problems.		0.771	
23	I'm easily depressed because of the sleep problems I've been having.		0.714	
1	I have trouble falling asleep at night.			0.890
2	I spend much time in bed at night until I fall asleep.			0.870
13	I have anxiety about not being able to sleep when I go to bed.			0.479
5	If I wake up at night, I find it difficult to fall asleep again.			0.440

Factor 1: DSD: Dysfunction due to sleep disturbance, Factor 2: ASD: Affective symptoms due to sleep disturbance, Factor 3: SQ: Sleep quality

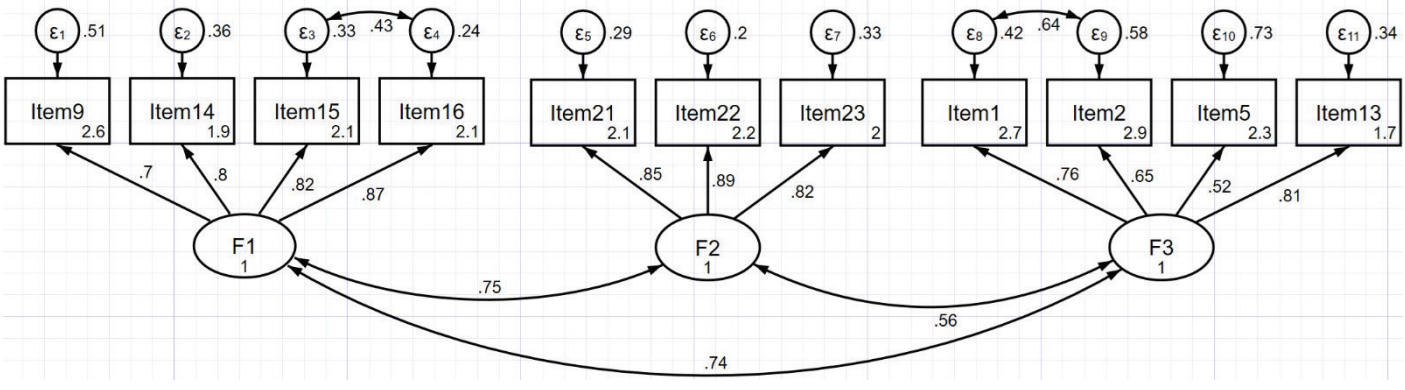

Figure 2. Confirmatory factor analysis diagram of the 3-factor structure of the Troy Sleep Scale

comparing the scores of the test and retest administrations. Table 3 presents the correlation results. The first-factor correlation of the scale, which was administered to 66 participants with an interval of one month and whose structure was discovered according to EFA, was 0.81, the second-factor correlation was 0.80, and the third-factor correlation was 0.86. For the 11-item total score, the correlation between the data from the first and second administration was analyzed, and a correlation value of 0.88 was obtained. The correlation values obtained correspond to high reliability.

Validity Evidence for the Troy Sleep Scale

Factor 1 IRT Validity Evidence

IRT analyses were conducted using data from 494 students. The generalized partial credit model (GPCM) calibrated the IRT factor item. The GPCM calculated S_χ^2 (degrees of freedom), RMSEA, level of significance, "a" (item discrimination) and "b" (item difficulty) parameters, and standard errors for each item separately (Table 4). According to the GPCM, the RMSEA threshold value for acceptable item fit is 0.08. With a value below this threshold, an item is considered to fit the model. The item fit statistics revealed that all items had RMSEA values below 0.05, indicating that the provided model fit according to the GPCM. The discrimination value, or "a" parameter, of an ideal scale item in IRT should be between 0.5 and 2. In the literature, the range for this parameter is between 0.75 and 2.50, which is considered acceptable. Based on the GPCM estimations (Log-likelihood, $p<0.05$), the compatibility of the items was confirmed. The item characteristic curves depicted that Items 9, 14, 15, and 16 worked well with their options in the response set. The item information function is a graphical representation that illustrates the range of the feature measured in the scale. The higher the peak of the curve in the item information function, the more information an item provides. Items 15 and 16 in Factor 1 were the most informative, while Item 9 provided relatively less information than the other items.

Factor 2 IRT Validity Evidence

According to the item fit statistics, all the items' RMSEA values

Table 3. Correlation level between initial and final administration of Troy Sleep Scale

Scale/ factors	n	r	p
Factor 1 Test* factor 1 retest administrations	66	0.808	<0.001
Factor 2 Test* factor 1 retest administrations	66	0.804	<0.001
Factor 3 Test* factor 1 retest administrations	66	0.860	<0.001
Whole Scale Test* Whole Scale retest administrations	66	0.878	<0.001

Table 4. Item parameters based on the GPCM for Factors 1, 2, and 3

Item no	a (SE)	b1 (SE)	b2 (SE)	b3 (SE)	b4 (SE)	S_χ^2	df	RMSEA
Factor 1								
9	1.475 (0.144)	-1.361 (0.130)	-0.189 (0.096)	1.161 (1.120)	2.767 (0.279)	18.308	12	0.033
14	1.646 (0.168)	0.014 (0.093)	0.629 (0.103)	1.491 (0.144)	2.293 (0.241)	17.196	13	0.026
15	4.856 (0.643)	-0.518 (0.064)	0.471 (0.062)	1.311 (0.084)	2.361 (0.173)	14.418	9	0.035
16	4.884 (0.656)	-0.681 (0.067)	0.323 (0.061)	1.114 (0.077)	2.008 (0.131)	14.823	7	0.048
Iteration=22 Log-likelihood: -2111.636 p<0.05								
Factor 2								
Item no	**a (SE)**	**b1 (SE)**	**b2 (SE)**	**b3 (SE)**	**b4 (SE)**	**S_χ^2**	**df**	**RMSEA**
21	2.809 (0.333)	-0.76 (0.079)	0.214 (0.072)	0.837 (0.082)	1.897 (0.140)	6.126	4	0.033
22	5.072 (0.846)	-0.499 (0.064)	0.375 (0.061)	1.214 (0.082)	2.030 (0.137)	8.243	4	0.046
23	2.165 (0.230)	-0.668 (0.086)	0.156 (0.080)	1.049 (0.100)	1.893 (0.158)	5.790	5	0.018
Iteration=100 Log-likelihood: -1711.795 p<0.05								
Factor 3								
Item no	**a (SE)**	**b1 (SE)**	**b2 (SE)**	**b3 (SE)**	**b4 (SE)**	**S_χ^2**	**df**	**RMSEA**
1	7.027 (1.968)	-1.479 (0.092)	-0.254 (0.058)	0.534 (0.061)	1.457 (0.089)	14.594	11	0.026
2	2.527 (0.303)	-1.766 (0.127)	-0.448 (0.078)	0.160 (0.075)	1.401 (0.106)	22.659	13	0.039
5	0.476 (0.062)	-1.694 (0.308)	0.960 (0.281)	1.275 (0.325)	4.106 (0.695)	31.338	24	0.025
13	1.197 (0.132)	0.199 (0.118)	0.829 (0.139)	1.560 (0.197)	1.695 (0.249)	35.134	17	0.047
Iteration=26 Log-likelihood: -2417.189 p<0.05								

SE: Standart error, RMSEA: Root mean square error of approximation, GPCM: Generalized partial credit model

were less than 0.05. Based on this result, it was determined that the three items of Factor 2 provided an adequate fit according to the generalizability theory (GPCM). The discrimination levels of Items 21 and 23 were optimal. The estimations based on the GPCM (Log-likelihood ratio, $p<0.05$) confirmed the fit of the items. The item characteristic curves revealed that all options for items 21, 22, and 23 were functional. Upon analyzing the item information functions of Factor 2 items, it was found that Item 22 was the most informative. Item 23 provided relatively less information than the other items (Table 4).

Factor 3 IRT Validity Evidence

Furthermore, the RMSEA values for all the items in Factor 3 were also less than 0.05. Consequently, it was concluded that the four items of Factor 3 provided an adequate fit according to the GPCM. Items 2, 5, and 13 discrimination levels for Factor 3 were ideal. The GPCM (Log-likelihood ratio, $p<0.05$) demonstrated the fit of the measurement tool items. The item characteristic curve of Item 13 revealed that the "most of the time" option was less effective than the other options. The remaining items functioned effectively with their respective options. Upon analyzing the item information functions of Factor 3 items, it was observed that Items 1, 2, and 5 were the most informative. Item 13 provided relatively less information than the other items (Table 4).

Concurrent Validity

The correlation between the scores obtained by the participants from the sleep assessment scale developed in this study and the scores obtained by the same participants from the PSQI was 0.73. In line with these results, the obtained correlation value corresponded to a robust and high-level correlation.[44-46] In this case, the concurrent validity level of the sleep assessment scale developed in this study was high. The Turkish form of the TSS is presented in Appendix 1.

Discussion

In this study, the TSS scale was developed to assess subjective sleep problems and their consequences and its psychometric properties were analyzed. The results showed that this scale is valid and reliable for medical students in the Turkish population. The 5-point Likert scale consists of 11 items, and the construct validity analyses in the study showed that the scale had 3 factors. When the factors were analyzed, it was determined that the items of the first factor were related to "DSD" the items of the second factor were related to "ASD" and the items of the third factor was related to " (SQ; problems with initiating and maintaining sleep)". The CFA confirmed this structure. In addition, to evaluate its criterion-based validity, its correlation with the PSQI, accepted as the gold standard in the assessment of sleep quality, was examined, and a strong correlation was found. The reliability value was calculated for all scale items, and the test-retest reliability value was also high. To evaluate the structural validity, EFA indicated that the scale had three factors, and this three-factor structure explained 66% of the total variance. The KMO and Bartlett's sphericity test values were significant in EFA. The initial, subtracted, and corrected item-total values of the final 11 items in the TSS were between 0.45 and 0.79. These values are within acceptable limits when compared to other scales such as the PSQI, Athens Insomnia Scale, and Jenkins Sleep Scale.[47-49] Subsequent CFA supported this three-factor structure. The literature shows these fit indices confirm this structure.[27,28,30,32,34] Internal reliability results were similar to or better than the PSQI, Athens Insomnia Scale, and Jenkins Sleep Scale scores. When the test-retest correlation for the TSS was analyzed as another reliability indicator, a high correlation level was observed. Criterion-based validity analysis of the TSS was performed by examining its correlation with the PSQI scores, which are accepted as the gold standard for sleep. The results showed a strong correlation between the TSS and the PSQI. The present findings demonstrated the potential utility of a three-dimensional assessment of sleep disturbance by scoring three factors of the TSS rather than a single sleep quality index. Notably, the sleep efficiency, perceived sleep quality, and daily disturbance subscales of the PSQI's three-factor validation study were similar to those of the TSS.[50] Three-Factor Scale has the advantage of obtaining various assessments of sleep problems on a single scale. More information on the type and nature of sleep problems may be necessary to guide treatment choices. Despite these advantages, caution is advised when generalizing these findings, as they were obtained using only a young non-clinical population. It is also vital to recognize that these three factors may help to differentiate between those with and without sleep disorders. Sleep-related dysfunction, one of the factors on the TSS, is present in individuals with sleep disorders.[51] Sleep quality is closely related to an individual's physical, cognitive, or emotional functionality.[52,53] Sleep quality also affects cognitive areas, such as attention and memory (related to functionality).[54] In addition, quality of life, which is related to functionality, has been reported to be related to sleep quality.[55] There is a bidirectional relationship between mood and sleep disorders; sleep and symptoms are included in the diagnostic criteria for mood disorders, and sleep disorders are risk factors for the emergence and recurrence of depression.[56] Taken together, sleep disturbances are closely related to mood symptoms and functioning beyond sleep initiation, maintenance, and adequate sleep duration, and this has made this sleep scale helpful. The findings of this study should be evaluated considering its limitations. First, since it was conducted with university students and residents, it is not representative of the general population because it was administered to a limited age group. Second, this study was conducted on individuals with self-efficacy. This may limit the ability to determine the validity of these results in a broader population. Third, the scale was not administered to a clinical sample; it must be investigated for sleep disturbances due to mental disorders or other medical illnesses. Fourth, using PSQI as the only scale for concurrent validity is another weakness of the study. Despite these limitations, the study also has strengths. The fact that the scale was prepared considering Turkish culture and language features increased the comprehensibility of the scale. To our knowledge, a scale related to sleep in Turkish has not been developed before. In addition, the fact that IRT

analysis was performed while developing the scale is another strength of this study.

Conclusion

In conclusion, our research demonstrated that the TSS is a valid and dependable instrument for assessing sleep. This newly devised scale exhibited desirable properties, including self-administration, internal consistency, reliability, and construct validity, in a sample of university students. Consequently, it is a sound psychometric measurement tool for medical student populations. However, future studies are necessary to evaluate the scale's psychometric properties across various age groups, such as adolescents and the elderly, as well as in clinical samples with sleep disorders.

Ethics

Ethics Committee Approval: The research was completed as follows. The approval of Çanakkale Onsekiz Mart University Clinical Research Ethics Committee was obtained. (approval number: 2021- 07, date: 20.10.2021).
Informed Consent: Informant consent form was obtained from all participants, indicating their agreement to participate.

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Footnotes

Authorship Contributions

Concept: E.A., N.B., Design: E.A., N.B., Ç.T., Data Collection or Processing: E.A., N.B., Analysis or Interpretation: E.A., Ş.A.K., Ç.T., Literature Search: E.A., N.B., Ş.A.K., Ç.T., Writing: E.A., N.B., Ş.A.K., Ç.T.

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Appendix 1. English Forms of Troy Sleep Scale

The Troy Sleep Scale (English form)*

Answer the following questions taking into account your sleep habits in the last 1 (ONE) month:
1: Never
2: Rarely
3: Sometimes
4: Most of the time
5: Always

Item no.	Items	(1)	(2)	(3)	(4)	(5)
1	The sleep problem I experience at night prevents me from doing my work during the day.					
2	My night-time sleep problems impair my daytime functioning.					
3	I cannot focus on my work during the day due to insomnia at night.					
4	I suffer from forgetfulness during the day due to sleep problems at night.					
5	I am constantly nervous and irritable due to sleep problems.					
6	My tolerance for people is decreasing due to sleep problems.					
7	I'm easily depressed because of the sleep problems I've been having.					
8	I have trouble falling asleep at night.					
9	I spend much time in bed at night until I fall asleep.					
10	I have anxiety about not being able to sleep when I go to bed.					
11	If I wake up at night, I find it difficult to fall asleep again.					

*The Troy Sleep Scale was developed in Turkish. English translations of the scale items are given for international readers to understand, but they should not be considered an English cultural adaptation