Comparison of subjective sleep quality and daytime sleepiness with whole-night polysomnography findings in sleep apnea patients

Pedersen, Nina Rani

UNIVERSITY OF SPLIT
SCHOOL OF MEDICINE

Nina Rani Pedersen

COMPARISON OF SUBJECTIVE SLEEP QUALITY AND DAYTIME SLEEPINESS WITH WHOLE-NIGHT POLYSOMNOGRAPHY FINDINGS IN SLEEP APNEA PATIENTS

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Assist. Prof. Ivana Pavlinac Dodig, MD, PhD

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LIST OF ABBREVIATIONS

AHI - Apnea-Hypopnea Index

APAP - Auto titrating positive airway pressure

ARAS - Ascending reticular activating system

AV - Block - Atrioventricular block

BPAP - Bi-level positive airway pressure

BQ - Berlin questionnaire

CBT - Cognitive behavioral therapy

CHF - Congestive heart failure

COPD - Chronic obstructive pulmonary disease

CPAP - Continuous positive airway pressure

EEG - Electroencephalography

EMG - Electromyography

EOG - Electro-oculography

ESS - Epworth Sleepiness Scale

GERD - Gastroesophageal reflux disease

NREM - Non rapid eye movement

OA - Oral appliances

PAP - Positive airway pressure

PG - Polygraphy

PSG - Polysomnography

PSQI - Pittsburgh sleep quality index

REM - Rapid eye movement

RNS - Reactive nitrogen species

ROS - Reactive oxygen species

SCN - Suprachiasmatic nucleus

SEM – Slow-rolling eye movement

SLD - Sublaterodorsal nucleus

SSS - Stanford Sleepiness Scale

TMN - Tuberomammillary nucleus

UPPP - Uvulopalatopharyngoplasty

VLPO - Ventral lateral preoptic area

1. INTRODUCTION

1.1. Sleep

For decades sleep has been a research subject perceived as a big mystery (1). It was thought to be a passive state, but later we have found that sleep is a very active phase.

We sleep around one third of our life (2) so a good quality and quantity of sleep has a huge impact on our health and emotions (1). But, why is that so? What is happening during sleep and why is it so important for human kind? There are a lot of unanswered questions concerning sleep and we still do not have a complete theory explaining it. But during the latest years sleep studies and sleep medicine as a discipline have grown, and now we know a lot more about sleep, its functions, physiology and pathology.

Many have tried to define sleep, but we still strive to get one good definition. The definition adopted in this thesis is that sleep is defined on the basis of both the physiological changes that occur in the brain's electrical rhythms and the behavior of the person (1). The criteria for the behavior is reduced response to external stimulation, lack of mobility or slight mobility, characteristic sleeping posture, elevated arousal threshold, reversible unconscious state and an impaired cognitive function (2,3).

1.1.1. Sleep stages

Electroencephalography (EEG), electro-oculography (EOG), and electromyography (EMG) are used to measure the physiological criteria of sleep. With these three measurements sleep is divided into two states:

- Non rapid eye movement (NREM) sleep which accounts for 75-80% of sleep time in adults (1) and can be further divided into three stages, N1, N2 and N3 (2);
- Rapid eye movement sleep (REM) accounting for 20-25% of sleep in adults (1).

EEG, EOG and EMG will show a different pattern between being awake (Figure 1) and during sleep (Figures 2-5), but there will also be a difference between the sleep stages. The characteristics of the sleep stages are summarized in Table 1.

Table1. Characteristics of sleep stages.

Typical waveform characteristics of the different sleep stages

R&K	ASSM	Frequencies	Amplitude	Specific Waveforms	Eye Movement	Submental EMG
Wake	W	>13 Hz beta with eyes open 8-13 alpha with eyes closed	Lowest amplitude		Blinks/REM	High
Stage 1	N1	Mixed frequencies: 4-7 Hz theta	Low amplitude	Vertex sharp (V) waves	SEM	Medium
Stage 2	N2	4-7 theta with <20% 0,5-2 Hz delta	Slightly higher	K-complexes Spindles	Few	Low
Stage 3	N3	4-7 Hz theta and > 20% delta	High Delta			
REM	R	Mixed frequencies: 4-7Hz theta and 8-13 Hz alpha	Low amplitude	Sawtooth waves of 2-6 Hz	REM	Lowest

REM, rapid eye movement, SEM, slow-rolling eye movements.

Taken from Claudio Bassetti, Zoran Dogas and Philippe Peigneux. Sleep medicine textbook.1st ed. Regensburg: European Sleep Research Society; 2014 (3).

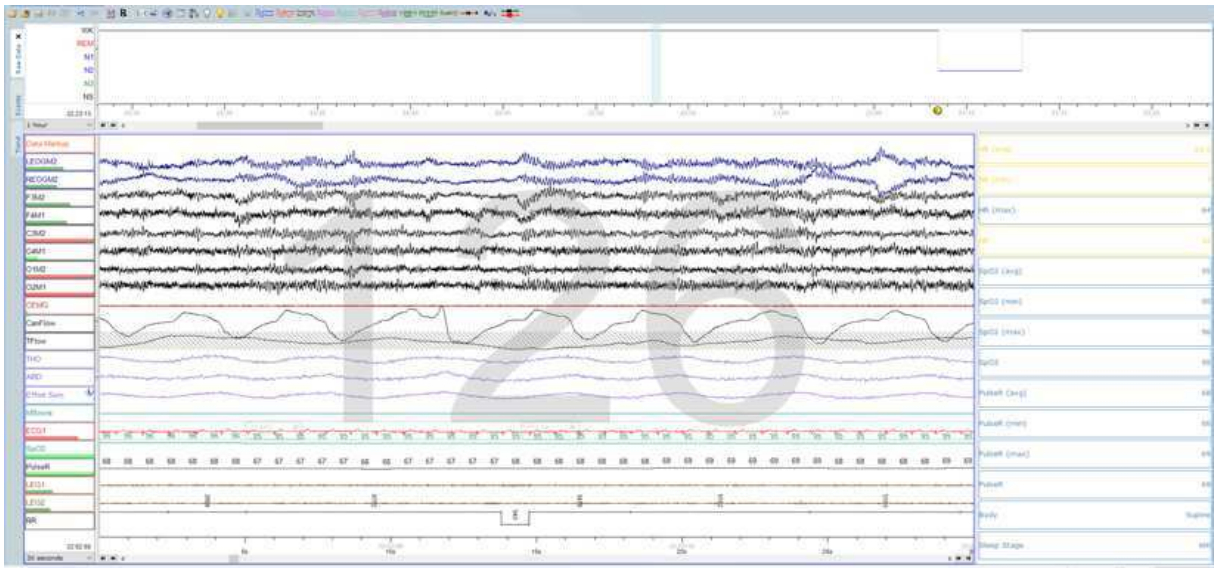

Figure 1. EEG in wake stage. A representative epoche (30 seconds) from whole night polysomnography; recording taken from Split Sleep Medicine Center patient recording database.

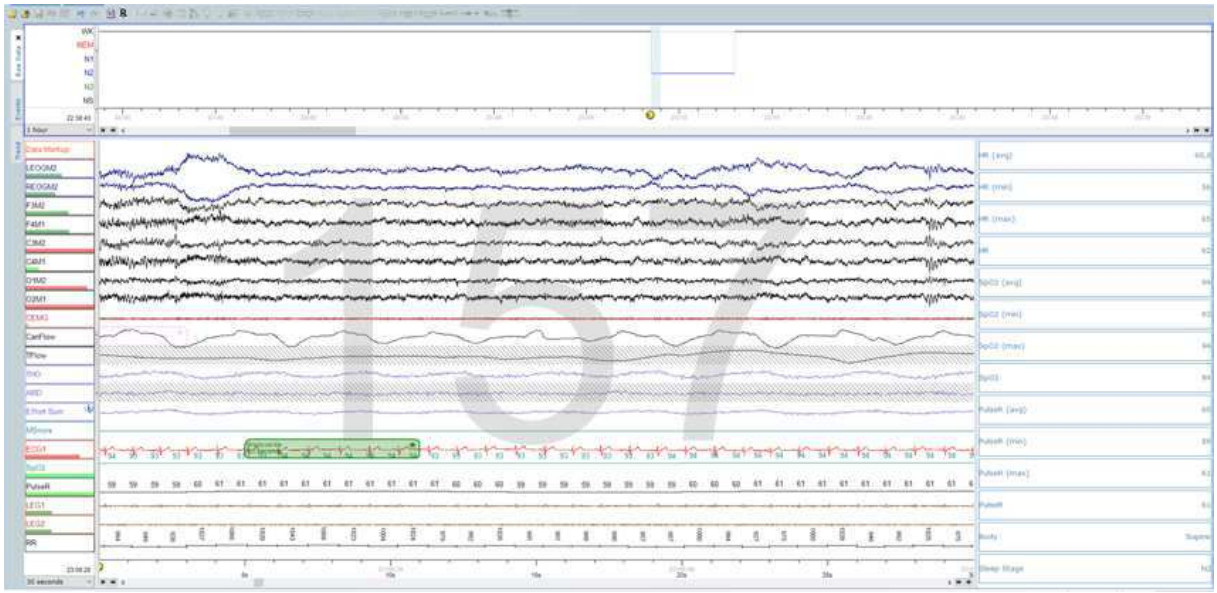

Figure 2. Sleep stage N1 represents the transition from wakefulness to sleep and the arousal threshold is lowest in N1 (4). A representative epoche (30 seconds) from whole night polysomnography; recording taken from Split Sleep Medicine Center patient recording database.

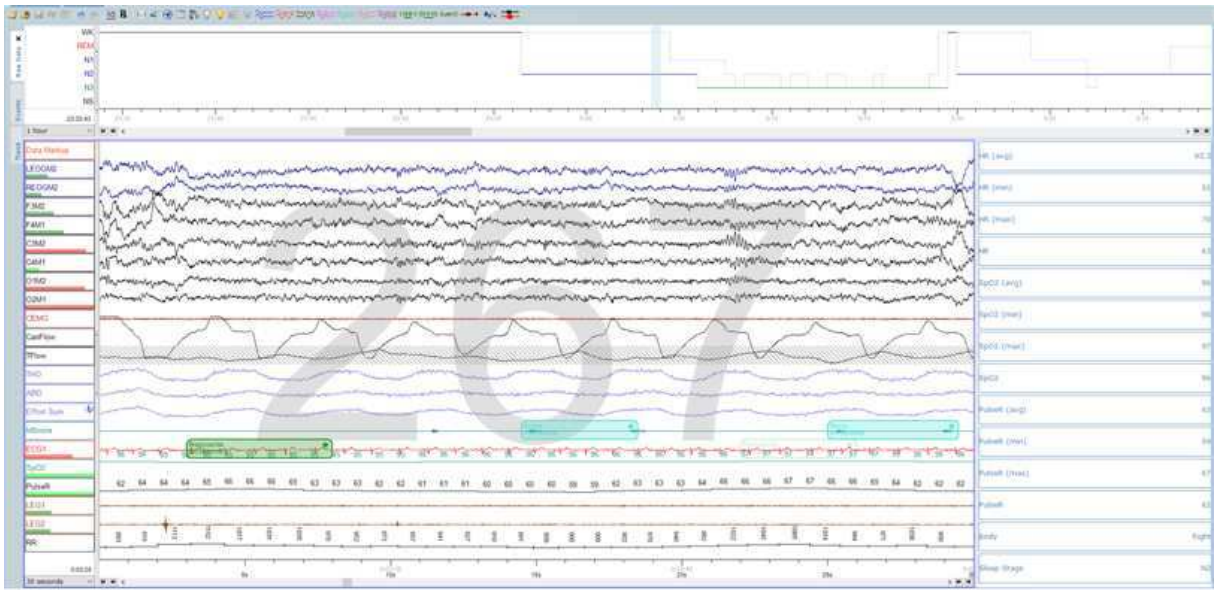

Figure 3. Sleep stage N2 is the sleep stage which in adults accounts for the greatest proportion of total sleep time. A representative epoche (30 seconds) from whole night polysomnography; recording taken from Split Sleep Medicine Center patient recording database.

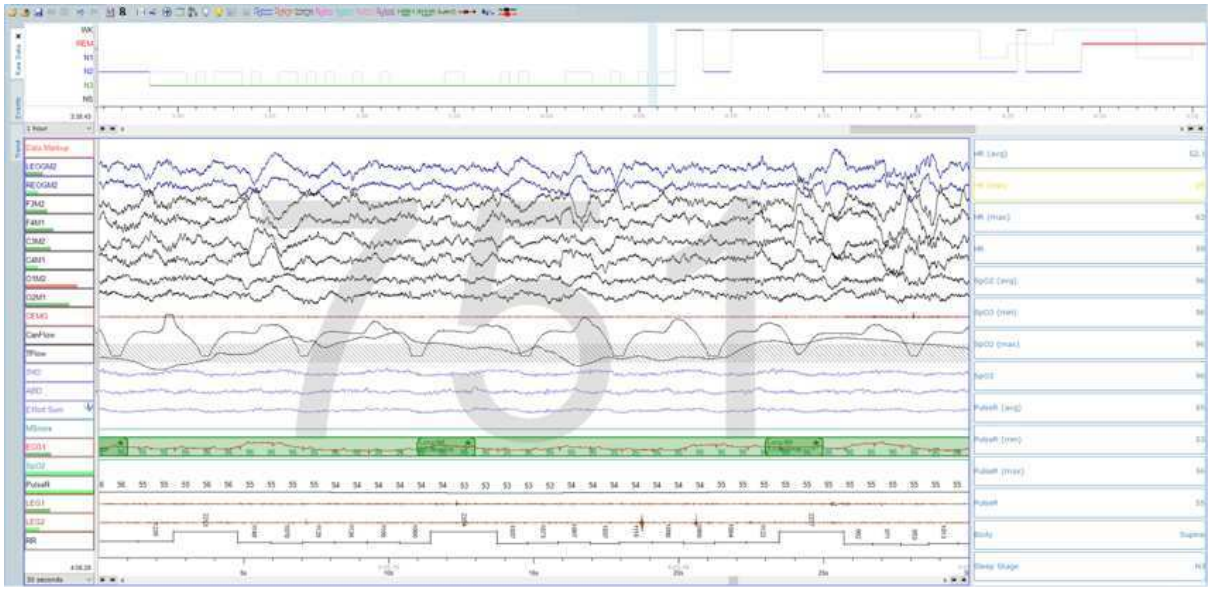

Figure 4. N3 stage. This stage is deep sleep. Nightmares, sleepwalking and bedwetting may occur. If there is waking in this stage, the feeling of disorientation may be felt for a few minutes. A representative epoche (30 seconds) from whole night polysomnography; recording taken from Split Sleep Medicine Center patient recording database.

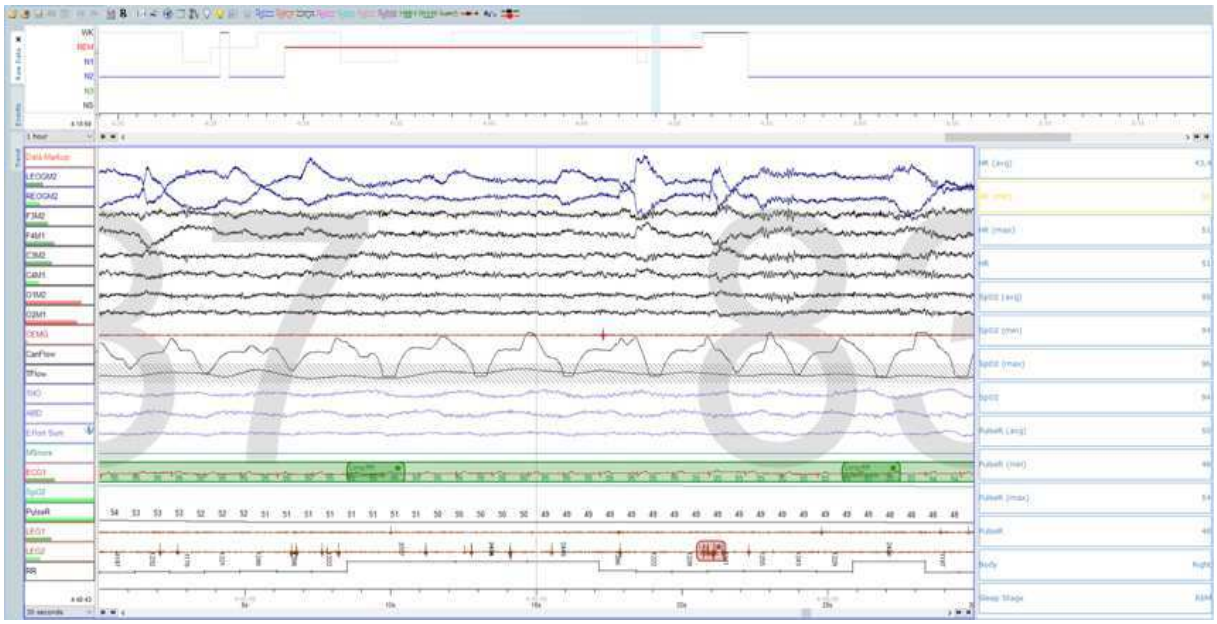

Figure 5. REM sleep is similar to the wake EEG, but without any postural muscle tone. A representative epoche (30 seconds) from whole night polysomnography; recording taken from Split Sleep Medicine Center patient recording database.

The two states, NREM and REM sleep, are alternating in a cyclic manner where each cycle lasts from 90-120 min and are in a total of 3-5 cycles in adults. In the sleep cycles not all of the sleep stages will necessarily be presented (4). In the first cycle N1 will be presented, then the following cycles can miss stage. During the second half of the night, there is usually just an alteration between stage N2 and REM.

N1 stage (Figure 2) is the first sleep stage and is known as the light sleep. In this stage the brain activity will slow down and the muscle tone will slowly decrease. This is also where there can be a feeling of falling and there will be a sudden muscle contraction. It is easy to wake up from this stage (5). The percentage of N1 sleep stage is 2-5% of the total sleep time (4). Slow rolling movements of the eyes can be seen in N1 stage, similar as during drowsiness with eyes closed.

In N2 stage (Figure 3) the eyes stop moving and the brain activity further slows down. The body temperature and the heart rate decreases (5). The slow rolling movements of the eyes disappear during the N2 stage. The percentage of N2 sleep stage is 45-55% of total sleep time (4).

N3 stage (Figure 4) is known as deep sleep stage. In this stage nightmares, sleepwalking and bedwetting may occur. If there is a waking in N3 stage, the feeling of disorientation for a few minutes following waking may be felt (5). The percentage of sleep stage N3 should be 5-20% (4).

The remainder of the night (about 20-25% of the total sleep time) is carried out in REM stage (4), shown in Figure 5. During the REM phase we can see the classic rapid eye movements in all directions. These sharp deflections in the EOG can also be seen during wakefulness with open eyes. The EOG in REM sleep will have two components: tonic which is without rapid eye movements and phasic where there is rapid eye movement (4). The density of the eye movements is increasing progressively towards the later REM sleep stages (4). There is also muscle atonia where the brain stem neurons inhibit spinal motor neurons (2). The muscle atonia is caused by the ventral portion of the sublaterodorsal nucleus (SLD). The SLD neurons increase firing during REM sleep and are firing at their maximum. They are glutamatergic and produce the muscle atonia by activating inhibitory interneurons in the spinal cord and the ventral medulla (6).

Other important features of REM sleep are phasic changes in blood pressure and heart rate, irregular respiration and phasic tongue movements. Moreover, periods of apnea or hypopnea (3,4) may appear and be even more expressed than during NREM stages.

One of the main functions of REM sleep is consolidation of learning and memory by regulation of neuronal synapses and facilitation of neuronal plasticity. The support to this idea is brought by results of many animal studies showing that REM sleep deprivation impairs formation of spatial and emotional memories.

There are some speculations that REM sleep also prepares wakefulness by stimulating the central nervous system. This belief raises from the fact that virtually all REM stages are immediately followed by wakefulness, that humans and animals are more alert when woken from the REM stage compared to the deep NREM stages and that the amount of REM stages increase towards the end of sleep (6).

Newborns spend a majority of sleep time in a REM-like sleep stage. It is called active sleep in newborns because of the lack of cortical EEG features present in adult sleep. This led to a hypothesis that REM sleep might be important for the development of the brain. Researches also suggest a possibility that muscle twitching, that occurs against a background of muscle atonia, functions to aid sensorimotor system development. During these twitches multiple brain regions are activated. More specifically, hippocampus, cerebellar cortex and the red nucleus are all activated during REM sleep, but not during similar motor activity in wakefulness (6).

1.1.2. Neurophysiological regulation of sleep

Concerning physiological changes during sleep several neurochemical systems are included. The ascending reticular activating system (ARAS), a structure composed of several nuclei and neural circuits, is believed to play an important role in regulation of sleep and wakefulness, as well as sleep-wake transition (7). It consists of dopaminergic, serotonergic, noradrenergic, histaminergic, cholinergic, glutamatergic, and orexin hypothalamic neurons that all exert direct and indirect influences on cerebral cortex, promoting wakefulness. More precisely, serotonergic neurons mainly located in the dorsal raphe nucleus, noradrenergic neurons in the locus coeruleus and cholinergic neurons in the pontine brainstem are all included, as shown in Figure 6. There are also systems located more rostrally in the forebrain: cholinergic neurons in the basal forebrain, histaminergic neurons localized in the tuberomammillary nucleus (TMN) and the orexin system in the tuberal hypothalamus, which are the first neurons that excite all the other wakening systems (7).

During sleep, GABAergic and galanin-containing neurons in the ventral lateral preoptic area (VLPO) of the anterior hypothalamus inhibit neurons of the ARAS including:

- histaminergic neurons in the TMN;
- hypothalamic orexin neurons;
- brainstem serotonergic, noradrenergic, dopaminergic and cholinergic neurons.

Inhibition of the all above mentioned structures of the ARAS promotes NREM sleep.

During REM sleep, monoamines, particularly noradrenaline and serotonin, are even further reduced. This leads to increased cholinergic inputs to the thalamus, resulting in EEG appearance of arousal. Brainstem circuits include neurons that inhibit tonic muscle activity during REM sleep (7).

The 24-h circadian rhythm serves to coordinate the external world with the internal time. It is a rhythm in physiology and behavior that is generated by internal molecular clock. It is known that the most important regulator of the circadian rhythm is the suprachiasmatic nucleus (SCN) in the anterior hypothalamus. The SCN's task is to synchronize the peripheral tissues that contain the molecular clock machinery required for local circadian oscillations and rhythmic gene expression (8).

For proper functioning, the circadian network needs to receive and respond to different time signals, Zeitgebers. The most important example of the Zeitgebers is light (9). A behavioral manifestation of the circadian rhythm, expressed mostly as a person's propensity to sleep at a particular time during the 24-hour period, is known as chronotype. Early types (larks) or late types (owls) are the extremes of different chronotypes. The difference is influenced by genetics, development and by light. Studies have shown that mutations in Cry1 are linked to Familial Delayed Sleep Phase syndrome (9). However, any disturbance of the circadian clock and rhythm can lead to major health complications like metabolic syndrome, psychiatric illness and cognitive impairment (9).

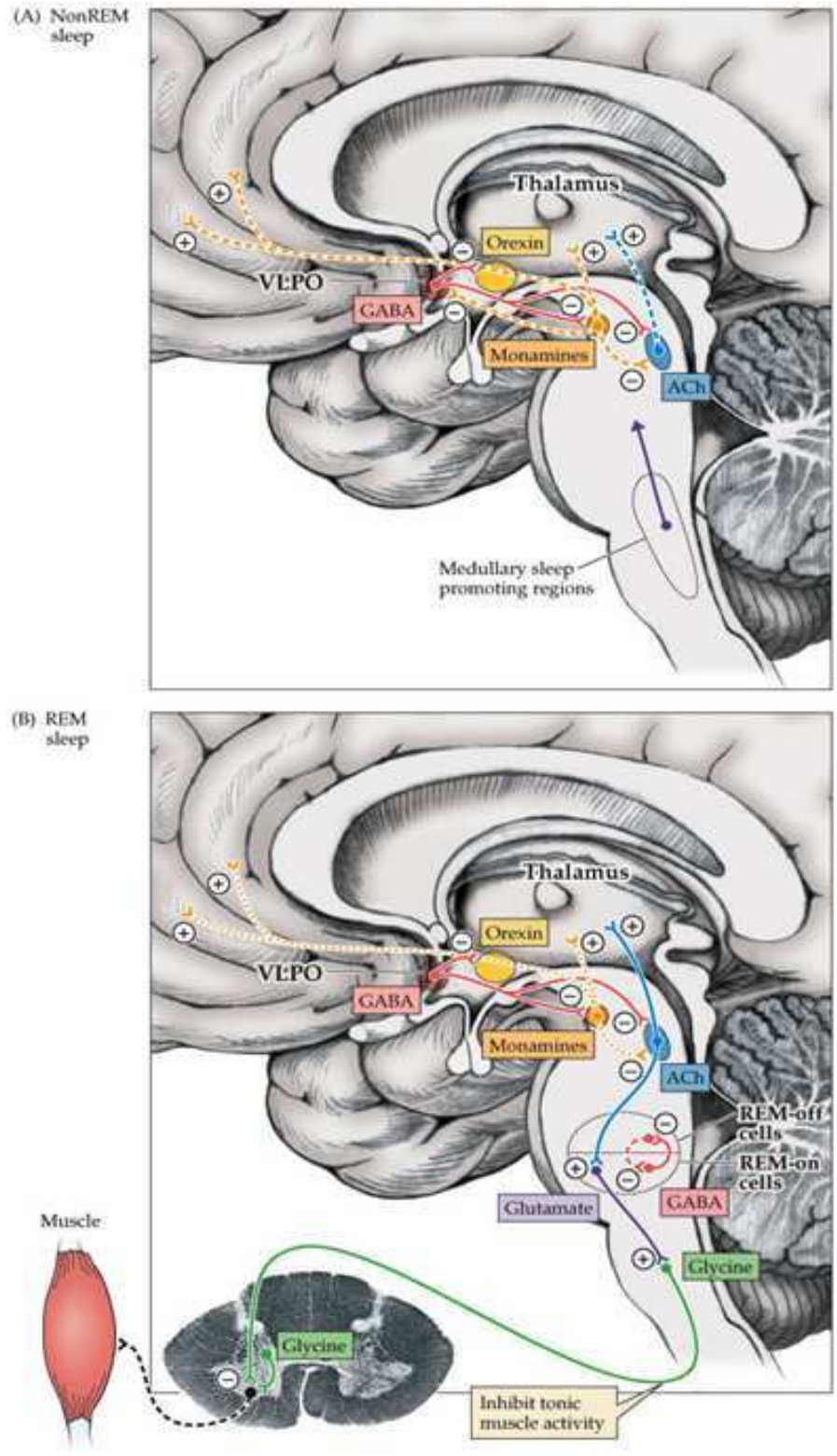

Figure 6. Differences in central nervous system activity in NREM and REM sleep.

Taken from Spinal cord section modified from DeArmond SJ, Fusco MM, Maynard MD. 1989. Structure of the Human Brain: A Photographic Atlas. 3rd Ed. Oxford, New York (10).

1.2. Diagnostic procedures in sleep medicine

1.2.1. Screening tests

The screening tests are frequently used in sleep medicine to assess the risk for sleep disorders and to measure subjective sleep quality (4). The most frequently used screening tests that are going to be described in this thesis are: Berlin questionnaire, STOP-BANG questionnaire, Pittsburgh Sleep Quality Index, Epworth Sleepiness Scale, and Stanford Sleepiness Scale.

Berlin questionnaire (BQ)

This questionnaire was constructed in 1999 and its goal is to identify risk factors for sleep apnea (11). It can be self-administered, it is easy to use and can quickly identify high and low risk sleep disordered breathing (12).

The Berlin questionnaire consists of 10 questions and includes additional information about weight and height. The questionnaire is divided into 3 categories: first category contains 5 questions about snoring and cessation of breathing, the second category consists of 4 questions about excessive daytime sleepiness and the last category has 1 question about arterial hypertension (13). If there are 2 or more positive categories in this test, it indicates high risk of OSA (13). Study conducted on clinical population demonstrated that BQ had moderate to low sensitivity, specificity, positive and negative predictive values, depending on the OSA severity (14). However, to achieve higher predictive properties of the Berlin questionnaire, the patient's bed partner or roommate should also be asked to confirm the questions concerning snoring, if possible (15).

STOP-BANG questionnaire

This questionnaire was developed in 2008 and was originally meant to screen for OSA in the surgical population (16). The goal was to make an easy to use, reliable and concise tool for screening patients having increased risk for OSA (17).

The STOP questionnaire contains 4 questions and the mnemonic stands for STOP: S is for Snoring, T stands for Tiredness, O is for Observed apnea and P is for High blood pressure.

BANG defines demographic items where B stands for BMI, A for Age, N for Neck circumference and G for Gender (male) (16).

In the STOP questionnaire, a score between 0-1 indicates a low risk for OSA, and a score of 2 or more indicates high risk for OSA. With the use of the extended form of the questionnaire (STOP-BANG), predictive properties of the questionnaire are better in comparison to the STOP questionnaire. In the STOP-BANG questionnaire, a score of 0-2 indicates a low risk for OSA, a score of 3-4 indicates moderate risk, and a score from 5-8 indicates a high risk for moderate to severe OSA (17). The sensitivity of the STOP-BANG score ≥ 3 to predict OSA depends on the OSA severity and is 83.9% for mild OSA, 92.9% for moderate OSA, and even 100% in the group of severe OSA patients (16).

In conclusion, due to the high sensitivity and its simplicity this test is highly used in OSA patients (16).

Pittsburgh sleep quality index (PSQI)

This questionnaire is the most widely used generic measure of sleep quality in both research and clinical settings and was created in 1988 (18). The main goals to develop PSQI were to provide reliable, valid and standardized subjective measure of sleep quality which will be able to discriminate between "good" and "poor" sleepers, providing an assessment of different sleep disturbances affecting sleep quality. Moreover, the authors aimed to provide a questionnaire that's easy for both, patients to use and for doctors to interpret (19). It is a self-rated questionnaire which goal is to assess the subjective sleep quality and sleep disturbances over 1 past month (19). It was originally created in English, but it is now translated into other languages and proven both reliable and valid when translated (20).

Epworth Sleepiness Scale (ESS)

ESS was published in 1991 and its goal is to measure general levels of daytime sleepiness (21). It is the most used subjective sleepiness scale in clinical practice. It is easy to use, and it can be performed by the patient without any help from the physician (22).

ESS has a good test-retest reliability and correlates with the results on the other subjective sleepiness scales. It shows improvement in treatment studies of patients with sleep apnea and narcolepsy. There is also a positive correlation with the likelihood of falling asleep

behind the wheel (22). There is a weak correlation between ESS and OSA severity, but it is still considered the best tool for awareness of sleepiness (21).

Stanford Sleepiness Scale (SSS)

SSS goal is to measure current subject's sleepiness level (23). It consists of 7 degrees of severity (22), ranging from very alert to excessively sleepy (23). The SSS measures sleepiness at a very particular moment. This test is better at monitoring sleepiness in one specific person over time than using it to compare different individuals. SSS is sensitive to daily activity changes in sleep inclination and deprivation (4). It can be used repetitively, and can be repeated in short intervals, unlike the ESS (22).

1.2.2. Polygraphy (PG)/polysomnography (PSG)

Polysomnography is a method that was developed to physiologically describe and examine human sleep (24). PSG consists of continuous and simultaneous recording of multiple monitors: EEG, ECG, EOG, EMG, airflow and oxygen saturation are all included (4). The records used in PSG are shown in Figure 7.

PSG is an expensive, time consuming and sophisticated examination and is not always necessary. Portable monitoring such as polygraphy has been introduced as a substitute in patients suspected of having OSA (25). It can be more convenient for the patient due to the fact that they can sleep at home, and it also has a lower cost compared to PSG. Still, it is not as accurate as PSG (4) and therefore PSG is still the gold standard in diagnosing OSA (25).

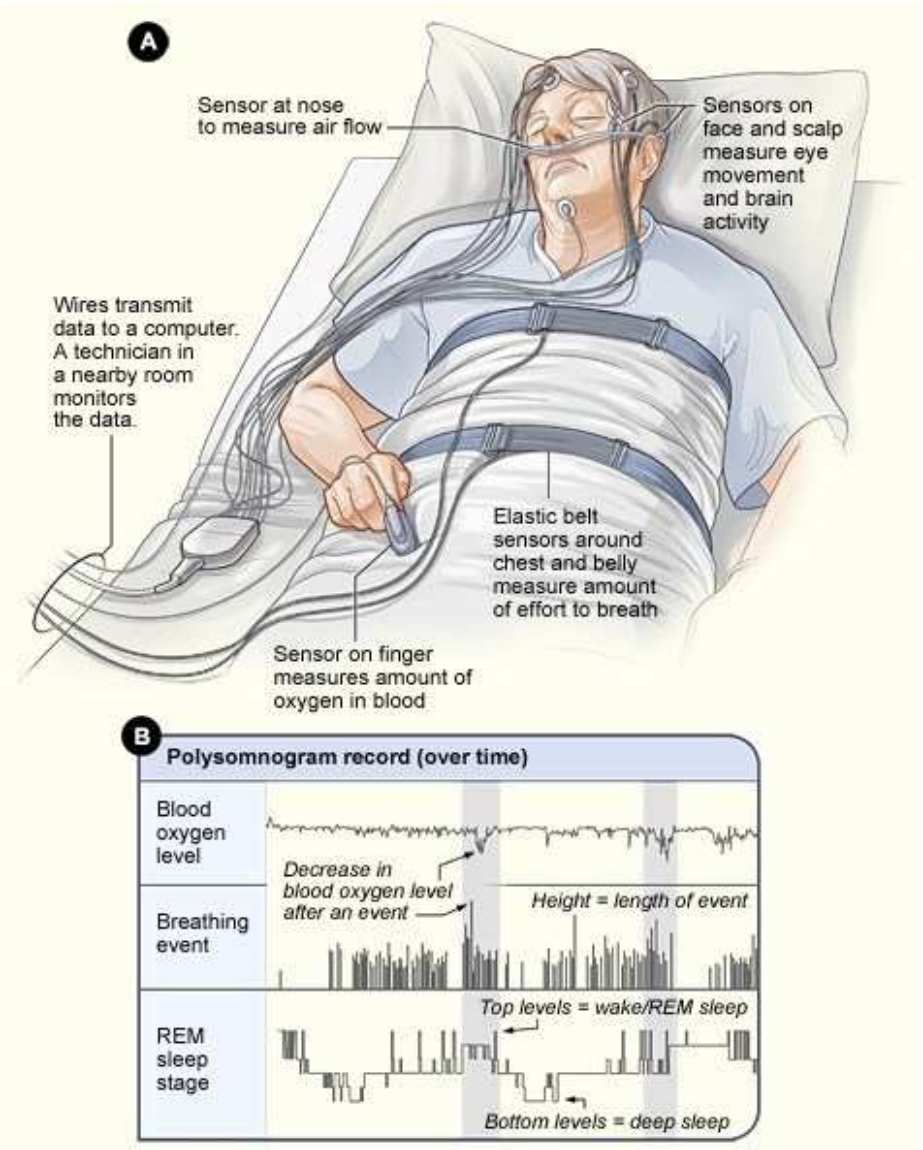

Figure 7. PSG measurements.

Taken from Amsleep.org [Internet] The American sleep apnea society. Available from https://amsleep.org/ (26).

1.3. Sleep disorders

Sleep disorders are one of the most common health complaints for the clinicians. Around half of the adults in the western world experience intermittent sleep disturbance, and 15-20% of them report chronic sleep problems (18).

Enough quality sleep is necessary for optimal health but also for safety. Alteration in timing of sleep and amount of sleep are associated with many different diseases (27), such as cardiovascular diseases.

1.3.1. Obstructive sleep apnea

Obstructive sleep apnea (OSA) is an increasingly recognized and treated sleep disorder It is a common disorder and an important cause of morbidity and mortality (28). OSA will be the main disorder discussed in this thesis.

The disorder is characterized by repetitive episodes of partial (hypopnea), or complete (apnea) upper airway obstruction during sleep (29). The anatomy of the upper airways during normal breathing and OSA is shown in Figure 8 (30).

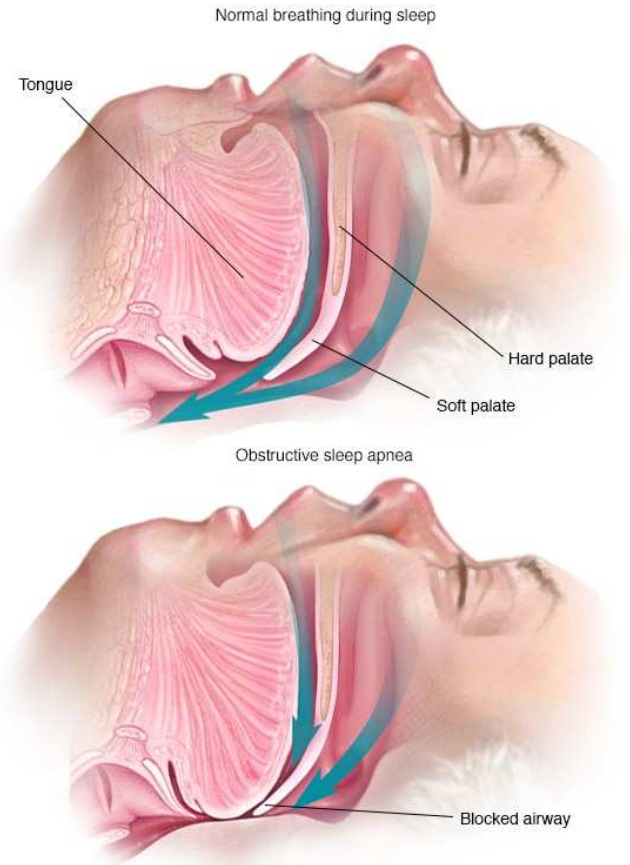

Figure 8. Normal breathing during sleep and obstructive sleep apnea.
Taken from MayoClinic.org [Internet]. May Clinic. Available from https://www.mayoclinic.org/diseases-conditions/obstructive-sleep-apnea/symptoms-causes/syc-20352090 (30).

This is accompanied by intermittent hypoxemia, increased respiratory effort, and sleep disturbance (29). The main manifestations of this condition are respiratory pauses during sleep, followed by loud snorts (29). The clinical impacts beside snoring are headaches when patient wakes up (31), daytime sleepiness (5), frequent nightmares (29), decrease of cognitive performance (32), and an extreme burden on cardiovascular and metabolic systems. The frequency of anxiety in OSA patients is also higher than in the general population (29).

Some studies suggest that OSA prevalence is as much as 2-4% in men and 1-2% in women of average age (32). But there are reasons to think that there is a higher number and a lot of unreported cases. The risk of getting OSA increases with age and obesity is seen in as much as 70% of OSA patients (34). In addition, male gender is one of the most important risk factors for this syndrome (29), although it can occur in any age, body type and gender.

OSA is defined and diagnosed by using apnea-hypopnea index (AHI). It is provided from overnight PSG or PG and is calculated as the number of episodes of breathing cessation per hour of sleep. Usually OSA is diagnosed if the AHI is above 5. AHI between 5 and 15 indicates mild OSA, between 15 and 30 indicates moderate OSA and above 30 indicates severe OSA. Other biomarkers that are monitored during PG/PSG include measures of hypoxemia, measurement of sleep disruption and the duration of obstructive events (34). The activity of the pontomedullary pacemaker neurons is preserved, so the thoracic muscles are innervated properly, and their activity can be seen in EMG record (33).

The degree and the frequency of the obstructions will have a great impact on the severity of the clinical presentation of the patient. Tiredness, sleepiness and sleeping during the day can affect both social life and work. In some of the more serious cases dangerous situations could easily arise. About 7% of motor vehicle accidents for a population of male drivers involved in a motor vehicle accident are attributable to OSA (35). OSA patients also have nearly twofold increased odds of work accidents (35).

A new and upcoming field is the study of genetics and OSA. Unfortunately, these studies have been lagging far behind studies done on other chronic diseases and their genetic involvement. There are good reasons to believe that OSA is heritable, and there is evidence of both a direct genetic contribution to OSA susceptibility and indirect contributions (34). Indirect contribution would be phenotypes such as obesity, specific craniofacial structure, impaired neurological control of upper airway muscles and of sleep and circadian rhythms (34). However, neither indirect, nor direct genetic factors are believed to be inherent following Mendelian patterns and many candidate genes that interact with many environmental factors

are involved (34). For example, polymorphisms in TNF-α, as well as mutations in PTGER3, IL-6, and e-NOS genes are seen as a risk factor for OSA (34).

1.3.1.1. Comorbidities

The obstructive events can lead to different notorious physiological consequences seen in OSA patients. Inflammation, oxidative stress, hypoxemia, sleep fragmentation and an increased sympathetic tone all together gives a higher risk for insulin resistance which can further lead to metabolic and cardiovascular diseases (36).

The upper airways, from the nares to the larynx, is a flexible and collapsible tube. Activation of dilator muscles maintains the upper airway patency to counteract factors that promote upper airway closure during sleep (4). When there is an obstruction in the upper airway, as can be seen in OSA patients, the tidal volume will fall with the consequent decrease of the oxygen saturation and an increase in carbon dioxide. Intermittent hypoxia excites peripheral arterial chemoreceptors which evoke persistent sympathetic activation. An increased sympathetic tone then causes vasoconstriction and tachycardia and the blood pressure increases (37).

As there is an increased respiratory effort against a narrowed or completely blocked airway, a reflex bradycardia and atrioventricular block (AV block) may occur. When the apnea stops, a recovery tachycardia may develop, and supraventricular and ventricular ectopy may occur in susceptible individuals (37). Moreover, increased preload and afterload, left shift of the interventricular electrical axis and a reduction in left ventricular compliance might also be the consequences. This may result in worsening of preexisting congestive heart failure (37).

OSA is linked with increased oxidative stress and reactive oxygen species/reactive nitrogen species (ROS/RNS) (38). More precisely the hypoxia-induces stress leads to release of inflammatory cells, elevation of leptin, reduced fibrinolytic activity and increased platelet adhesiveness (37). Also, repetitive hypoxia and reoxygenation causes mitochondria and endoplasmic reticulum dysfunction, NADPH oxidase overactivation, xanthine oxidase, uncoupling NO synthase and an induced imbalance of the pro-oxidant and antioxidant molecules which gives a rise to series of oxidative stress response. In the brain oxidative stress can lead to neuron injury and cognitive dysfunction, usually seen in OSA patients (39). It is important to point out that oxidative stress occurring due to the long-term intermittent hypoxia is further promoting breathing instability by worsening the pharyngeal muscle dilator function (37).

It is known that OSA has adverse effects on endocrine glands (40-42). The most frequent endocrine comorbidity in OSA patients is diabetes mellitus type 2. It can also be seen the other way around, that type 2 diabetes patients often develop OSA. Several studies have reported that OSA is associated with poorer glycemic control and it is a risk factor for glucose dysmetabolism. Moreover, studies using PG/PSG for accurate diagnosis of OSA showed a robust positive association between OSA severity and levels of HbA1c in patients with type 2 diabetes (40). Independent of obesity, OSA is also associated with increased insulin resistance and glucose intolerance (41). Intermittent hypoxia, increased sympathetic tone, and dysregulation of the hypothalamo-pituitary axis, might be mechanisms linking OSA to insulin resistance and impaired glucose tolerance, further leading to diabetes mellitus type 2 (42).

There is also data suggesting a link between OSA and gestational diabetes and even type 1 diabetes, in terms that patients with type 1 diabetes have higher prevalence of OSA than the general population (40). In some females, due to hyperinsulinism that shifts the androgen-estrogen balance of the ovarian hormone synthesis towards the androgen side, polycystic ovarian syndrome may appear (37).

Obesity is the major risk factor for OSA (43), and epidemiological studies have demonstrated that there are increased odds of developing OSA when gaining weight. It is estimated that 58% of OSA patients with moderate to severe type is due to obesity (43).

Patients also report a rapid weight gain in the year prior to the OSA diagnosis. Even though we do not fully understand the mechanisms underlying the relationship between OSA and obesity, some data suggest that sleep deprivation is associated with an increase in appetite hormones, further leading to altered eating patterns and weight gain (43). However, fat distribution seems to have even more important role than obesity itself and increased waist/hip ratio and neck circumference correlates better with OSA severity than obesity in general (4). Imaging studies have shown that retropharyngeal fat deposition may reduce the upper airway diameter and promote breathing difficulties (37). Nevertheless, weight reduction can reduce the severity, or even eliminate OSA in some patients, (37) which is an important aspect.

Concerning the cardiovascular system, OSA is associated with major pathogenesis (44). Cardiac arrhythmias and sudden cardiac death can be seen. Intermittent hypoxia and chronic sleep fragmentation may shift the sympatho-vagal balance toward sympathetic predominance and a vagal withdrawal. This can further lead to myocardial electric instability. It has been shown that OSA patients are susceptible to this adverse sympathoexcitation during the REM sleep. There is also seen a difference between genders when it comes to ventricular repolarization, where females have longer action potentials, a higher susceptibility to

arrhythmias and predisposition to arrhythmogenic effects of some drugs when compared to the men of the same age (44). Some studies suggest an association between pulmonary hypertension and OSA, but there are still no final conclusions yet (45).

There is an association between stroke and OSA. Mild OSA was seen in 72% of patients following a stroke or transient ischemic attack, and AHI > 20 in 38% of these patients (37).

Many psychiatric disorders, such as depression and anxiety have been associated with OSA (46). A systematic review has shown that the prevalence of depression varied from 7% to as much as 63% and anxiety 2.9–70% in OSA patients. The big difference was attributed to different factors such as the use of different mood scales. OSA patients with comorbid major depression reported longer and more severe episodes of depression when compared to depressive patients without OSA, and the CPAP treatment was successful in reduction of comorbid depressive symptoms (47). Previous study supports the theory that the more severe OSA is, there would be a higher percentage of patients with depression (48), but a study performed at Bergen University hospital surprisingly found that increased severity of OSA was actually associated with less anxiety and depression (49). In conclusion, the link between depression, anxiety and OSA needs to be more profoundly investigated.

Previous studies have indicated that OSA patients have gastroesophageal reflux disease (GERD) symptoms, consisting of heart burning, acid regurgitation and sleep deficiency (50), much more frequently than people in the general population (51). The reason might be negative intrathoracic pressure gradients which is seen in OSA patients and may lead to symptoms of GERD (51). Indeed, it has been shown that around 50% of GERD symptoms that occurred in OSA patients were in fact related to the apneas or hypopneas (4). Furthermore, a study using endoscopically diagnosed GERD found that GERD was associated to a more severe OSA, and that the symptoms of GERD were associated with worsened sleep quality (51).

1.3.1.2. Treatment

There are two major categories of OSA treatment, surgical or non-surgical.

The surgical treatment might include nasal surgery, hypopharyngeal surgery, oral surgery, the hypoglossal nerve stimulation, or tracheostomy in very rare occasions (52). Uvulopalatopharyngoplasty (UPPP) is the most common surgical procedure for OSA patients. The procedures done in UPPP and the consequences of the surgery on the upper airways are shown in Figure 9. This surgery consists of tonsillectomy, reorientation and trimming of anterior and posterior tonsillar pillars and excision of posterior palate and uvula (53).

A study investigating the effects of UPPP for OSA treatment demonstrated that six-month post-surgery all patients had significant improvements in sleep properties (snoring index, AHI, respiratory distress index, and arterial oxygen saturation) and symptom improvements was found in 64% of cases (54).

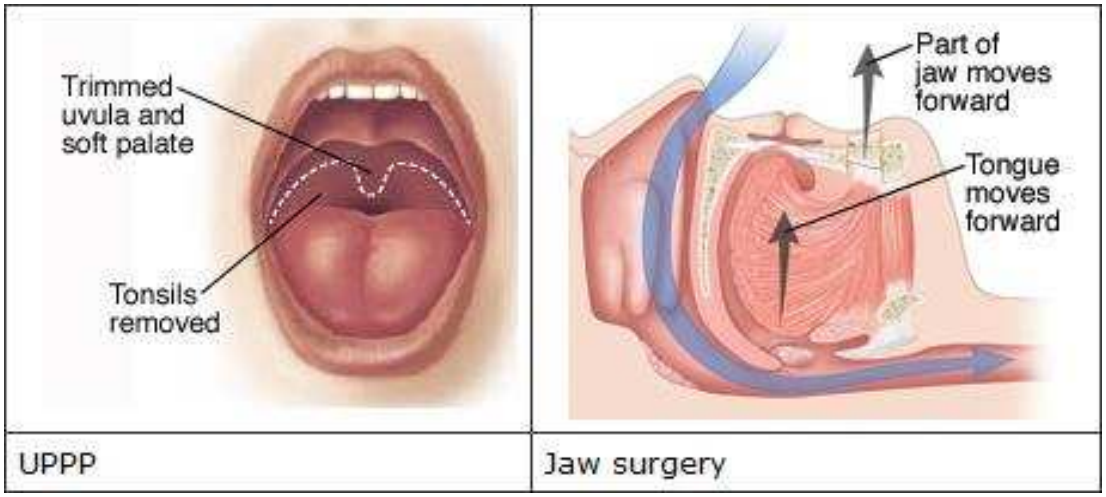

Figure 9. UPPP surgery.
Taken from MountNittany.org [Internet]. Available from https://www.mountnittany.org/articles/healthsheets/6299 (55).

Part of the non-surgical treatment is positive airway pressure (PAP), oral applicants, drugs, transcutaneous electrical stimulation and positional therapy (52). PAP is the most common treatment for OSA. PAP has three modes: continuous positive airway pressure (CPAP), bi-level positive airway pressure (BPAP) and auto titrating positive airway pressure (APAP) (52). The standard treatment for severe OSA is CPAP (56), and in it shown in Figure 10 (57).

Figure 10. CPAP treatment.
Taken from Cancercare.com [Internet] Cancer care of western New York. Available from https://www.cancercarewny.com (57).

It is usually recommended to patients with an AHI > 30/hour and for symptomatic patients (4). Still, it can also be selectively used in the mild and moderate type (52), but the benefit of CPAP for mild OSA and no associated medical or psychiatric disorders is more uncertain (4). The compliance to the CPAP therapy is 40–80% (52).

CPAP is able to overrun OSA by keeping the upper respiratory tract open during sleep (56). Its functions as a pneumatic splint maintaining patency of the nasopharyngeal airway (4). It consists of a CPAP machine which makes the pressure gradients and a tube that transmits this pressure to the CPAP mask. The mask can cover only the nose (nCPAP) or nose and mouth (full face mask) (58).

By preventing airway collapse and vibrations, different studies have shown that CPAP can improve everything from snoring to awakening, nocturia, wheezing and asphyxia. There is also seen improvement in excessive daytime sleepiness and a reduction of car accidents following regular CPAP use (52). A number of studies have also suggested that treatment with CPAP could attenuate oxidative stress levels in OSA patients (39). Both symptomatic improvement and long-term outcomes benefits are found in both meta-analyses and

randomized controlled trials investigating effects of CPAP use in OSA treatment (58). It also looks like the longer CPAP is used, the better the improvement for long-term prognosis of cardiovascular disease is (52).

The adverse effects of all the PAP`s might be skin rupture, conjunctivitis, nasal congestion, airway dryness, pneumothorax, intestinal obstruction (52). If there is an intolerance to CPAP, both BPAP and APAP can be used (52). BPAP will give a lower level of expiratory positive airway pressure and a higher level of inspiratory positive airway pressure. It can be used in older age patients, higher AHI, more pronounced desaturations, higher ESS scores, Chronic obstructive pulmonary disease (COPD) and Congestive heart failure (CHF) (52). APAP automatically adjust the pressure between 5-20 mmHg. It provides more of both comfort and compliance than CPAP. Patients with different comorbidities, like CHF, COPD, or central apnea, may not be eligible for APAP (52).

When the supine sleep AHI is at least twice that of sleeping in a non-supine position, it is considered as a type of positional or supine obstructive sleep apnea (4). The airways more easily collapse in a supine position and the end-expiratory lung volume is reduced. This reduces the negative pressure in the chest and the lung oxygen is reduced (52). The treatment might be lying in any other position than supine. The effect is highly depended on the patient's ability to find a comfortable non-supine sleep position (52). The therapy traditionally consists of placing 3-4 tennis balls in a pocket in the back of a pajama top - the tennis ball technique (4), which prevents the patients turning to a supine position. Unfortunately, the long-term compliance is very poor. In a study less than 10% of the patients continued this technique after 30 months (52). There have been different alternatives to the tennis balls, like the cervical pillow (4) mattress for prone sleep, vibrotactile positional feedback, but this area needs more research (52).

Oral appliances (OA) are dental splints that keep the mandible in a desirable position that prevents the upper airway from collapsing while sleeping. OA are the second most common therapy used when treating OSA, first is CPAP. OA are cheap, simple, reversible and quiet (56). That is also why many patients prefer them before CPAP. OA are effective in around 80% of patients that are snoring and patients with mild to moderate OSA and around 30% of patients with severe OSA. Positional OSA patients seems to have a higher success rate (4). The type of OA used seems to play a role in the effectiveness. The custom-made type has been demonstrated more effective than the boil-and-bite type. The adverse effects are dry mouth or tooth/gum discomfort, excessive salivation, muscle tenderness and jaw stiffness. The costume

made type can remove these adverse effects; otherwise the side effects will usually resolve with time (56).

Rather than to be either or, both CPAP and OA could potentially complement each other. The combination has been reported successful. A study found that patients that where compliant to CPAP (> 4 h/night) improved their sleep further once they had an option to use OA when they did not use CPAP (59).

Drug therapy including acetazolamide, medroxyprogesterone, serotonin agents and modafinil have all been studied as potential OSA treatment (4). Enhancement of upper airway muscle tone during sleep, increase of the ventilatory drive, reduce of REM sleep and alleviation of excessive sleepiness are all mechanisms where pharmacologic agents potentially might improve OSA signs and symptoms (4). Unfortunately, to this date, there is no single pharmacological agent that can be used for primary treatment of OSA (37). More studies are needed to fully understand this field.

As an addition to any therapeutic mode, in general, OSA patients are recommended to stop taking certain drugs that are known to worsen or induce apnea. Smoking, alcohol, benzodiazepines, narcotics, muscle relaxants and sedatives are all recommended to be stopped. It is also important to discuss sleep hygiene and potentially dangerous activities (4).

1.3.2. Central sleep apnea

Central sleep apnea appears due to a temporary failure of the pontomedullary pacemaker neurons to generate a breathing rhythm. The inspiratory neural output that is needed for the nerves innervating the inspiratory thoracic muscles is not working and this causes stop of inspiratory ventilation and absence of naso-oral airflow. The complete absence of more than 10 seconds is defined as an apnea. The central apneas can occur normally during the sleep onset or can be caused by many different disorders like congestive heart failure, opioid treatment etc. Central apneas may appear in all ages and both genders (33).

1.3.3. Insomnia

Insomnia is characterized by difficulty falling asleep or difficulty maintaining sleep. The most common symptoms can be frequent awakenings, problems returning to sleep after awakenings, or waking up too early and not being able to return to sleep (60). There is a feeling of not being refreshed after sleep and an impairment of daytime functions. These complaints

must have been problematic for at least 4 weeks to be diagnosed as insomnia (61). In the general population around 1/3 will experience symptoms of insomnia and 10-15% will meet the criteria of the disorder insomnia (62). Out of these around 50% has a chronic type (60).

The risk factors for insomnia are highly comorbid with psychiatric disorders (63). Other risk factors are female sex, older age (> 60 years), night/rotating shift work, traveling across time zones, psychosocial distress, pregnancy, poor physical health (congestive heart failure, sleep-disordered breathing), poor mental health (depression, anxiety, schizophrenia), substance use or medication side effects (62).

The main diagnostic procedure in assessment of insomnia is whole-night PSG. However, a sleeping log or diary can offer an important insight in patients' signs and symptoms and help in insomnia evaluation (64).

There is evidence suggesting hyperarousal pathophysiology that includes elevated cortisol levels and adrenocorticotropic hormone during the early sleep and an elevated whole-body metabolic rate during both sleep and wakefulness. Increased high frequency EEG activity in NREM sleep and a reduced parasympathetic tone in the heart rate variability have also been confirmed. Small wake-sleep differences in regional brain metabolism are also found in people with insomnia compared to healthy sleep (61).

The first line therapy of insomnia is cognitive behavioral therapy (CBT) (63). It has been shown in different randomized control trials that CBT works better in both short- and long-term outcomes in comparison with sleep medicines like e.g. zopiclone. There was an improvement in sleep efficiency from 81.4% pretreatment to 90.1% after 6 months. The patients using zopiclone, surprisingly, had a decrease in sleep efficiency from 82.3% during pretreatment to 81.9% after 6 months (65). CBT consists of sleep hygiene education, including regular exercise, balanced diet, avoiding alcohol use and ensuring the proper sleeping environment (in terms of noise, temperature and reduced lightning). There is also a strict schedule of bedtime and rising time and the time allowed in bed. A part of the CBT is education of the patient with the main goal to teach to identify and treat fears and beliefs concerning sleep. Insomnia patients are also instructed how to control muscular tension and how to control and relax (65).

1.3.4. REM sleep behavior disorder (RBD)

In this disease there is a loss of the mechanisms that cause the atonia and paralysis normally seen in REM sleep. The result is inappropriate motor behavior during REM sleep,

usually manifested as sporadic limb jerks, kicking and punching. Shouting can also be heard (6).

The pathophysiology of this disease is not currently known. Animal models suggest an interruption in REM muscle atonia and disinhibition of brainstem motor pattern generators, especially in the pontine tegmentum. In adults with RBD neuroimaging shows evidence of structural lesions in the brainstem, implicating the dorsal midbrain and pons (37).

Unfortunately, many of patients diagnosed with RBD will develop neurodegenerative diseases like Parkinson's disease and Lewi bodies 6-15 years following the RBD diagnosis (6), which can suggest that RBD is a neurodegenerative disease itself. RBD can also occur due to narcolepsy and OSA or as a side effect of drugs such as antidepressants.

It is diagnosed using whole night PSG, although some screening questions can help in evaluation of RBD patients. The treatment consists of treatment of underlying causes, changing in sleep environment and drugs such as melatonin or clonazepam (66).

1.3.5. The most common complaints of patients with sleep disorders

Although there is so much difference in etiology and pathophysiology of various sleep disorders, sometimes they might present with similar symptoms (5,60). Poor sleep quality and excessive daytime sleepiness are among the most common complaints in patients suffering from various sleep disorders. Poor sleep quality includes troubles with falling asleep, frequent wakening and not feeling refreshed after a sleep. In many cases, the objective corresponding parameter of the subjective sleep quality is sleep efficiency. This objective parameter can be obtained from the whole-night PSG and represents the quotient between time spent sleeping and time spent in bed. It is expressed as percentage and the higher number indicates better sleep efficiency. Still, it does not provide any information about sleep architecture and thus cannot be sufficient in sleep evaluation (4). Subjective sleep quality can be assessed with different questionnaires and scales, with the PSQI being the one of the most frequently used questionnaires in assessment of the subjective sleep quality (18-20). Another very prominent symptom of the various sleep disorders, especially OSA, is excessive daytime sleepiness, resulting from frequent arousals and microarousals related to respiratory events (5). Usually, in a clinical setting, the subjective daytime sleepiness is assessed with Epworth sleepiness scale (21,22).

2. AIM AND HYPOTHESES

The aim of this thesis is to compare subjective sleep quality measured by the Pittsburgh Sleep Quality Index and excessive daytime sleepiness measured by the Epworth Sleepiness Scale with objective whole-night polysomnography findings in OSA patients from Split Sleep Medicine Center (SSMC).

Hypoteses:

- Sleep efficiency assessed by whole-night polysomnography will positively correlate with sleep quality assessed by Pittsburgh Sleep Quality Index in OSA patients.
- OSA patients with poor subjective sleep quality assessed by Pittsburgh Sleep Quality Index will have impaired sleep architecture.
- OSA patients with excessive daytime sleepiness will have impaired sleep architecture.
- OSA severity measured by AHI will positively correlate with excessive daytime sleepiness assessed by the Epworth sleepiness scale.
- OSA severity measured by AHI will positively correlate with subjective sleep quality assessed by Pittsburgh Sleep Quality Index.

3. SUBJECTS AND METHODS

3.1. Subjects

The subjects recruited in this study are OSA patients from the Split Sleep Medicine Center. From 2008-2018 a total of 317 patients diagnosed with OSA by whole night PSG were included in this study. Patients who were diagnosed OSA with PG were not included since PG does not provide data about sleep architecture and sleep efficiency that were important in this research. Adults, both males and females, were included and their ages ranged from 18 to 82 years. Exclusion criteria were age less than 18 years or the presence of severe mental disability.

3.2. Methods

Prior to going to sleep, the patients filled in the questionnaires, with the assistance of the medical staff, if needed. Following completion of the questionnaires, the patients were hooked up with the electrodes for PSG and were put in the bed to sleep.

3.2.1. Questionnaires

Epworth Sleepiness Scale (ESS) was used to measure patient's general level of daytime sleepiness. This is a subjective test where the patient has to rate on a scale from 0-3 (where 0 represents no chance of dozing and 3 represents high chance of dozing) if they have dozed in 8 specific situations over the recent time. These situations are: Sitting and reading, Watching TV, Sitting inactive in a public place, Being a passenger in a motor vehicle for an hour or more, Lying down in the afternoon, Sitting and talking to someone, Sitting quietly after lunch (no alcohol) and Stopped for a few minutes in traffic. The score achieved on the ESS is the sum of answers to these eight questions and may be between 0-24, where the higher numbers indicate higher daytime sleepiness. A score of 10 or more indicates the presence of excessive daytime sleepiness. In this research the Croatian version of the ESS that has been previously validated was used (67).

Pittsburgh sleep quality index (PSQI) consists of 19 items and it offers 7 component scores and 1 global score. The 7 components are Subjective sleep quality, Sleep latency, Sleep duration, Sleep efficiency, Sleep disturbance, Sleep medicine usage and Daytime function. The maximum score that can be achieved on this questionnaire is 21 and the higher scoring numbers indicate worse sleep quality. In this study Croatian version of the PSQI was used to assess patient's subjective sleep quality (20).

3.2.2. Polysomnography

For the objective view on sleep the whole night PSG was used recorded with Alice 5 and Alice 6 LDE devices (Philips, Respironics, Amsterdam, The Netherlands). As mentioned before, PSG consists of continuous and simultaneous recording of multiple monitors: EEG, ECG, EOG and EMG. In EEG, the voltage was recorded from scalp electrodes representing summed potential activity of cortex neuronal somas and dendrites. The voltages varied between 5 and 200 mV and the frequency somewhere between 0.5 and 45 Hz. In this study, the international 10-20 system of placement of the electrodes was used and, following the system, the electrodes were placed 10 or 20% of the distance to specific landmarks, both on the right and the left side of the scalp.

EOG was used to measure a potential difference between the positively charged cornea and the negatively charged retina. Two electrodes were used, one placed 1 cm above and lateral to the outer canthus of the eye and the other one 1 cm below and lateral to the outer canthus of the other eye according to Rechtschaffen and Kales criteria (37).

EMG measures the electrical activity of muscle fibers and nerve impulses. Thus, the electrodes were attached to the mentalis and submentalis muscles. Additional bipolar electrodes were placed on the anterior tibialis muscle to record limb movements.

PSG recording also included respiration monitoring, by detecting changes in pressure between inspiration and expiration in the oronasal airflow, monitoring of the saturation of the blood with oxygen by pulse oximeter and monitoring efforts of the thoracic and abdominal muscle walls.

All patients were recorded with whole-night PSG during one night. All the standard operative procedures for adults in accredited sleep medicine centers in Europe brought by European Sleep Research Society were followed during the PSG recording (68). The PSG recordings were automatically scored, but later on they were manually corrected by experienced sleep medicine stuff. The data achieved by PSG that was used in this study included: AHI indicating OSA severity, sleep efficiency calculated as ratio between time spent sleeping and time spent in bed, and sleep architecture expressed as amount of each sleep stage.

3.3. Data collection and statistical analysis

All data, including PSG measures, ESS and PSQI, was collected and summarized in a table with the use of Excel software. All statistical procedures were carried out in the MedCalc (MedCalc, Ostend, Belgium). Categorical variables were shown as whole numbers and percentages and quantitative variables as means and standard deviations. Age was shown as

median and minimum and maximum, and the amount of each sleep stage was presented as percentage. In comparison of the sleep architecture between mild, moderate and severe OSA patients one-way ANOVA was used. Correlations between sleep efficiency and PSQI, between ESS score and AHI, as well as AHI and PSQI were expressed with the use of Pearson's correlation coefficient. Student’s t-test was used in evaluation of sleep architecture differences between good and poor sleepers, and among patients with normal and excessive daytime sleepiness. The level of statistical significance was set at $P < 0.05$.

4. RESULTS

In the present research a total of 317 patients from the Split Sleep Medicine Center (SSMC) were included. 83 females with a median age of 60 and ranging from the age of 20 to 82 years, and 234 males with a median age of 55, ranging from the age of 18 to 80 years were recruited in the study. The demographic data of the study subjects are shown in Table 2.

Table 2. Demographic data of the subjects.

	Female N (83)	Male N (234)	Total N (317)
Age	60 (20-82)	55(18-80)	56 (18-82)
BMI (kg/m^2)	28.28±4.58	29.86±4.45	29.45±4.53
Height (cm)	165.30±6.53	180.85±7.21	176.80±9.80
Weight (kg)	77.43±13.29	97.82±16.26	92.481±17.93
NC (cm)	37.14±3.47	43.62±3.26	41.93±4.36

BMI=Body mass index, NC=Neck circumference
Variables are shown as means ± standard deviations.
Age is shown as median (min-max).

In Table 3, differences in sleep architecture among patients with mild, moderate and severe OSA are shown. Sleep architecture changed with OSA severity, with an increased amount of sleep stage N2 (66.41±11.93% in mild OSA, 69.12±11.43% in moderate OSA and 73.45±14.74% of sleep stage N2 in severe OSA, F = 8.635, $P < 0.001$; Table 3) and decreased amount of deep sleep stage N3 in more severe forms of OSA (11.67±8.89 % in mild OSA, 11.10±7.35% in moderate OSA and 6.88±7.63 in severe OSA, F = 12.701, $P < 0.001$; Table 3).

Table 3. Sleep architecture in different severities of OSA.

	OSA				
	Mild 5<AHI<15 N=107	Moderate 15<AHI<30 N=76	Severe AHI >30 N=133	*P**	F-value
N1 (%)	4.83±5.65	5.01±4.80	5.75±9.61	0.607	0.501
N2 (%)	66.41±11.93	69.12±11.43	73.45±14.74	0.001	8.635
N3 (%)	11.67±8.89	11.10±7.35	6.88±7.63	0.001	12.701
REM (%)	17.44±7.90	14.77±8.33	13.81±7.42	0.002	6.412
Sleep efficiency (%)	77.04±13.25	75.80±14.57	80.26±15.96	0.070	2.680

All values are presented as percentages and expressed as means ± standard deviations.
*Differences are tested with one-way ANOVA

Patients who had decreased sleep efficiency had higher score on PSQI, indicated by a negative statistically significant correlation between sleep efficiency assessed by whole night polysomnography and subjective sleep quality assessed by PSQI ($r = -0.21$, $P = 0.001$; Figure 11). In the analysis of correlation between sleep efficiency and PSQI score, 3 patients were excluded due to the fact that they did not sleep at all.

Patients suffering from more severe forms of OSA had more pronounced excessive daytime sleepiness and the relationship between AHI and score achieved on ESS showed a statistically significant positive correlation ($r = 0.25$, $P < 0.001$), as shown in Figure 12.

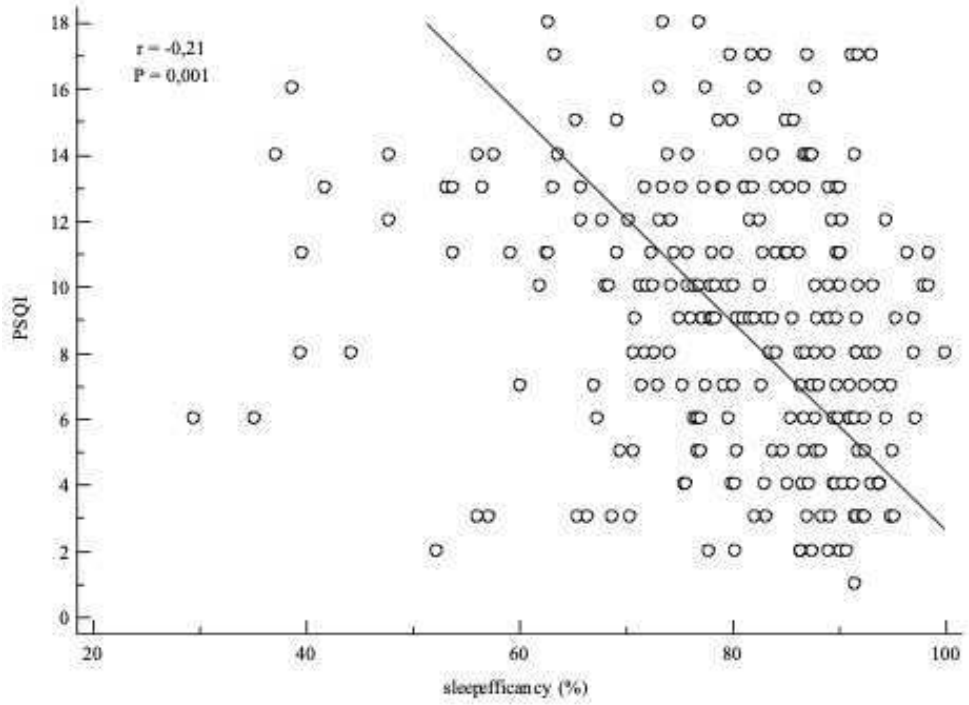

Figure 11. Correlation of PSQI and sleep efficiency (N = 239; 242 subjects answered PSQI, 3 subjects were excluded due to the fact that they had very low sleep efficiency).
Data were analyzed with Pearson's correlation coefficient.

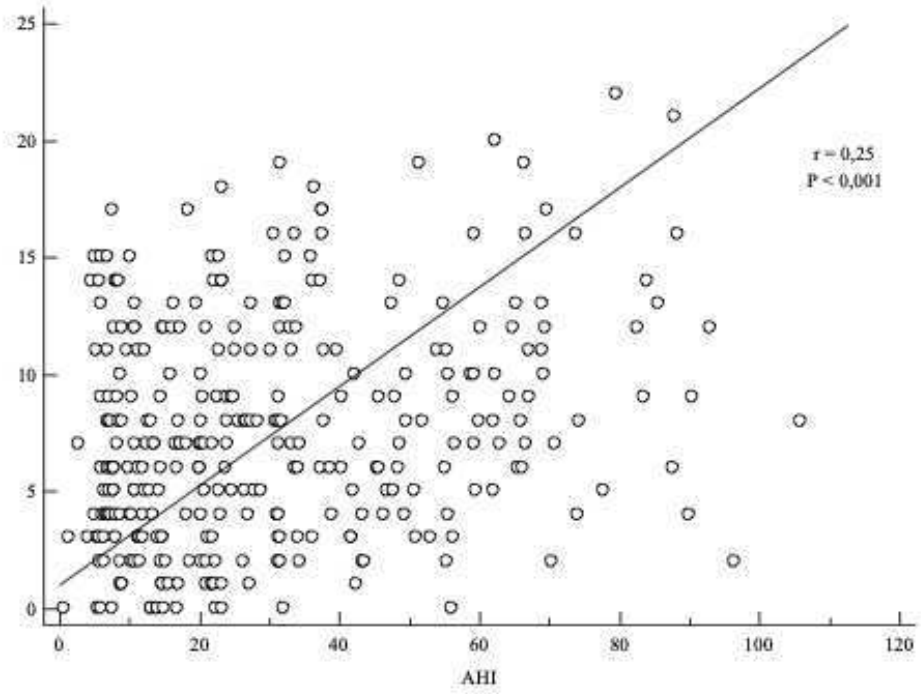

Figure 12. Correlation of ESS and AHI (N = 315).
Data were analyzed with Pearson's correlation coefficient.

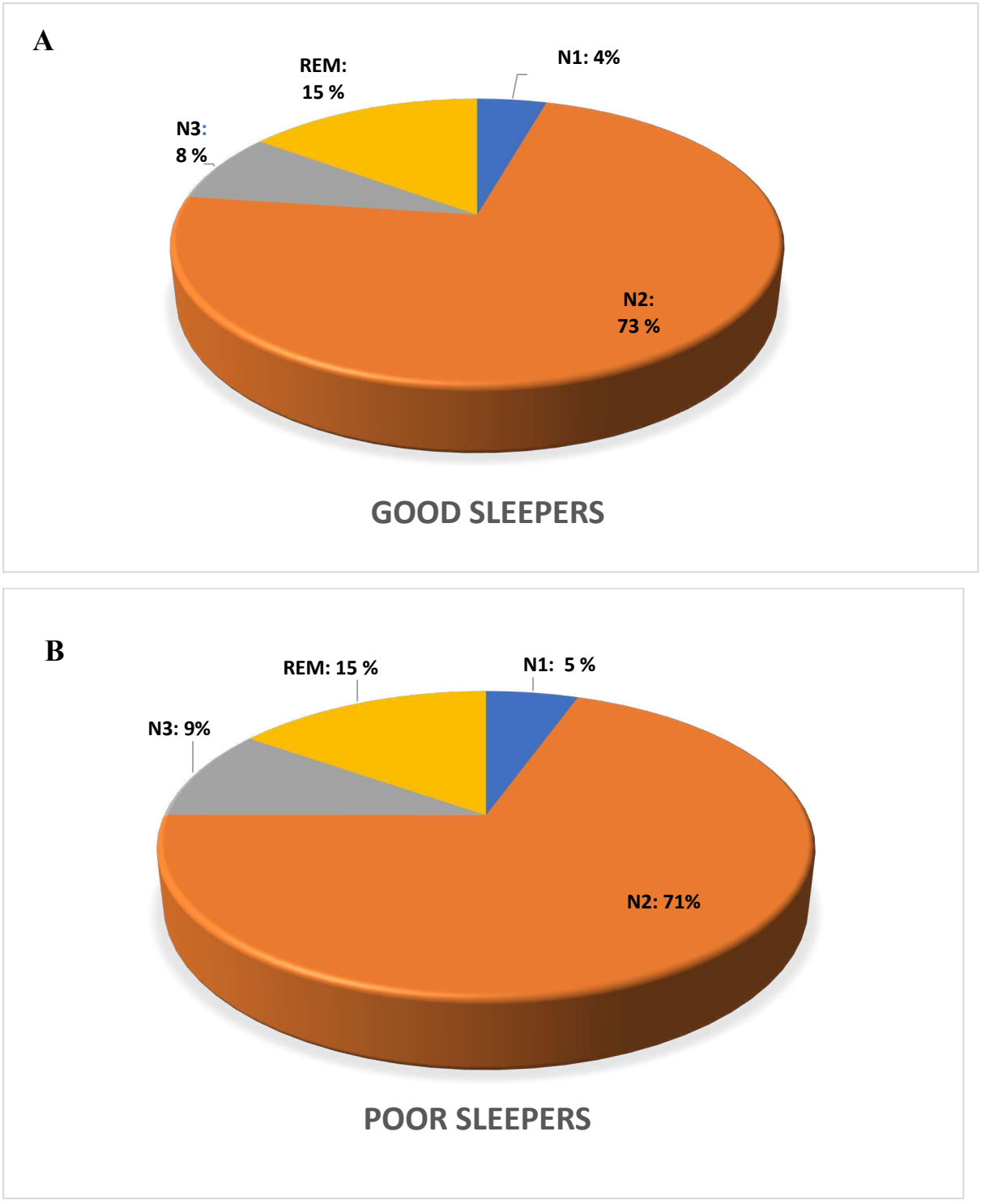

Figure 13. Sleep architecture in good (PSQI ≤ 5; panel A) and bad sleepers (PSQI > 5; panel B). There were no statistically significant differences in the sleep architecture between these two groups ($P > 0.05$).

1: N1 Sleep 2: N2 Sleep 3: N3 Sleep 4: REM sleep.

The differences were tested with Student's t-test for independent samples.

An average score achieved on PSQI among all subjects was 9.01 ± 4.11. According to the score achieved on the PSQI, all participants were allocated to either a group of good sleepers with PSQI score of 5 or less, or to a group of poor sleepers with PSQI score of more than 5. In the group of good sleepers, there was a total of 56 patients and 186 patients were in the group of poor sleepers. The remaining 75 patients did not fill in the PSQI questionnaire. When sleep architecture was compared between these two groups, there were no statistically significant differences in the percentage of any sleep stage between the two groups ($P = 0.401$ for sleep stage N1, $P = 0.811$ for sleep stage N2, $P = 0.422$ for N3 and $P = 0.485$ for REM sleep), as can be seen in Figure 13 A and B.

The average score that all included patients achieved on ESS was 7.47 ± 4.80. According to the achieved result on ESS, patients were considered to have either normal daytime sleepiness (ESS score less than 10) or to have excessive daytime sleepiness (ESS of 10 or more). In total, 218 patients had normal daytime sleepiness, 97 had excessive daytime sleepiness assessed by the ESS, and 2 patients did not fill the ESS questionnaire. When sleep architecture was examined among groups of patients with normal and excessive daytime sleepiness, there were no statistically significant differences ($P = 0.125$ for stage N1, $P = 0.782$ for N2, $P = 0.258$ for N3 and $P = 0.093$ for REM sleep), as shown in Figure 14.

Although not statistically significant, there was a slight negative correlation between OSA severity assessed by AHI and subjective sleep quality assessed by PSQI ($r = -0.123$, $P = 0.057$).

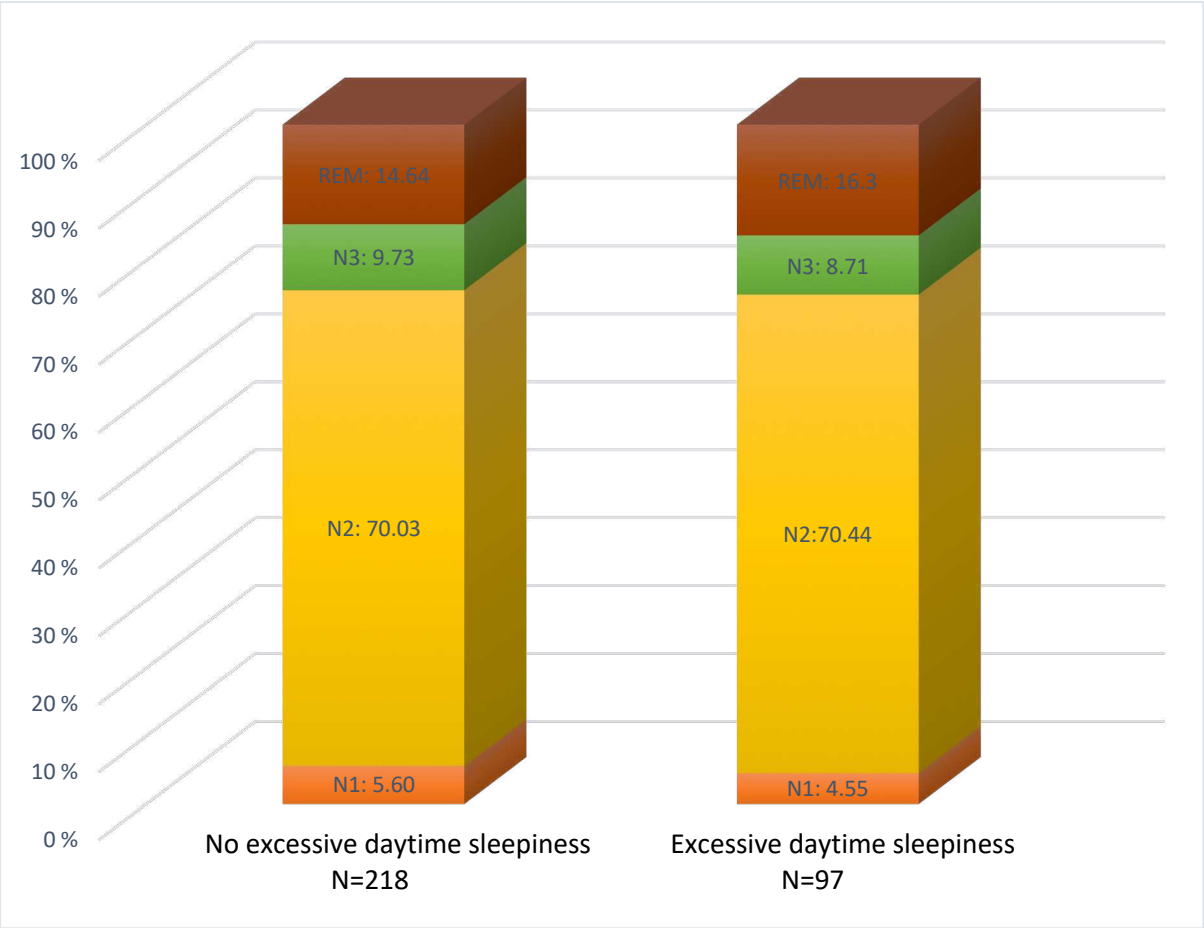

Figure 14. Sleep architecture in patients with and without excessive daytime sleepiness assessed by ESS. Normal daytime sleepiness was considered in case ESS score was <10 and excessive daytime sleepiness in case ESS score was ≥10. There were no statistically significant differences in sleep architecture among these two groups of patients ($P > 0.05$).
The differences were tested with Student's t-test for independent samples.

5. DISCUSSION

The main findings of this study indicate that patients suffering from more severe forms of OSA experience changes in sleep architecture and more pronounced excessive daytime sleepiness. Out of the objective sleep measures, only the sleep efficiency, but not sleep architecture of the OSA patients correlated with subjective sleep quality assessed by PSQI. Also, there were no differences in sleep architecture among OSA patients with and without excessive daytime sleepiness assessed by ESS.

It is well known that OSA increases duration of light sleep and reduces time spent in deep sleep stage (68). The results of the current study are similar, showing the association between OSA severity and the prolongation of the stages N1 and N2 and reduction of the stages N3 and REM. Respiratory disturbances seen in OSA are followed by reductions in arterial blood oxygenation which cause arousals. In such a way, OSA patients spent less time in deep sleep stage and more time in light sleep.

Similarly, it has been established that OSA severity influences daytime sleepiness. The most possible underlying mechanism is sleep fragmentation, resulting from repetitive arousals in response to breathing disturbances in OSA patients (70). However, no statistically significant differences in the sleep architecture were found in this study among patients with normal and excessive daytime sleepiness. Only subtle differences were seen in decreased amount of the N3 stage in patients with excessive daytime sleepiness, which also might be the consequence of frequent microarousals. Thus, it is likely that microarousals as responses to breathing cessations in fact slightly decrease the proportion of N3 stage in favor of N2 stage in this study. Consequently, the more severe OSA would lead to more frequent arousals and would finally result in slightly decreased proportion of stage N3 and increased daytime sleepiness. Findings supporting our results, showing the correlation between OSA severity and excessive daytime sleepiness, were obtained from the Sleep Heart Health Study, conducted on the community-dwelling adults (70). However, there is still a controversy on that topic and some studies failed to find the correlation between OSA severity and the level of the daytime sleepiness (71). Thus, further studies should clarify the role of OSA severity in daytime sleepiness, assessing changes in greater amount of participants to draw final conclusions.

In this study, it was observed that OSA patients had a higher value on the global PSQI score when the sleep efficiency was measured low, and, vice versa, the lower score on PSQI denoted a higher sleep efficiency. Sleep efficiency, calculated as a proportion of the sleep time in time spent in bed, in fact indicates sleep quantity more than sleep quality. The correlation found in this research gives the impression that PSQI could be used as a measure of good sleep efficiency in OSA patients, although it is mostly to assess the general sleep quality and is not

a method used to screen for specific disorders (18). Moreover, even use of PSQI is the most common in insomnia patients (19), these results indicate that PSQI can successfully indicate insufficient sleep quantity in OSA patients. In this study, sleep quality measured by sleep architecture was not significantly different between good and bad sleepers according to PSQI. Thus, all taken together might indicate PSQI as a good measure of sleep quantity, but the results while assessing sleep quality in OSA patients should be taken with caution.

This study did not demonstrate any differences in sleep architecture among OSA patients with and without excessive daytime sleepiness assessed by ESS. It is important to note that even though Epworth sleepiness scale is commonly used to assess daytime sleepiness in evaluation of the OSA patients, it is not specific enough to be considered OSA screening test (72). Moreover, even though it has excellent properties in measuring excessive daytime sleepiness, some of the OSA patients are missing daytime sleepiness as one of the most common symptoms. Sleep architecture might be impaired in OSA patients (70), as already discussed, but this does not necessarily mean straight-forward association with the excessive daytime sleepiness. This is due to the fact that daytime sleepiness is one of the most prominent symptoms of OSA and disrupted sleep architecture, which might appear in OSA. However, if the same analyses were carried out on the larger sample, maybe an association would be discovered. Having this in mind, the Epworth sleepiness scale should be used only as one of the instruments in the evaluation of OSA, and definitely not the only one.

The main complain of OSA patients is usually not decreased sleep quality, but they come to seek medical help for snoring. Moreover, OSA patients usually do not complain of poor sleep quality and are sometimes unaware, or even denying their problems. The paradox of a better perceived sleep quality among patients with more severe forms of OSA is in accordance with the finding of Wu et al. who found that more severe hypoxemia is associated with better subjective sleep quality among OSA patients (73). The possible explanation of this association may be hypoxemia-triggered depression and attenuation of perception, with more severe hypoxemia being a concomitant feature of more severe OSA.

This study had several limitations. First, out of the 317 participants, 75 did not answer the PSQI form, so the number of participants was even smaller in some analyses. Second, possible comorbidities which frequently appear in OSA patients and usage of medications that might influence sleep architecture, daytime sleepiness and sleep quality were not taken into consideration. Third, no control group of people with no OSA was composed, so it was not possible to compare the results of OSA patients with healthy subjects, but only between patients suffering from mild to severe OSA themselves.

The main aim of this research was to assess and compare the subjective sleep quality and daytime sleepiness and objective whole-night PSG findings in OSA patients. The obtained results demonstrated that OSA severity was associated with an impairment of sleep architecture and with more pronounced excessive daytime sleepiness. Sleep efficiency, but not sleep architecture of OSA patients correlated with subjective sleep quality assessed by PSQI. However, no differences in sleep architecture among OSA patients with and without excessive daytime sleepiness assessed by ESS were found.

6. CONCLUSIONS

1. There is a positive correlation between sleep efficiency assessed by whole-night polysomnography and sleep quality assessed by Pittsburgh Sleep Quality Index in OSA patients.
2. There is a positive correlation between OSA severity measured by AHI and excessive daytime sleepiness assessed by the Epworth sleepiness scale.
3. Sleep quality assessed by Pittsburgh Sleep Quality Index does not indicate impaired sleep architecture in OSA patients.
4. The level of daytime sleepiness assessed by Epworth sleepiness scale does not indicate impaired sleep architecture in OSA patients.
5. There is a slight, although not significant, negative correlation between OSA severity assessed by AHI and subjective sleep quality assessed by PSQI in OSA patients.

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8. SUMMARY

Objectives: Obstructive sleep apnea (OSA) is a disorder characterized by repetitive cessations of breathing during sleep. One of the most prominent symptoms of OSA is excessive daytime sleepiness, associated with micro arousals from sleep which are caused by respiratory events. Another feature of the OSA linked to respiratory related arousals might be impaired sleep architecture resulting in decreased subjective sleep quality. The main aim of this research was to assess and compare the subjective sleep quality and daytime sleepiness and objective whole-night polysomnography findings in OSA patients.

Patients and methods: A total of 317 adult OSA patients from the Split Sleep Medicine Center, with an age range from 18 to 82 years, were included in this study. All the patients filled in the questionnaires: Epworth sleepiness scale (ESS), assessing daytime sleepiness, and Pittsburgh Sleep Quality Index (PSQI), assessing subjective sleep quality. Following completion of the questionnaires, the patients underwent whole-night polysomnography.

Results: Sleep architecture changed with OSA severity, with an increased amount of sleep stage N2 (66.41 ± 11.93% in mild OSA, 69.12 ± 11.43% in moderate OSA and 73.45 ± 14.74% of sleep stage N2 in severe OSA, $F = 8.635$, $P < 0.001$) and decreased amount of deep sleep stage N3 in more severe forms of OSA (11.67 ± 8.89 % in mild OSA, 11.10 ± 7.35% in moderate OSA and 6.88 ± 7.63 in severe OSA, $F = 12.701$, $P < 0.001$). There was also a correlation between OSA severity and excessive daytime sleepiness assessed by ESS ($r = 0.25$, $P < 0.001$). Patients who had poorer sleep efficiency had worse subjective sleep quality assessed by PSQI ($r = -0.21$, $P = 0.001$). There were no statistically significant differences in sleep architecture among patients with good and bad sleep quality according to PSQI ($P > 0.05$), and among those with normal and excessive daytime sleepiness, according to ESS ($P > 0.05$).

Conclusions: The obtained results demonstrated that OSA severity was associated with an impairment of the sleep architecture and with more pronounced excessive daytime sleepiness. Sleep efficiency, but not the sleep architecture of OSA patients correlated with subjective sleep quality assessed by PSQI. However, no differences in sleep architecture among OSA patients with and without excessive daytime sleepiness assessed by ESS were found.

9. CROATIAN SUMMARY

Hrvatski naslov: Usporedba subjektivne kvalitete spavanja i dnevne pospanosti s nalazima cjelonoćne polisomnografije u pacijenata s opstrukcijskom apnejom tijekom spavanja

Ciljevi: Opstrukcijska apneja tijekom spavanja (OSA) poremećaj je obilježen ponavljanim prekidima disanja tijekom spavanja. Jedan od najistaknutijih simptoma OSA-e je prekomjerna dnevna pospanost, povezana s mikrobuđenjima koja su uzrokovana respiratornim događajima. Još jedna značajka OSA-e izazvana buđenjima može biti narušena arhitektura spavanja koja bi mogla rezultirati smanjenom subjektivnom kvalitetom spavanja. Glavni cilj ovog istraživanja bio je procijeniti i usporediti subjektivnu kvalitetu spavanja i dnevnu pospanost te objektivne polisomnografske nalaze u OSA bolesnika.

Pacijenti i postupci: Ukupno 317 odraslih OSA pacijenata iz splitskog Centra za medicinu spavanja, u dobi od 18 do 82 godine, uključeno je u ovu studiju. Svi pacijenti popunili su upitnike: Epworthovu ljestvicu pospanosti (ESS) koja procjenjuje dnevnu pospanost i Pittsburghški indeks kvalitete spavanja (PSQI) koji procjenjuje subjektivnu kvalitetu spavanja. Nakon popunjavanja upitnika, pacijenti su podvrgnuti cjelonoćnoj polisomnografiji.

Rezultati: Težina OSA-e utjecala je na arhitekturu spavanja, posebice povećanjem količine N2 stadija spavanja (66,41 ± 11,93% u blagoj OSA-i, 69,12 ± 11,43% u umjerenoj OSA-i i 73,45 ± 14,74% u teškoj OSA-i; F = 8,635, $P < 0.001$) i smanjenjem količine dubokog spavanja N3 u težim oblicima OSA-e (11,67 ± 8,89% u blagoj OSA-i, 11,10 ± 7,35% u umjerenoj OSA-i i 6,88 ± 7,63 u teškoj OSA-i; F = 12,701, $P < 0.001$). Postojala je i korelacija između težine OSA-e i prekomjerne dnevne pospanosti procijenjene pomoću ESS (r = 0,25, $P < 0.001$). Lošija subjektivna kvaliteta spavanja procijenjena pomoću PSQI bila je povezana s manjom učinkovitošću spavanja (r = -0,21, $P = 0,001$). Nije bilo statistički značajnih razlika u arhitekturi spavanja u bolesnika s dobrom i lošom kvalitetom spavanja prema PSQI-u ($P > 0,05$), te među onima s normalnom i prekomjernom dnevnom pospanošću, prema ESS-u ($P > 0,05$).

Zaključci: Dobiveni rezultati pokazali su da je težina OSA-e povezana s narušenom arhitekturom spavanja i s izraženijom dnevnom pospanošću. Učinkovitost spavanja, ali ne i arhitektura spavanja OSA bolesnika bila je u korelaciji sa subjektivnom kvalitetom spavanja procijenjenom pomoću PSQI-ja. Međutim, nisu nađene razlike u arhitekturi spavanja u OSA bolesnika sa i bez prekomjerne dnevne pospanosti procijenjene pomoću ESS.

10.CURRICULUM VITAE

Personal Information
Name: Nina Rani Pedersen
Date of birth: 02.11.1986
Place of birth: Kerala, India
Nationality: Norwegian
E-Mail: ninaranipedersen@gmail.com

Education:
09.2002-07.2005 High School, Kristiansand Katedralskole, Kristiansand, Norway
09.2008-07.2010 Psychology, University of Oslo, Norway
09.2013–07.2014 University of Bratislava, Martin, Medical School, Slovakia
10.2014-07.2019 University of Split School of Medicine, Split, Croatia