

## **”NIGHT, NIGHT, SLEEP TIGHT”**

Effects of Exercise and Light on Sleep  
Physiology

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**Abstract**

Sleep is easily taken for granted until the day you no longer can sleep.

Disturbances with insufficient sleep is an escalating societal problem. Sleep is essential for human functioning and the relationship between sufficient quantity, quality of sleep and physical as well as mental performance is evident. At a public health level, the effects of impaired sleep are innumerable, hence handling of sleep enhancement, without the severe side-effects of pharmacotherapy, is of paramount importance to our society. Recent research proposes exercising to improve sleep. Another branch of research proposes interventions to phase shift the circadian rhythm since fast societal changes in human lives with the invention of electrical light and blue light has caused suppression of melatonin that plays an important part in sleep physiology. The aim of this literature review has been to objectively compile and analyse if there is an effect, of early daytime outdoor exercise in natural light environments, on sleep quantity and quality, an effect that can enhance sleep quantity and quality, overall wellbeing and possibly be used as a non-pharmacological intervention for treatment of sleep disturbances without drug side effects.

*Keywords:* Sleep, sleep disturbances, circadian rhythm, exercise, light, non-pharmacotherapy intervention

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## Introduction

*"I'll sleep when I'm dead"* was the American rock singer Warren Zevon's quipped attempt to shrug off the necessity of sleep. The truth though, is that you will die faster without sufficient quantity and quality of sleep (Itani, Jike, Watanabe, & Kaneita, 2017). In the light of the above, the third part of our lives that we spend asleep (Lu & Zee, 2010) deserves some more attention.

Although there have been decades of ceaseless sleep research the exact function or functions of sleep has not been clearly revealed (Anaclet & Fuller, 2017). Most researchers though agree today upon the fact that sleep is essential for well-being as well as for longevity (Heyde, Kiehn, & Oster, 2017). Recommendations are that adults should sleep for seven to nine hours each night for optimal functioning and well-being (Hirshkowitz et al., 2015). Many people do not sleep enough, and sleep-disturbances is an escalating societal problem (Fortier-Brochu, Beaulieu-Bonneau, Ivers, & Morin, 2012). Insufficient sleep quantity and quality are interconnected with future morbidity and mortality (Kovacevic, Mavros, Heisz, & Fiatarone Singh, 2018). In the general population, 25-30% of adults live through occasional sleeping problems (Fortier-Brochu et al., 2012). Approximately 10-15% worldwide suffer from sleep disturbances severe enough to meet criteria for an insomnia sleep disorder diagnosis (Matthews, Arnedt, McCarthy, Cuddihy, & Aloia, 2013). Sleep quantity and quality becomes reduced by disturbances and increases the risk for impaired immune function (Besedovsky, Lange, & Born, 2012), various forms of cancer (Blask, 2009), cardiovascular disease, obesity, hypertension, and type 2 diabetes (St-Onge et al., 2016), anxiety and depression (Ford, 1989). Exploring the impact of potential health consequences due to inappropriate sleep duration has become a salient public health issue and sleep improvements constitute a critical step to improve public health (Liu et al., 2017).

The causes of all those sleep issues vary. Fast-societal changes in human lives

have brought circadian phase shifts and nocturnal suppression of melatonin through the invention of electrical light, shift work and sleep suppressing blue light of smartphones, tablets, computers, and televisions (Kuse, Ogawa, Tsuruma, Shimazawa, & Hara, 2014). Various life stressors, depressed mood, or physical illness are other causes of sleep disturbances, causes that are not always so easy to pin down (Smagula, Stone, Fabio, & Cauley, 2016). Whatever the cause is, more and more people, are turning to sleeping pills for relief (Glass, Lanctôt, Herrmann, Sproule, & Busto, 2005). Sleeping pills which on long-term use can have severe side effects and health consequences, side-effects such as rebound insomnia, depression, anxiety, cognitive impairment, cancer and overall mortality (Glass et al., 2005). At a public health level, effects of impaired sleep are many (Rosekind et al., 2010). Excessive sleepiness during the day can cause attention problems, judgment errors, productivity loss at work, as well as a higher risk for vehicular accidents (Rosekind et al., 2010). Thus, handling of sleep enhancement needs to be done with alternative treatments (Glass et al., 2005) and is of paramount importance to our society (Rosekind et al., 2010). Even though the function or functions of sleep remains a scientific controversial puzzle in which there is a lack of consensus (Krueger, Frank, Wisor, & Roy, 2016), the time has come when we have enough body of facts, to at least understand the necessity to take better care of the third part of our lives that we spend asleep. The relationship between sleep quantity and quality, affective states, cognitive achievement, physical performance is today clear (Tononi & Cirelli, 2014).

According to Kovacevic et al. (2018) and Kredlow, Capozzoli, Hearon, Calkins & Otto, 2015) sleep might be effectively enhanced with the use of exercise as a non-pharmacological intervention. Our lives are also intimately related to the outdoor environment through the interplay between our molecular biological clocks and the cycle of the sun (Partch, Green, & Takahashi, 2014). One study was found where the effect of exercise on

sleep physiology was simultaneously evaluated with outdoor light exposure (e.g., Murray et al., 2017). Mostly, previous studies have only focused on one thing at the time, either on the effects of exercise on sleep (e.g., Chennaoui, Arnal, Sauvet, & Léger, 2015; Kovacevic et al., 2018; Kredlow et al., 2015) or on circadian rhythms and sleep (e.g., Stothard et al., 2017; Wams et al., 2017). The present thesis, by contrast to most of earlier studies, reviews how affecting the circadian phase rhythm in combination with exercise can enhance sleep to an even greater extent.

The aim of this literature review is to objectively compile and analyse if there is an effect, of early daytime outdoor exercise in natural light environments, on sleep quantity and quality, an effect that can enhance sleep quantity and quality, overall wellbeing and possibly be used as a non-pharmacological intervention for treatment of sleep disturbances without drug side effects. To determine the interventional effect this literature review will examine the facts from previous research on how exercise affects sleep physiology. Furthermore, this literature review will gather and analyse information on how bright early daylight can influence the circadian rhythm and impact sleep quality and quantity. The thesis will present a brief historical and evolutionary perspective and continue to present sleep, sleep function, how natural outdoor light influences our rhythms, and briefly present the sleep disorder insomnia as well as consequential effects of sleeping pills. Furthermore, the thesis will present research on how exercise positively can affect sleep physiology. Following this, the discussion will start with research findings combined with a presentation of limitations and future research directions, with an aim to create a conclusion with prospects. The conclusion drawn from this literature review is that early daytime outdoor exercise is an effective non-pharmacological intervention to enhance sleep without drug side effects.

### **A brief historical perspective on daily rhythms, sleep and exercise**

The rise of the Hominin evolution started approximately 3-2,8 million years ago, as known today (DiMaggio et al., 2015). Since the human internal origin of oscillations in physiology, metabolism and behaviour evolved millions of years ago these rhythms operate at the same rate as the solar day (Blask, 2009). A tiny pair of nuclei nested deep within the human brain influence our perception of time and help us to manage predictable environmental changes, such as the day cycles (Golombek & Rosenstein, 2010). Natural cycles like geomagnetic influences, rotation, transitions, tidal movements, availability of prey and other foods in combination with social interactions are thought to have been contributory in the evolutionary acquisition of a time sense (Golombek & Rosenstein, 2010). Nevertheless, even though the evolutionary acquisition of a time recognition perhaps arose through many different natural cycles, environmental time cues such as light are relatively accurate and most certainly participated in forming our behaviour and physiology (Golombek & Rosenstein, 2010).

Before the industrial revolution humans were exposed to sunlight during the day and darkness during the night with only few other light sources such as moonlight, starlight, and fires (Blask, 2009). Our evolutionary inherited healthful lifestyle, with days of exposure to bright outdoor light and nights of darkness and sleep, has been jeopardized to a high degree (Blask, 2009). Societal changes have brought dim indoor lighting during daytime and exposure to bright lights and blue lights during the evenings and nights (Blask, 2009).

The invention and arrival of electrical light, only a little over 130 years ago, rapidly changed how we live our lives (Blask, 2009). The advent of the later digitalization also helped to shape today's fast-paced twenty-four hours a day, seven days a week societies (Blask, 2009). As an unanticipated consequence of our recently excessive increase in light

exposure '24/7', the human evolutionary heritage of the daily rhythms has caused sleep disturbances followed by metabolic disorders, as well as dysfunctional immune systems and several other diseases (Blask, 2009). The consequences of light on human rhythms have been in-depth studied with the center of attention on how sleep, mood, and cognitive functions are affected by light changes in the environment (LeGates, Fernandez, & Hattar, 2014). Life in our modern era goes hand in hand with disruptions of natural rhythms and sleep disturbances could be considered a sign of our times (Golombek & Rosenstein, 2010).

These natural daily rhythms were first seen in 1832 and were noted by Augustin Pyramus de Candolle in mimosa plants (Sollars & Pickard, 2015). Candolle watched their approximate rhythm of 24 hours in folding and unfolding their leaves during sustained light in the environment (Sollars & Pickard, 2015). Candolle is credited for being the first to hypothesize that there must be an internal time-keeping mechanism within the plant (Sollars & Pickard, 2015). Because of the approximate 24-hour span of the rhythm, it came to be named 'circadian' rhythms from the Latin language where *circa* means 'about' and *dies* means 'day'. Through the following years, researchers have become more and more aware of the existence of a biological clock in all organisms (Sollars & Pickard, 2015). A primary advantage of our intrinsic circadian clock rhythm is to be able to predict changes, thus allowing organisms to prepare and react to future environmental challenges in an optimal way (Golombek & Rosenstein, 2010).

Brain regions involved in daily rhythms, regulation of sleep and wakefulness began to be identified about a hundred years ago by scientists through the epidemic of encephalitis lethargica (España & Scammell, 2011). Reid, McCall, Henry, and Taubenberger (2001) describes that encephalitis lethargica was by that time considered to be a strange neurological condition causing coma, insomnia, and catatonia. An influenza virus occurring in the same period causing the death of more than 20 million people was reasonably

hypothesized to be causally related to encephalitis lethargica (Reid et al., 2001). Patients infected with encephalitis lethargica had different symptoms depending on which brain region was injured (España & Scammell, 2011). The psychiatrist and neurologist Baron Constantin von Economo described encephalitis lethargica with insightful comments and with all the symptoms and relevant pathological, histological characteristics in detail (Reid et al., 2001).

Von Economo investigated patients post-mortem and found out that if posterior hypothalamus or rostral midbrain was injured, the patients had a devastating sleepiness. If the preoptic area were injured, the patients suffered from severe insomnia instead (España & Scammell, 2011). Modern biological techniques have made it possible to investigate archived samples of tissue from both diseases. Reid et al. (2001) conclude though, that although there are consistent epidemiology and pathology it is not possible to ignore that there could be other possible causes of encephalitis lethargica since there are various viral infections that can cause different forms of encephalitis. Encephalitis lethargica brought many insights to brain regions regulating sleep and wakefulness but remains a disease of unknown etiology (Reid et al., 2001).

### **An evolutionary perspective on exercise, sleep, and health**

During the hominin evolution, our ancestors lived as hunter-gatherers roughly for many thousands of generations during millions of years (O'Keefe, Vogel, Lavie, & Cordain, 2010). Exercise patterns for hunter-gatherers, that was necessary for their survival, covered activities as procurement of food and water, running away from predators, servicing shelter, preparing and maintaining clothing and social interactions (Booth & Lees, 2007). These daily physical activity routines often included hours of walking to and from water and food sources and required a substantially large amount of daily energy (O'Keefe et al., 2010). In addition to these daily challenges, women often carried around their children up to the age of four when gathering food, water and wood (O'Keefe et al., 2010). They spent many, many

hours caring for their children while walking long distances to collect resources for the group (O'Keefe et al., 2010). Our ancestors were active during the day, exposed to the natural solar light, which probably is more beneficial than indoor exercise when considering different health aspects, such as for example: vitamin D synthesis in the outer layer of the skin that protects us humans from several illnesses (O'Keefe et al., 2010). Humans are still genetically adapted for a very physically active lifestyle, such as hunters and collectors. Many of today's endemic health problems are due to a lifestyle that violates our evolutionary environmental adaptation (O'Keefe et al., 2010). Outdoor daytime exercise does not disrupt the circadian rhythm, melatonin production and the sleep cycle that generally is a problem in today's industrialized countries (Touitou, Reinberg, & Touitou, 2017). Sunlight exposure also stimulates the synthesis of vitamin D (Lee, O'Keefe, Bell, Hensrud, & Holick, 2008) and exposure to sunlight is the major source of vitamin D for humans (Holick & Chen, 2008). Inadequate resources of vitamin D is a potent risk factor for several illnesses, such as cardiovascular disease, cancer and several other health problems (Holick, & Chen, 2008). In addition, the fast-societal changes in human lives have also brought circadian phase shifts and nocturnal suppression of melatonin (Blask, 2009). Melatonin suppression entails repression of the immune function and increases the risk of developing various types of cancer (Blask, 2009). Our outdoor physically active ancestors automatically received health benefits through their lifestyle (O'Keefe et al., 2010). Their exposure to sunlight and outdoor exercise improved mood and emotional stress decreased compared with indoor exercise nowadays (O'Keefe et al., 2010).

Environmental adaptation is according to Charles Darwin's viewpoint essential for the survival of gene pools (Booth & Lees, 2007) Mechanisms controlling sleep and waking have been suggested by genetic studies to have been preserved throughout evolution which emphasizes their immense importance for brain function (Brown et al., 2012).

Furthermore, Booth and Lees (2007) suggest that during the evolution of human genome metabolic pathways were inevitably selected to support physical activity, which was necessary for survival. Physical inactivity is, therefore, the real root of many chronic diseases today (Booth & Lees, 2007). Environmental adaptations of genes during the time span that humans have been living on Earth consisted most certainly of a lot of bodily physical activity, before the industrial revolution (Booth & Lees, 2007). Gene adaptations that make organisms more suited to live, reproduce and survive under new environmental conditions are more probable to be selected and produce a new phenotype (Booth & Lees, 2007). Environment-gene interaction during evolution can explain how environmental changes can lead to maladaptation including health problems (Booth & Lees, 2007). Problems occur due to the industrialized and digitalized, fast-paced twenty-four hours a day, seven days a week societies, many humans now live in (Blask, 2009).

Exercise and physical activity are decreasing in society although there is a large body of research that shows how inactivity undoubtedly increases the risk of cardiovascular diseases, osteoporosis, type 2 diabetes, breast cancer, colon cancer among other diseases (Booth & Lees, 2007). Furthermore, research presents objective metrics of improved sleep quantity when exercise is performed regularly (Kredlow et al., 2015). Insufficient sleep, possibly due to inactivity, has been acknowledged to also decrease mood, cause depression, anxiety disorders, multiply the risk for dementia and increases the causes of overall mortality (Chennaoui et al., 2015). Regular exercise has beneficial effects on sleep and might be explained by several interacting pathways regulating circadian rhythm, immune system, metabolism, thermoregulation, vascular system, endocrine system and emotions (Chennaoui et al., 2015). Pathways that were altered through the millions of evolutionary years that our ancestors lived their lives as hunters and gatherers (Raichlen & Polk, 2012). Regular exercise

is supported to be used as a normative for immediate effect on sleep quality and to give an even larger improvement over time (Kredlow et al., 2015).

### **What is sleep?**

Sleep is an altered state of consciousness distinguished by its self-regulatory and easily reversible state (Fuller, Gooley, & Saper, 2006). Almost a third of the human lifespan consists of sleep, and due to the evident relationship between sleep, physical and mental performance, sufficient amount of sleep is indispensable (Boostani, Karimzadeh, & Nami, 2017). Sleep is also characterized as behaviours with multiple interactions between both intrinsic and extrinsic factors to maintain a homeostatic balance between sleep and wakefulness (Fuller et al., 2006). Primarily sleep is regulated by the interaction of two factors, namely the circadian factor which steers the timing of sleep, and the factor of homeostasis, which mirrors the need of sleep (Borbély, 1982; Menet & Rosbash, 2011). The homeostatic pressure increases during wakefulness and decreases while sleeping, and when the homeostatic pressure is combined with the circadian mechanism, the quantity of sleep is determined (LeGates et al., 2014). Furthermore, sleep is generated actively and involves areas of the Central Nervous System (CNS) extending from the spinal cord to the forebrain. There are complex interactions between CNS nuclei that control wakefulness, and nuclei that control different sleep states (España & Scammell, 2004). The neuronal systems that interact between wakefulness and sleep are regulated by reciprocally inhibitory and excitatory neurons in the brainstem and in the hypothalamus (Fuller et al., 2006).

In addition to the neuronal system's regulation, the circadian rhythm is also an important factor involved in the regulation of wakefulness and sleep (Fuller et al., 2006). All organisms display daily rhythms in behaviour and physiological processes, generated internally by a biological clock (Sollars & Pickard, 2015). Rhythms that display an approximately 24-hour sleep-wake cycle are, as previously mentioned, called circadian

rhythms (Sollars & Pickard, 2015). To maintain a circadian rhythm, the suprachiasmatic nuclei (SCN) plays a key role in synchronizing molecular mechanisms through signaling pathways to achieve regulation in the sleep-wake switch (Albrecht, 2012). Furthermore, the SCN conduct adjustments of the daily environmental changes and uses integrating neural connections as well as paracrine signals to indirectly or directly supervise several endocrine rhythms, (e.g., rhythms of melatonin and glucocorticoids), and behavioural rhythms (e.g., rhythms of daily body temperature, activity and rest cycle) (Menet & Rosbash, 2011). These SCN supervised rhythms act in turn, as synchronizing cues (Menet & Rosbash, 2011).

The SCN consists of a tiny pair of nuclei nested deep within the brain (Golombek & Rosenstein, 2010), located in the anterior hypothalamic area, and operates as the primary circadian oscillator where its neurons rhythmically alter metabolism and firing rates (Sollars & Pickard, 2015). Light cues reach the retina of the eye and align the biological clock with the environmental light-dark cycle (Menet & Rosbash, 2011). SCN has an important role as a central pacemaker in rhythms for hormonal release, body temperature and locomotor systems (Heyde et al., 2017). The circadian rhythm also has an important role in the long-term hippocampal-dependent memory function (Menet & Rosbash, 2011). Research also emphasizes that hippocampal circadian oscillations are necessary for the formation of memory (Menet & Rosbash, 2011). Furthermore, when light enters the retina of the eye and aligns SCN it influences our perception of time and helps us to manage predictable environmental changes (Golombek & Rosenstein, 2010).

Problems with our time perception can be caused by environmental blue light sources that also have wavelengths of light that affect the SCN (Kuse et al., 2014). Our evening and night exposure to blue light sources such as smartphones, tablets, computers, and televisions can cause problems and possibly phase shift our internal rhythms, as we today are being more and more exposed to technologies with blue light (Kuse et al., 2014). Exposure to

blue light in the evening has been reported to be problematic because its short wavelength suppresses melatonin, compared with for example orange to red light with a longer wavelength that does not suppress melatonin (Wood, Rea, Plitnick & Figueiro, 2013). As stated by international classification criteria of sleep disorder, there are today eighty-four distinct sleep disorders defined (Boostani et al., 2017).

### **What is the function of sleep?**

During sleep, humans do not eat, drink or reproduce, in addition, they are also vulnerable due to decreased reactivity to the environment, despite this, sleep is necessary for our survival (Krueger et al., 2016), why? Although humans spend about a third of their lifespan asleep (Lu & Zee, 2010) and there have been decades of ceaseless sleep research, the function or functions of sleep is still not clearly revealed (Anaclet & Fuller, 2017). The functions of sleep remain contentious even though researchers agree about the fact that sleep exerts a powerful influence over many aspects of our lives from our moods, to our cognitive abilities, to the functioning of the organs in our bodies (Heyde et al., 2017). Anaclet and Fuller (2017) also point out that adequate amount and quality of sleep is a *sine qua non* for human functioning, in other words, no sleep, no life. Today there is an available body of facts indicating that sleep is essential for a proper function of the immune defense (Besedovsky et al., 2012). Sleep has been shown to boost synaptic remodelling as well as memory consolidation, where memory improves already after short naps and performance increases with a night's duration of sleep (Heyde et al., 2017).

The 'synaptic homeostasis hypothesis' (SHY) has been elaborated, and also developed by Tononi and Cirelli (2014). According to the SHY hypothesis, sleep improves the cognitive functions and makes the process easier by an extensive downscaling and restoring of synaptic strength to save energy and fine-tune synaptic plasticity (Tononi & Cirelli, 2014). In the opinion of Tononi and Cirelli (2014) sleep is possibly the price we must

pay for brain plasticity. This fact about cognitive functional improvement through sleep accords with results of previous studies at a structural, molecular and electrophysiological level (Heyde et al., 2017). Sleep has quite recently, also been proposed to have a significant function in metabolic homeostasis of the brain because of removal of brain metabolites during the sleep. The plasma membrane transport of metabolites, which are a substance formed in or necessary for metabolism, is suggested to be a homeostatic mechanism supported by sleep (Xie et al., 2013). The fluid fluxes that occur during sleep clear  $\beta$ -amyloid that can cause neuritic plaques and neurofibrillary tangles and the restorative function of sleep is proposed to remove neurotoxic waste substances that accumulate in CNS during wakefulness (Xie et al., 2013).

### **Transitions from wakefulness to sleep states**

Wakefulness and sleep states can be distinguished behaviourally but can also in most species be measured through electrical field activity in cortical neurons and muscle cells. Measures can be made with an electroencephalogram (EEG) where electrodes are placed on the scalp, and with an electromyogram (EMG) where electrodes are placed on or in skeletal muscles, and with an electrooculogram (EOG) where electrodes are placed near or over muscles that are responsible for eye movement (Brown, Basheer, McKenna, Strecker, & McCarley, 2012). Sleep can be divided into rapid eye movement (REM) and non-rapid eye movement (NREM) and those states switch with an approximately 90-minute ultradian oscillation between the states in humans (Phillips, Robinson, & Klerman, 2013). During wakefulness, an EEG shows alpha (7,5-12,5Hz) and beta (12,5-25Hz) activity. At the onset of sleep, the EEG begins to change from a high-frequency low voltage waves in the wakefulness state to a higher voltage, and slower waves (3,5-7,5Hz) which are referred to as theta activity. These changes may take from about 15 seconds to a minute (Wright, Badia, & Wauquier, 1995). The EEG then slows down more and more during NREM sleep to high-voltage, slow

wave (0,5-3,5Hz) delta activity, after which slow-waves diminishes during a period from about 40 minutes to an hour or more. Then another sudden changeover during a few seconds occurs, from NREM into REM sleep which consists of theta and beta activity with lower voltage and higher frequency (5-8Hz) (Saper, Chou, & Scammell, 2001; Saper, Fuller, Pedersen, Lu, & Scammell, 2010).

During the time frame of sleep, an individual may switch back and forth between NREM to REM sleep, with intermittent transitions to times of wakefulness. The intervals of the NREM, REM, and wakefulness phases differs with age and health of the individual, yet the switches between these states are generally fast in contrast with interval length (Saper et al., 2001; Saper et al., 2010). A healthy adult sleeps approximately about 8 h a day (Miyazaki, Liu, & Hayashi, 2017). Characteristically a cycle of NREM and REM usually lasts for 1,5 h and during a night four or five cycles takes place (Miyazaki et al., 2017).

It is known that a balance between both sleep states is important for a healthy life (Brown et al., 2012), and there is a knowledge today, of how an abnormal imbalance between the states NREM and REM commonly occur as an early symptom in varying forms of psychiatric disorders (Miyazaki et al., 2017). REM sleep is known to be the sleeping state where vivid dreams take place, otherwise, the function or functions of REM sleep remains mostly unexplored (Brown et al., 2012). NREM sleep, on the other hand, is known for its participation in growth hormone secretion, memory consolidation, removal of brain metabolites as well as involved in synaptic plasticity (Miyazaki et al., 2017). There are still many questions regarding the sleep-wake system that remains to be dealt with, such as the distinct fundamental mechanisms and functions of REM vs NREM sleep (Cooper, Abrahamsson, & Prosser, 2018). A key to a further understanding of the brain's complexity might lay in the future comprehension of NREM and REM functions (Miyazaki et al., 2017).

Furthermore, questions like why the sleep cycles regularly shifts are important as well as an understanding of what controls these changes (Cooper et al., 2018).

### **Interactions between wakefulness and sleep systems**

Neuronal systems act reciprocally to arise wakefulness and promote sleep. The ascending arousal system is a wakefulness promoting system that extends from the brainstem through the thalamus and hypothalamus to the basal forebrain (BF) and to the cerebral cortex (Schwartz & Roth, 2008). The ascending arousal system is involved in executive functions i.e., higher order processes such as attention, conscious awareness, and memory formation by weaving the neuronal firing together within cortical sites and by synchronizing these cortical sites with subcortical areas (Brown et al., 2012). These functions are also involved in our cognitive ability to make decisions (Brown et al., 2012).

Wakefulness is generated and supported by the neuronal distributed ascending arousal system composed of neurotransmitters, receptors and specific neuronal pathways (España & Scammell, 2011). When these neuronal pathways reach different nuclei along the way, neurotransmitters norepinephrine (NE), dopamine (DA), serotonin (5-HT), histamine (HA), acetylcholine (ACh), and the neuropeptide orexin, also known as hypocretin are produced and discharged (España & Scammell, 2011). The monoaminergic neurotransmitters: NE, 5-HT, HA, and DA arouses cortical and subcortical regions. Basal forebrain (BF) neurons use ACh and gamma-aminobutyric acid (GABA) to arouse cortex. Released ACh is also used to activate neurons in the brainstem, thalamus, and in the hypothalamus (España & Scammell, 2011).

Sleep-promoting systems, on the other hand, is partly a combination of interacting neurons inhibiting the ascending arousal system and partly a homeostatic and circadian rhythm process that interact in sleep-wake states (Schwartz & Roth, 2008). The ventrolateral preoptic nucleus (VLPO) operates as a regulator in the brainstem to change and

maintain stability between sleep-wake states (Schwartz & Roth, 2008). An activated VLPO starts to inhibit monoaminergic arousal nuclei with the inhibitory neurotransmitters galanin and GABA, thus promoting sleep. There is a direct and mutual inhibition between the VLPO and the monoaminergic cell groups that form a flip-flop switch, which produces sharp transitions between the wakefulness and sleep states (Saper, Scammell, & Lu, 2005). The SCN plays an important role in regulating the circadian rhythm and homeostatic processes with its synchronizing and coordinating influence on sleep-wake systems (Schwartz & Roth, 2008). Light input from the visual photoreceptor system is shared by various brain areas and light cues reach sleep-promoting neurons in the VLPO (Cajochen, 2007). The visual photoreceptor system also reaches the noradrenergic locus coeruleus (LC) system, a system that is involved in the circadian adjustment of arousal (Cajochen, 2007). REM sleep is mainly controlled by neurons in the pons with influence on ACh and GABA, whereas NREM is mostly operated by neurons that suppress the ascending arousal system with the nucleoside adenosine (España & Scammell, 20011).

The specific neuronal pathways, transmitters, and receptors that make up the ascending arousal system communicate with sleep-promoting neurons in the VLPO, situated in the hypothalamus, through the flip-flop changing mechanism that generates separate sleep-wake states with sudden transitions (Schwartz & Roth, 2008). Transitions between the states of wakefulness and sleep can occur rapidly due to reciprocal balance between excitation and inhibition in neuronal firing rates (Vyazovskiy et al., 2009). Each state of wakefulness and sleep will, however, in turn, enhance its own stability because the activity of each system will inhibit the other system to decrease its own inhibitory feedback (Lu & Zee, 2010). Orexin neurons seem to prevent unstable frequent transitions between wakefulness and sleep states by its excitatory activity. Orexin has also an indirect inhibitory effect on the VLPO and has therefore been proposed to be a stabilizer between the states of wakefulness and sleep (Lu &

Zee, 2010). There are still many questions regarding the sleep-wake interaction system that remains to be solved and furthermore, how shifts between sleep states enhance the restorative effect of sleep; these sleep-wake shift changes are suggested by Cooper et al. (2018) to lie in extracellular processes.

### **Neurotransmitters and neuromodulators involved in sleep-wake regulation**

Certain neurotransmitters and neuromodulators play roles in regulating the sleep-wake cycles, in this section, a few will be examined and reviewed for their role.

#### **Norepinephrine (NE)**

Previous studies have shown that NE is one of the many factors that regulate wakefulness and sleep. NE is produced by LC nuclei in the brainstem (Foote, Aston-Jones, & Bloom, 1980) and by the adrenal medulla (Silverberg, Shah, Haymond, & Cryer, 1978). Foote et al. (1980) proposed that NE supports to generate arousal under conditions that require high attention, for example during a cognitive challenge or under stress. Excessive release of NE is interconnected with anxiety though and might be a participating component that causes insomnia (España & Scammell, 2011).

#### **Dopamine (DA)**

DA plays several important roles in the brain and the body and is involved in regulation of diverse physiological and behavioural processes, such as reward, motivation, learning, and motor function. Besides that, DA contributes strongly to effects of wake states. Extracellular levels of DA are high during intervals of wakefulness and lower during NREM sleep, proposing that DA neurons must be active in promoting wakefulness (España & Scammell, 2011). DA is plentifully produced in the substantia nigra, in the ventral tegmental area, in the posterior hypothalamus as well as in many brainstem nuclei (España & Scammell, 2004).

**Serotonin (5-HT)**

5-HT affects, among other things, arousal and wakefulness, with a general suppression of REM sleep (España & Scammell, 2011). 5-HT also plays a role in the response to stress which might be an explanation for some aspects of stress-related sleep disturbances (Brown et al., 2012). Neurons that produce 5-HT are found in the dorsal raphe nucleus and along the middle of the brainstem. These 5-HT producing neurons are therefore involved in arousal of many brain regions such as the basal forebrain, thalamus, hypothalamus and the preoptic area (España & Scammell, 2011). 5-HT binds to varying receptors with different effects and has been shown to have an impact also on other behaviours than sleep and wakefulness (Hoyer, Hannon, & Martin, 2002). Mood, appetite, and anxiety, are some examples of other behaviours influenced by 5-HT (Hoyer, et al., 2002).

**Histamine (HA)**

HA plays a fundamental role in supporting wakefulness and moreover an essential role in both acquired and innate immunity as in allergy, inflammation, and autoimmunity (Haas, Sergeeva, & Selbach, 2008). HA also plays a role in improving attention, psychomotor behaviour and is probably involved in motivated behaviours, such as in the search for food (España & Scammell, 2011). The only source of HA in the brain is the tuberomammillary nucleus (TMN), a histaminergic nucleus located in the posterior hypothalamus (Haas, et al., 2008). The neuronal firing rates from TMN and the release of HA are high during wakefulness, decrease during NREM sleep and diminish during REM sleep (España & Scammell, 2011). Histaminergic antagonists raise the amount of sleep (Miyazaki et al., 2017).

**Acetylcholine (ACh)**

ACh operates both as a neurotransmitter and as a neuromodulator in the brain and promotes wakefulness (España & Scammell, 2011). Acetylcholine releasing nuclei are found in the brainstem in laterodorsal and pedunculopontine tegmental nuclei (LDT/PPT) and they release ACh to stimulate neurons in thalamus, hypothalamus and the brainstem (España & Scammell, 2011). There are many cholinergic areas in the brain with distinguishable functions, such as arousal, attention, memory, and motivation (España & Scammell, 2011).

**Orexin**

Orexin is a neuropeptide in the arousal system that endorses long sustained periods of wakefulness and suppresses REM sleep (España & Scammell, 2011). Recently researchers have found and identified substances that excite or inhibit the neural activity of orexin neurons (Ono & Yamanaka, 2017). Orexin's involvement in wakefulness and sleep became evident when it was discovered that narcolepsy occurs when there is a loss of orexin signaling (Nishino, Ripley, Overeem, Lammers, & Mignot, 2000). Orexin is produced in the posterior and lateral hypothalamus. Levels of orexin are highest during wakefulness (España & Scammell, 2011). Furthermore, orexin excites melanin concentrating (MCH) neurons in the lateral hypothalamic area (Ono & Yamanaka, 2017). MCH neurons have through experiments with narcoleptic mice proven to be important for sleep regulation (Ono & Yamanaka, 2017). In addition, orexin contributes to homeostatic challenges with arousal responses and is also involved in motivated behaviour like the searching for food (España & Scammell, 2011).

**Gamma-aminobutyric acid (GABA)**

GABA is an inhibitory neurotransmitter in the central nervous system (España & Scammell, 2011). GABA's main role is to reduce neuronal excitability throughout the nervous system and to inhibit the arousal systems (España & Scammell, 2011). But GABA is

not only participating in the reducing excitability processes of the arousal brain systems, GABA is also crucial in 'activated' wake states and in REM sleep (Luppi, Peyron, & Fort, 2017). GABAergic neurons are broadly spread in all structures of the brain (Luppi et al., 2017). The purpose of GABA in sleep evocation and upholding is well known and most drug treatments for insomnia target GABA receptors (Luppi et al., 2017). Multiple GABAergic neurons from the cerebral cortex to the medulla oblongata in the brainstem control both REM and NREM sleep (Luppi et al., 2017).

### **Adenosine**

Adenosine works as a neuromodulator and is believed to play a key role in mediating the homeostatic balance between sleep and wakefulness, promoting sleep and suppressing arousal (Chauhan et al., 2016). The metabolic rate is high in the brain during wakefulness, and in response to this challenge during brain metabolism adenosine may promote sleep (España & Scammell, 2011). In addition, Adenosine also plays an important role in the adjustment of blood flow to a variety of organs through the dilatation of blood vessels, which decreases blood pressure and oxygen demand (Chauhan et al., 2016). Apart from promoting sleep, adenosine also influences long-term synaptic plasticity, as well as cognition and memory through its receptor activation (Chauhan et al., 2016). Caffeine, found especially in tea and coffee, is a stimulant for the central nervous system and is an antagonist of adenosine receptors (Chauhan et al., 2016). The stimulant effects of caffeine are well known to help improve energy and alertness but can also contribute to extended wakefulness and insomnia in some cases (Rétey et al., 2007). Individual sensitivity to the effects of caffeine on sleep is due to a genetic variation in an adenosine receptor gene (Rétey et al., 2007). The sleep-wake and circadian systems are intimately aligned through organized regulation of activity patterns exploiting overlapping mechanisms interacting inside the extracellular space (Cooper et al., 2018). Adenosine can block photic phase shifts through

acting on receptors and thus phase-shift the SCN clock involved in the circadian rhythm (Cooper et al., 2018).

### **Melatonin**

Melatonin is a multifunctional hormone that helps to regulate the sleep-wake cycle and support a healthy immune function (Blask, 2009). It is produced during the dark hours in the pineal gland and helps to regulate and to stabilize circadian rhythms, crucial for optimal generalized physiology (Reiter, Tan, & Galano, 2014). The night-time production of melatonin is inhibited each day when we receive the bright daylight through our photosensitive retinal ganglion cells, located near the inner surface of the eye (Reiter et al., 2014). The prevailing light period is restricted by the wavelength of 460-480 nm, blue light, and inhibits melatonin synthesis during daytime or when exposed to light in these wavelengths (Reiter et al., 2014). Therefore, night shift workers who are exposed to light at night inhibits their melatonin production which leads to interference with the circadian rhythm and in turn can cause sleep disturbances and in the long run also a suppression of the immune system (Blask, 2009). Other environmental blue light sources that humans are being more and more exposed to are today's technologies, such as smartphones, tablets, computers, and televisions (Kuse et al., 2014). Frequent elongated exposure to blue light waves during the dark hours has been shown to have negative health impacts since it disrupts the circadian rhythm, normal sleep schedule, and cognitive performance, while the natural bright daylight increases people's alertness, energy, and mood (Cajochen et al., 2011). Stothard et al. (2017) demonstrated that melatonin rhythm in humans adapts to natural light-dark cycles but becomes delayed in modern environments with electrical lightning. Researchers believe that the photosensitive retinal ganglion cells react on the blue light which suppresses the melatonin production and stimulates the SCN (Cajochen et al., 2006). SCN, the central circadian pacemaker, then participate in the regulation of melatonin when transferring

photoperiodic information to the pineal gland where synthesis from the amino acid tryptophan to melatonin is inhibited or starts (Reiter et al., 2014). Furthermore, besides regulating the sleep-wake cycle, melatonin also works with enzyme regulation and as an aid in molecular functions (Reiter et al., 2014). As an aid melatonin has the capacity to regulate oxidative processes and act as a safeguard against free-radical mutilation of fundamental molecules which is indispensable for optimal cellular functioning (Reiter et al., 2014). Another function of melatonin is detoxification of free radicals that protects molecules from harm and damage during physiologically stressful conditions such as for example; ionizing radiation, ischemia injuries, and toxicity from drugs among other things (Reiter et al., 2014).

The two most studied factors that produce a specified effect on circadian rhythms oscillations are light and melatonin (Golombek & Rosenstein, 2010). Although melatonin has been found to possess opportunities to phase shift the circadian rhythm, it remains clear that light is the primary agent for that task (Golombek & Rosenstein, 2010).

### **Circadian rhythm, light and its effect on sleep physiology**

As earlier mentioned, circadian rhythms display an approximately 24-hour sleep-wake cycle, and all organisms display daily rhythms in behaviour and physiological processes, which are generated internally by a biological clock (Sollars & Pickard, 2015). These circadian rhythms are continuing without interruption due to a reinforced network of cellular clock systems working through interconnected and descriptive feedback loops for replications of proteins and clock genes (Heyde et al., 2017). Even if the circadian rhythm is an intrinsic mechanism with an approximate, though not exact, rhythm of 24 hours (Sollars & Pickard, 2015), the involvement of light is a necessity to continuously adjust the circadian phase to the external environment (Golombek & Rosenstein, 2010). The Nobel Prize in Physiology or Medicine was awarded to Jeffrey C. Hall, Michael Rosbash, and Michael W. Young 2017 who found out the principles of how a self-contained biological clockwork can

maintain a circadian rhythm with several details that explain the clock's stability, function and exactly how light can synchronize the clock (The official site of the Nobel Prize, 2017).

If the circadian rhythm is left without light cues, it will gradually diverge from the exterior environment until the shift in phase is inadequate for survival (Golombek & Rosenstein, 2010). As an example, if a diurnal animal is circadian rhythmically phase-shifted with 6 minutes each day, the animal will in only 10 days be rhythmically moved forward 1h with respect to its natural cycle (Golombek & Rosenstein, 2010). After approximately 3 months the animal will become nocturnal instead of diurnal, which can be fatal for survival (Golombek & Rosenstein, 2010).

Guo et al. (2016) found that circadian neuron feedback controls the sleep activity profile in *Drosophila* flies. There is an indication that the dorsal clock neurons integrate environmental information with the circadian molecular rhythm and affect the sleep-wake profile. Dorsal clock neurons are sleep-promoting cells that release glutamate to inhibit pacemaker neurons to affect the sleep-wake cycle (Guo et al., 2016).

Sleep quality and sleep architecture are linked with preceding exposure of light in the environment (Wams et al., 2017). Wams et al. (2017) conducted a research study where healthy subjects were provided ambulatory polysomnography (PSG) and wrist actigraphs to measure exposure to light, activity, rest, sleep architecture, and sleep quality. The study by Wams et al. (2017) indicates that timing and amount of light exposure are closely linked to the quality of sleep and sleep architecture. Wams et al. (2017) observed a greater accumulation of slow-wave sleep ( $p < .05$ ), when subjects were exposed to early, maximal (more than 10 lux) intensity of light Wams et al. (2017) also performed dim-light laboratory analyses of melatonin release onset through salivary tests to exactly establish endogenous circadian rhythm phases in this study. Melatonin regulates the sleep-wake cycle and is a multifunctional hormone important in the support of a healthy immune function (Blask,

2009). Wams et al. (2017) highlights that there is a direct connection between the timing and amount as well as the wavelength of light exposure and sleep that follows. Wams et al. (2017) further propose that the timing and intensity of exposure to light exerts a modifying or controlling influence on both circadian rhythm-driven sleep and the pressure of homeostatic sleep. Likewise, Stothard et al. (2017) found that the circadian rhythm is sensitive to seasonal alterations and decreased amount of sunlight exposure during the day and that expanded exposure to electrical light leads to a delay in sleep timing. Wams et al., (2017) highlights that subjects with later first exposure to light above 10 Lux also received less amount of bright light and therefore woke up more often during sleep that followed and had a higher percentage of REM sleep. Subjects exposed to the high amount and maximal intensity of early light exposure gained more NREM sleep (Wams et al., 2017).

Stothard et al. (2017) provide findings that although the circadian rhythm in humans adapts to environmental changes in season, it becomes delayed in modern societies. Modern frequent elongated exposure to electrical light and blue light effect and diminish the circadian reactivity and delay the natural biological night (Stothard et al., 2017). Human circadian rhythm is delayed in both winter and summer due to electrical light exposure when compared to natural light-dark cycles (Stothard et al., 2017). Studies have been made with the purpose of seeing if it is possible to phase shift the circadian rhythm to facilitate night workers to change night-work, to a day-sleep schedule (Baehr, Fogg, & Eastman, 1999; Youngstedt et al., 2016). These studies showed that light indeed is a possibility to phase-shift circadian rhythms to a night-work, day-sleep schedule by the exposure to late night bright light (Baehr et al., 1999; Youngstedt et al., 2016). Touitou et al. (2017) found that although light and melatonin has been proposed to shift the circadian rhythm it did not ameliorate the adjustment to shift work. Menet and Rosbash (2011) point out that our modern shift working lifestyle leads to internal desynchronizations which alter brain functions. For instance,

nutritional food intake under our natural phase of the rest period causes intrinsic signals to be produced at inconvenient circadian times. As a result, a battle of conflicting signals occurs between the properly timed signals from the extrinsic environment and the wrongly induced internal signals (Menet & Rosbash, 2011). In the worst-case scenario, everything throughout the body will be desynchronized, such as neuronal outputs, hormonal rhythms and metabolites, which has been reported as a phenomenon in animal studies with the aim to study a model of night work (Menet & Rosbash, 2011).

### **Insomnia**

In society today, the sleep disorder insomnia is an escalating problem that many people suffer from (Riemann et al., 2015). The sleeping disorder insomnia is an irregularity in the sleep-wake neurobiology switch, with changing to the waking state frequently during sleep (Riemann et al., 2015). Insomniacs have shown to have increased global brain metabolism in neuroimaging studies, both during sleep and the waking state, possibly due to hyperarousal and insufficient restoration during sleep (Tononi & Cirelli, 2006). Non-restorative sleep in insomnia is correlated with tiredness, concentration problems, cognitive deterioration, as well as changes in mood and irritability (Tononi & Cirelli, 2006). The cognitive impairments seen in insomnia involve both working memory, episodic memory as well as problem-solving (Fortier-Brochu, et al., 2012). This sort of disturbance might also negatively influence and affect healthy brain plasticity (Riemann et al., 2015), and as previously mentioned, according to Tononi and Cirelli (2014) sleep is possibly the price we must pay for brain plasticity. Brain plasticity refers to the brain's ability to both structurally and functionally modify its connections or re-wire itself (May, 2011). These modifications are an intrinsic property of the CNS and occur to alter the organization in accordance with the external or internal environment (May, 2011). This ability of the brain to change can for the individual cause beneficial development or maladaptive behaviours (May, 2011). The

common features such as, fatigue, concentration problems, irregular moods and cognitive impairment, which often are seen in the insomnia disorder might be the outcome of dysfunctional synaptic homeostasis during sleep (Tononi & Cirelli, 2006). The impaired synaptic homeostasis might partly result from synaptic overburden and from recompensed modification in the neuronal excitability (Tononi & Cirelli, 2006).

Several different factors can cause insomnia and often factors are coexisting (Leibowitz, Lopes, Andersen, & Kushida, 2006). Three described factors that facilitate the development of acute or chronic insomnia are: 1. Predisposing, which means that someone is genetically more inclined or more genetically sensitive to obtain the condition; 2. Precipitating, meaning that the cause is an event or situation, typically one that is bad or undesirable and happens suddenly, unexpectedly, or prematurely; 3. Perpetuating factors, meaning ongoing undesirable situational factors (Leibowitz et al., 2006). Perpetuating factors could as an example be shift work schedule, where approximately 20% of the workforce that suffers from circadian-related transient insomnia (Golombek & Rosenstein, 2010). In addition, there is an unknown prevalence of sleep disorders related to jet lag which also can be associated with circadian-related transient insomnia (Golombek & Rosenstein, 2010).

Many subtypes of insomnia exist, usually with different causes (Leibowitz et al., 2006). Subtypes of insomnia can be psychophysiological, idiopathic insomnia, adjustment insomnia, paradoxical insomnia, insomnia caused by drugs or substances, and medically induced insomnia (Leibowitz et al., 2006). These subtypes can also coexist (Leibowitz et al., 2006). Sleep studies performed with positron-emission tomography on subjects with insomnia show increased brain activity when compared with subjects without sleep disturbances (Saper, Scammell, & Lu, 2005), activity in corticolimbic sites that encompasses the medial temporal lobe as well as the medial prefrontal cortex (Saper et al., 2005). These activity inputs might maintain a state in hyperarousal, which in an emergency can be crucial,

such as when a surgeon must stay awake for an operation (Saper et al., 2005). However, this hyperarousal might override the circadian and homeostatic regulation of sleep during various stressful events which eventually can result in undesirable and debilitating insomnia according to Saper et al. (2005). The morbidic mechanism of insomnia remains unsettled (Tsuneki, Wada, & Sasaoka, 2017), and many millions of people suffering from insomnia around the world are turning to medication in their search for more sleep (Riemann et al., 2015).

### **Consequences of frequent use of sleeping pills**

Insomnia or dysfunctional sleep cause in fact that more and more people in society today are turning to sleeping pills for relief of their sleep disturbances (Glass et al., 2005). Sleeping drugs are amongst the most frequently prescribed medicines today (Brown et al., 2012). Drugs to induce sleep can on long-term use have severe side effects and consequences (Glass et al., 2005), as well as increase the risk of involvement in injurious road traffic crashes (Nevriana, Möller, Laflamme, & Monárrez-Espino, 2017). Drug treatments may also affect the quality of being alert the following day and consequently impact performance (Chennaoui et al., 2015). Drug treatments with Benzodiazepines are commonly used as medications for dysfunctional sleep (Glass et al., 2005). Also, a new generation sleep drugs, called non-benzodiazepines or Z-drugs, i.e., zopiclone, zaleplon, and zolpidem are frequently used (Sanger, 2004). These are all sedative-hypnotic drugs that induce sleep (Glass et al., 2005). Benzodiazepines have been found to reduce nonrapid eye movement (NREM) stages 3 and 4 of sleep, also defined as slow-wave sleep, hence the restorative effect of sleep diminishes (Carskadon & Dement, 2011). In addition, benzodiazepines can have dreadful side effects, such as rebound insomnia, depression, anxiety, increased fall risk, cognitive impairment, cancer and overall mortality, and are therefore not advised for long-term use (Glass et al., 2005). Z-drugs first appeared on the market as a better alternative than

benzodiazepines with the intention to lower the risk for addiction (Barros, Opaleye, & Noto, 2018). Recent research though has shown that the effects of Z-drugs are similar with those of benzodiazepines regarding both the dependence risk, cognitive performance, behavioural and psychomotor performance, as well as mortality (Barros et al., 2018). A large study recently conducted, also shows that both frequent and new users of Z-drugs like Zopiclone, Zolpidem are involved in higher occurrences of injurious road traffic crashes (Nevriana et al., 2017). Despite risks and side effects, pharmacotherapy is to the greatest extent used as a treatment for insomnia and many people continue using it for prolonged periods (Glass et al., 2005). The handling of sleep enhancements is emphasized to be done with alternative treatments by Glass et al. (2005). Sleep might be effectively enhanced with the use of exercise as a non-pharmacological intervention (Kovacevic et al., 2018).

### **Exercise and its effect on sleep**

An epidemiological survey by Urponen, Vuori, Hasan, and Partinen (1988) showed that many of the participants evaluated exercise with a sleep-promoting effect. The purpose of the survey was to evaluate self-perceived factors that could promote or disturb sleep among urban middle-aged people in Finland ( $N = 1600$ ). The rate of survey response was 75% with results that lack of exercise was evaluated and perceived to impair sleep quality and a third of the respondents felt that sleeping improved after exercise even though sleep quality also is subjectively perceived to be determined by numerous factors (Urponen et al., 1988).

A research study by Murray et al. (2017), confirms that outdoor morning exercise confers sleep benefits. According to Murray et al. (2017), the time spent exercising outdoors can be used as an important non-pharmacological approach to improve both the sleep quality and the sleep duration. In the research study by Murray et al. (2017) a sample of 360 U.S. adult women (with the mean age of  $55.38 \pm 9.89$  years, and a body mass index of

27.74±6.12) was used, to wear a global positioning system device and an actigraph with accelerometers on the wrist for seven days and seven nights and on the hip for seven days, for objective measurement of three variables: 1) sleep; 2) moderate to vigorous exercise/physical activity; 3) outdoor time. A generalized mixed effects model, to assess moderate to vigorous exercise in relation with time spent outdoors and sleep, was used. The time of the day, the season, and demographics were also considered in the evaluation of measurements. Sleep scores were calculated for four measures: 1) sleep efficiency (percentage of time spent in bed that the adult was asleep), 2) total sleep time (the sum of the number of sleep minutes during the sleep period), 3) sleep onset latency (scores reflected the number of minutes that it took for the adult to fall asleep), and 4) the number of minutes until the first awakening was also measured after sleep onset. Exercise/physical activity was measured through accelerometers worn on the hip where a sum score was generating the total number of time in minutes spent in moderate to vigorous activity. Daily outdoor time was calculated with a Qstarz BT1000X GPS device which logged location coordinates, distance, speed, elevation, and time with an accuracy of three meters and recorded location every 15 second. Murray et al. (2017) configured the device with satellite information to detect outdoor locations and the sum scores represents the amount of time spent outdoors. The time of the day measurements was classified either as morning (6 am - 11:59 am) or afternoon (12 pm – 5:59 pm), and total time spent outdoors was sum scored as either morning or afternoon represented. Murray et al. (2017) found a significant ( $p=0,04$ ) interaction between the moderate to vigorous exercise/physical activity and time spent outdoors with the preceding total sleep time, but not for preceding sleep efficiency, nor sleep latency. Increased time outdoors in the afternoon compared with time spent outdoors in the morning showed lower sleep efficiency but did not have any effect on the total sleep time. According to Murray et al. (2017) the time of the day spent outdoors may be important when assessing interactions between exercise and sleep, but

more experimental research in larger populations is needed.

Moderate to intensive exercise was in a review by Chennai et al. (2015) found to be a non-pharmacological treatment of interest to improve sleep in poor sleepers. Long-term exercise program is usually needed to observe significant effects on sleep from exercise, although some effects on sleep quality were noted also in shorter periods of exercising. Moderate to intensive regular exercise was found to increase brain-derived neurotrophic factor (BDNF) and growth hormone (GH) as well as commonly found to increase slow wave sleep and total sleep time. Furthermore, body temperature is affected both during exercise and recovery, and Chennai et al. (2015) suggest that exercise can influence sleep also through changes in body temperature since body temperature is an important factor in regulating sleep. According to Chennai et al. (2015), two meta-analyses showed that the effects of acute exercise on sleep architecture displayed a small increase in slow wave sleep and rapid eye movement sleep latency as well as a decrease in the amount of rapid eye movement sleep. When the exercise took place four to eight hours prior to bedtime it had a positive effect on the sleep latency and decreased wake time after sleep onset, but the effect was negative if exercise was performed less than four hours or more than eight hours prior to bedtime. But it has also been put forward that exercising prior to bedtime may not distort sleep architecture (which was evaluated by questionnaire or by actigraphy). Chennai et al. (2015) point out that it is hard to discriminate direct or indirect exercise-induced changes on sleep, since exercising leads to overall improvements in basic metabolic rate, glucose control, immune function, cardiac function and body composition. The beneficial effects on sleep from regular exercising might be explained by the facts that many different pathways interact metabolic effects, with the immune system, thermoregulation, vascular effects, endocrine effects, as well as effects on mood and circadian rhythm according to Chennai et al (2015). More research is needed though, to understand the complex physiological effects of exercise on sleep, and even

if all physiological effects of exercise on sleep are not fully examined and understood, Chennai et al. (2015) recommend exercise training to be prescribed as a non-pharmacological treatment of sleep disturbances.

Adrenocorticotrophic hormone (ACTH) is secreted in response to stress and is an important part of the hypothalamic pituitary adrenal (HPA) axis that controls the secretion of glucocorticoids such as cortisol (Chennaoui et al., 2015). The HPA axis is the primary circuit in the brain that integrates perceived stressful events with the autonomic neuroendocrine system for physiological balance (van Dalfsen & Markus, 2018). The HPA axis and sleep interact in several different ways (Buckley & Schatzberg, 2005). Sleep is suggested to play a crucial mediating role in the adaptation of the neuroendocrine system, an adaptation of the stress responsiveness and in maintaining adequate stress reactivity by influencing cortisol reactivity. (van Dalfsen & Markus, 2018). Sleep fragmentation, as seen in insomnia, increases cortisol levels and consequently increases activity in the HPA axis which promotes sleep fragmentation (Buckley & Schatzberg, 2005). A vicious cycle of these two facts might be the cause of an initiation and perpetuation of chronic insomnia (Buckley & Schatzberg, 2005). Exercise has shown to stimulate the HPA axis and subjects who regularly exercise display an adaptation of the HPA axis activity due to reduced sensitivity to glucocorticoids and hence improves their tolerance to other life stressors effects (Duclos & Tabarin, 2016). Exercise has, in laboratory animal studies, also proven to accelerate resynchronization of the circadian clock to new light/dark cycles when imposition of phase shifts was done (Melancon et al., 2014).

Different results between experimental reports on the effect of exercise in night workers have been found, where the experiments were performed with an aim to phase-shift sleep schedule in night workers when simultaneously being exposed to nightly bright light (Baehr et al., 1999; Youngstedt et al., 2016). Some of the experimental studies found that it

was possible to phase shift the circadian clock with bright light in combination with exercise but not with the exercise alone (Youngstedt et al., 2016). While other experimental studies found that exercise had no significant effect on the phase shift of the circadian rhythm (Baehr et al., 1999). Results from Youngstedt et al. (2016) ANOVA revealed no significance for phase shifts following bright light alone vs. exercise alone. The phase shift following bright light + exercise was marginally greater. One of the experimental studies found that both high and low-intensity exercise during the night caused phase delays by the following day (Youngstedt et al., 2016).

A meta-analytic review by Kredlow et al. (2015) supports the use of exercise to improve both subjective and objective metrics of sleep, as an evidence-based intervention. Another systematic review and meta-analysis of randomized controlled trials done by Rubio-Arias, Marín-Cascales, Ramos-Campo, Hernandez, and Pérez-López (2017) found that aerobic exercise for 12 weeks had a beneficial effect on quality of sleep although the severity of insomnia was not significantly reduced. Kredlow et al. (2015) found that the subjective effects of exercise on sleep were as good as the perceived effects of pharmacotherapy or behaviour therapy for insomnia disturbances. Beneficial effects of exercise on sleep metrics are immediate and regular exercise proves to give an even greater effect (Kredlow et al., 2015). An American national data survey study found that morning exercisers reported significantly better sleep quality and quantity as well as reporting least likeliness to awake unrefreshed. Those who exercised less than four hours before sleep showed no difference in sleep quality when comparing to non-exercisers, although evening exercise was not associated with sleep disturbances, not even in self-evaluated poor sleepers (Buman, Phillips, Youngstedt, Kline, & Hirshkowitz, 2014).) The recommendations by Buman et al. (2014) are that sleep wise it is better with morning exercise, but it is also sleeping wise better to exercise in the evening than to not exercise at all if the only possible time to exercise is in the evening.

*"Early to bed and early to rise makes and man healthy, wealthy and wise"* was once judiciously said by Benjamin Franklin. Even if his proverb is considered old, it is clearly related to sleep, circadian rhythms, and cognitive performance and therefore particularly applicable here.

### **Discussion**

The aim of this literature review has been to objectively compile and analyse if there is an effect, of early daytime outdoor exercise in natural light environments, on sleep quantity and quality. An effect that can enhance sleep quantity and quality, overall wellbeing and possibly be used as a non-pharmacological intervention for treatment of sleep disturbances without drug side effects. To determine the interventional effect this literature review has examined the facts from previous research on how exercise affects sleep physiology. Furthermore, this literature review has gathered and analysed information on how bright early daylight can influence the circadian rhythm and impact sleep quality and quantity. According to the research study done by Murray et al. (2017), outdoor morning exercise confers sleep benefits, and they found a significant ( $p=0,04$ ) interaction between the moderate to vigorous exercise/physical activity and time spent outdoors with the preceding total sleep time that increased in relation to time exercising outdoors in the morning. Though, considering that the research study by Murray et al. (2017) was performed during a very short period of time (seven days and seven nights), it would be interesting to see more longitudinal studies, to see if the effect increases over time. The research study done by Wams et al. (2017) where healthy subjects were provided ambulatory polysomnography (PSG) and wrist actigraphs to measure exposure to light, activity, rest, sleep architecture, and sleep quality clearly indicate that timing and amount of light exposure is closely linked to quality of sleep and sleep architecture. Wams et al. (2017) also performed dim-light laboratory analyses of melatonin release onset through salivary tests to exactly establish endogenous circadian

rhythm phases. The conclusion provided by Wams et al. (2017) that sleep quality and sleep architecture is directly associated with preceding exposure and timing of light in the environment since slow-wave sleep increased after early preceding light exposure, this also agrees with what Guo et al. (2016) found in their study on *Drosophila* flies. Guo et al. (2016) that found out how circadian neuron feedback controls the sleep activity profile in the flies and that dorsal clock neurons integrate environmental information with the circadian molecular rhythm and affect the sleep-wake profile. Furthermore, the findings by Wams et al. (2017) are also in line with previous evolutionary research. As O'Keefe et al., (2010) emphasizes that our ancestors were active outdoors during the day, exposed to the natural solar light. Blask, (2009) reminds us that before the industrial revolution humans were exposed to sunlight during the day and darkness during the night with only minor light sources such as moonlight, starlight, and fires. As Touitou et al. (2017) found out, that light and melatonin, did not ameliorate the adjustment to shift work, which probably is in accordance with our evolutionary heritage, that we humans are not genetically predisposed to shift our rhythm back and forth. It might only be possible to phase shift our rhythms to always live with a night-work, day-sleep schedule if exposed to the right wavelength and amount of light at the right time for a night-work, day-sleep schedule. Or will it, as Menet and Rosbash (2011) pointed out, probably just lead to internal bodily desynchronization and alter brain functions? In addition, Stothard et al. (2017) demonstrated desynchronization when melatonin rhythm in humans adapts to natural light-dark cycles but becomes delayed in modern environments with electrical lighting. A delayed and suppressed melatonin secretion entails repression of the immune function and increases the risk of developing various types of cancer according to Blask (2009). Is it as Wams et al. (2017) suggest, time to reassess models belonging to the present time when considering sleep regulation and pay attention to newly studied factors? Factors that belong to our past, maybe we need to take a step back in time

and consider how our human genome is designed to function in the natural environment. Sleep disturbances, as for example insomnia is according to Riemann et al. (2015) an escalating commonly occurring problem in societies today. When thinking carefully about how the rise of the hominin evolution started accordingly to DiMaggio et al. (2015) approximately 3-2,8 million years ago, and how human internal origin of oscillations in physiology rhythms has according to Blask (2009) evolved to operate at the same rate as the solar day. It is easy to relate sleep disturbances to rapid environmental changes when Blask (2009) reminds us of the short period of time that has passed since the invention and arrival of electrical light. Humans have lived their lives only for about 130 years with electrical lightning. Blask (2009) points out problems occurring due to the industrialized and digitalized, fast-paced '24/7' societies, many humans live in today. It is therefore easy to agree with the suggestion by Wams et al. (2017) that these findings could change our present comprehension of how sleep is regulated. Findings by Wams et al. (2017) emphasizes on the influence timing of light exposure has on sleep quality. The awarded Nobel Prize winners in Physiology or Medicine 2017 established exactly how light can synchronize the circadian clock rhythm (The official site of the Nobel Prize, 2017). Their studies confirm the importance of exposure to light. Is it so, that sleep firstly and mostly is regulated by the early exposure to bright outdoor light? And that early daytime outdoor exercise, therefore in addition to the bright light exposure, also can enhance the production of neurotransmitters, neuropeptides, neuromodulators neurohormones involved in the sleep-wake system to improve the quantity and quality of sleep? It is very easy to take sleep for granted until the time comes when you no longer can sleep enough, whatever the cause is. Today more and more people experience severe sleeping problems with impaired daily functioning. When considering the severe side-effects and possible consequences of sleeping drugs, alternative sleep enhancers is of utmost and paramount importance for society. The conclusion that can

be drawn from sleep loss implications, although it is not explicitly stated, suggests a desirable or necessary course of action to take since there is a great deal at stake at a public-health level. Finding out all the mechanisms that regulate our sleep holds an assurance of ameliorated cognitive performance and health.

This thesis, as previously discussed in the chapter “Exercise and its effect on sleep”, proposes exercise in natural blue light as a possible alternative to pharmacotherapy for sleep disturbances, by an intervention that positively can affect our sleep quantity and quality as well as our circadian phase rhythms through early outdoor exercise, and thus enhancing the sleep as well as overall well-being.

### **Limitations and Future Directions**

Limitations in this literature review are that since this is a relatively new area of investigation, to simultaneously combine daylight with exercise to understand the effects on sleep physiology, unfortunately, only one study was available to review. To my knowledge, relations between specified time outdoors in a specific wavelength of light, which are examined simultaneously with the time of exercise and its effect on sleep physiology has not previously been explored in other studies. A hypothesis is that in combination these two factors, bright daylight + regular exercise in the right amount and at the right time of the day, have an even greater effect when used together as a sleep enhancer than when used independently. Future directions could be to combine these two factors simultaneously in interventional larger populational studies, to evaluate and confirm the possible enhanced effect on sleep quantity and quality. Furthermore, future directions could also be to investigate the amount of time and the timing of the day where exercise and light exposure has the best effect on sleep enhancement. Wams et al. (2017) hypothesize that the amount of, and timing of direct light input observed by the retina in the eye, which then travels to the sleep 'switch' in the ventrolateral preoptic nucleus is altering the sleep stages. This hypothesis

also needs to be further investigated and a future direction for research could be to analyse delta power decay and investigate the relationship between sleep intensity and light exposure, as suggested by Wams et al. (2017). Confirmation from further interventional studies could improve our understanding of sleep regulation (Wams et al., 2017). The studies discussed in this review exemplify the importance of exposure to early daytime natural light in combination with exercise. Furthermore, most studies found was done on healthy subjects. Many future research areas remain to delineate the precise mechanisms that regulate the cerebral blood flow (CBF) and other factors, not only in healthy volunteers but in a myriad of clinical populations that suffer from sleep disorders. Many factors need to be considered to gain comprehension of the use of exercise and natural light exposure as a neuromodulator intervention to enhance sleep. More longitudinal research studies are also necessary to determine beneficial effects. Studies examining several parameters simultaneously, like the exercise in combination with timed exposure to a specific wavelength of light over a longer period since exercise have shown to give an even larger improvement on sleep quality over time, although also immediate effects have been shown. Longitudinal studies, preferably with subjects suffering from sleep disturbances since previous studies have been performed with healthy subjects. Tononi and Cirelli (2014) hypothesize that insufficient restoration during sleep is the cause of insomnia since insomniacs have shown to have increased global brain metabolism in neuroimaging studies, both during sleep and the waking state and that sleep is possibly the price we must pay for brain plasticity. As of May, (2011) pointed out the brain can both structurally and functionally modify connections or re-wire itself, both in beneficial and maladaptive ways. Healing takes time. Maybe many forms of sleep disturbances are caused by maladaptive brain connections and wirings due to environmental changes like for example shift-work or because of extended exposure to light into the night cycle, or maybe as Menet and Rosbash (2011) pointed out that everything in the body will be desynchronized in

a worst-case scenario if the circadian clock gets disrupted, including hormonal rhythms as the rhythm of melatonin. Is it bodily desynchronization or brain maladaptive rewiring, or both, that causes insomnia and other sleep disturbances? We need to find the patience to heal in our stressful society. We humans are so keen to search for quick fixes (such as sleeping pills, with inevitable consequences) so that we can continue our way of life, caught up in a fiercely competitive struggle for wealth or power, in other words, continue to run the treadmill of the rat race. Longitudinal studies are required to examine the healing effects of several parameters over time, as for example a certain amount of exercise in combination with timed exposure to a specific wavelength of light. To my knowledge relations between sleep, amount of exercise, and specified time outdoors in a specified wavelength of light examined simultaneously, has not been previously explored in any longitudinal study.

### **Conclusion and Future Prospects**

Sleep is necessary for human functioning (Anaclet & Fuller, 2017) There is an evident relationship between sleep quantity, quality, affective states, cognitive achievement, physical performance and overall human well-being (Tononi & Cirelli, 2014). Insufficient sleep is interconnected with future morbidity and mortality (Kovacevic et al., 2018). Thus, handling of sleep enhancement is of paramount importance to our society (Rosekind et al., 2010). Possible non-pharmacological effective interventions to improve quality and quantity of sleep for people with insomnia problems is fundamentally important for well-being and longevity. Early daytime outdoor exercise is an effective intervention to use for improvement of circadian phase rhythm and better sleep. Sleep quality, quantity, health, and well-being are also known to improve by the exercise. The conclusion drawn from this literature review is that early daytime outdoor exercise is an effective non-pharmacological intervention to enhance sleep without drug side effects.

I conclude this thesis with a sentence well said by Dr. Rafael Pelayo who is specialized in sleep medicine:

*"Your life is a reflection of how you sleep, and how you sleep is a reflection of your life."*

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