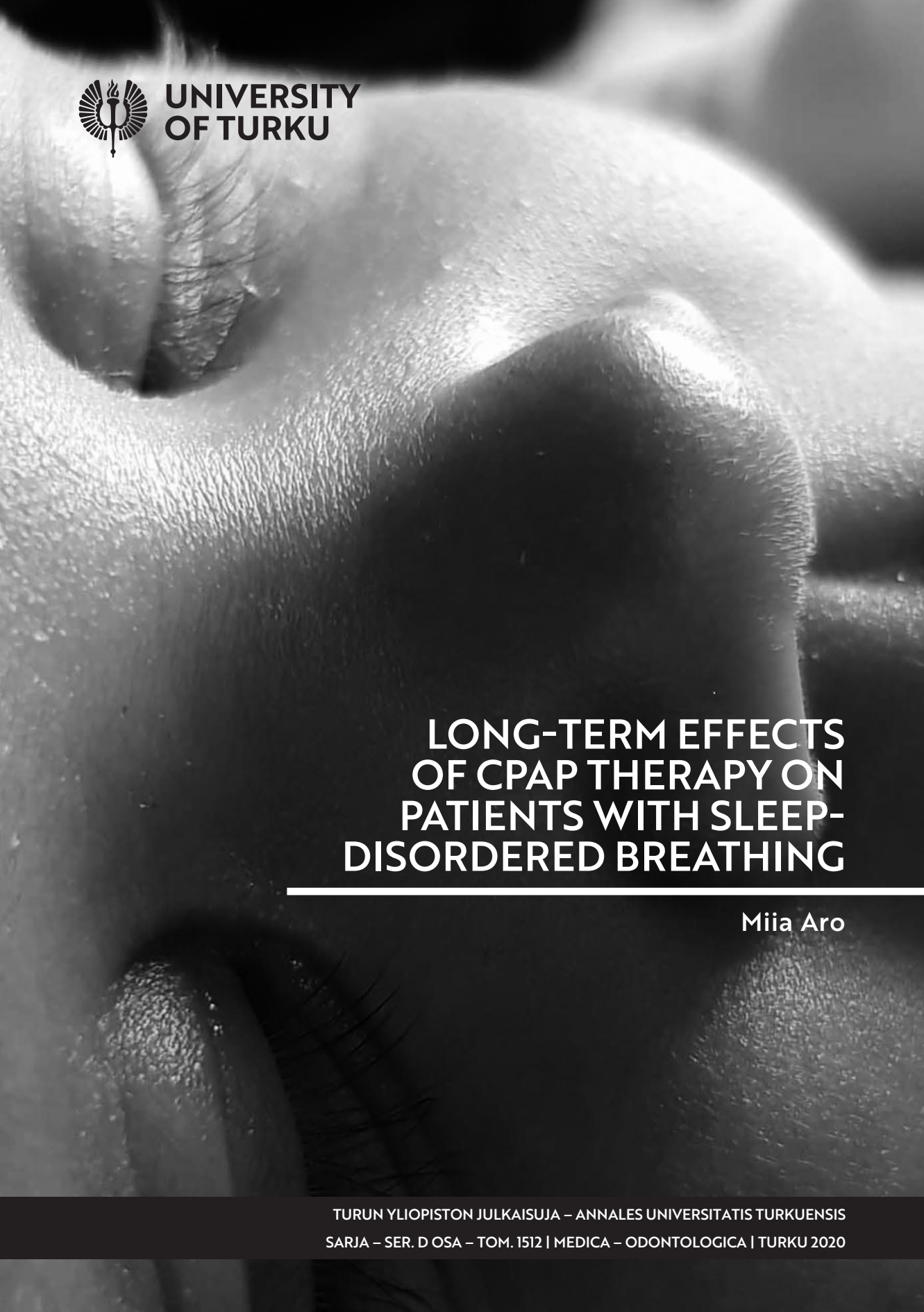

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The originality of this publication has been checked in accordance with the University of Turku quality assurance system using the Turnitin Originality Check service.

Cover Image: Eeva Elamo

ISBN 978-951-29-8198-4 (PRINT)
ISBN 978-951-29-8199-1 (PDF)
ISSN 0355-9483 (Print)
ISSN 2343-3213 (Online)
Painosalama Oy, Turku, Finland 2020

To Antti

I don’t stop when I´m tired, I only stop when I´m done.
-Marilyn Monroe-.

UNIVERSITY OF TURKU
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MIIA ARO: Long-term Effects of CPAP Therapy on Patients with Sleep-Disordered Breathing
Doctoral Program in Clinical Research (DPCR)
November 2020

ABSTRACT

The population of patients suffering from sleep-disordered breathing (SDB), especially obstructive sleep apnoea (OSA) is rising. OSA is often treated with continuous positive airway pressure (CPAP), but data on the long-term effects are scarce. SDB is an umbrella term for different types of SDB, that may have a similar nocturnal breathing disorder, while the underlying mechanisms are different as well as the risks that come from having an untreated condition. In the future, treatment will be more individualised, and CPAP therapy might not be the first or the best choice for all patients. Thus, more information on the long-term effects of CPAP therapy is needed.

In order to study the lifestyle, weight changes, and leptin and Insulin-like Growth Factor 1 (IGF-1) concentrations during long-term CPAP therapy, patients who were referred to the Pulmonary ward of the Turku University Hospital for suspected sleep apnoea were enrolled in the study (n=223). Patients were given an array of questionnaires on sleep duration and quality, sleepiness, depressive symptoms and anxiety, cravings for different food categories, and exercise habits. All had a cardiorespiratory polygraphy (PG), and their blood was drawn following an overnight fast. After three years of follow-up, the patients were divided into CPAP users (n= 76) and non-users (n= 73), and all measurements except the sleep study, were repeated. The use of medication for comorbidities was evaluated for women referred to Paimio Hospital between 1994-1998 for suspected sleep apnoea (n= 601). The medication data were derived from the National Reimbursement registration three years before, and three years after CPAP initiation or the sleep study. Women were divided into CPAP users (n=66) and the control group (n= 122). The SDB type was also considered in the analysis.

In our study, long-term CPAP therapy alleviated SDB symptoms, depressive symptoms, and anxiety efficiently. However, it did not influence lifestyle or exercise habits, and the patients did not lose weight. Increase in weight was associated with a good adherence to CPAP. In women, leptin concentrations increased, especially if they used CPAP. IGF-1 concentrations did not change. Medication use for comorbidities continued to increase regardless of CPAP therapy and CPAP users already had more comorbidities before the CPAP therapy initiation. However, the increase in medicine use did not differ between the CPAP users and non-users. The type of SDB also did not influence medicine use.

In conclusion, patients with SDB should have sufficient life-style counselling as well as CPAP therapy. CPAP therapy does not automatically decrease medication use and thus the cost. Earlier diagnosis and treatment of SDB before end-organ manifestations might instead reduce health care costs. The different profile for female SDB patients should also be noted and remembered.

KEYWORDS: Sleep disordered breathing, CPAP, OSA, lifestyle, leptin, medicine use, comorbidities

TURUN YLIOPISTO
Lääketieteellinen tiedekunta
Kliininen laitos
Keuhkosairausoppi ja kliininen allergologia
MIIA ARO: Pitkäaikaisen CPAP-hoidon vaikutukset unenaikaista hengityshäiriötä sairastavilla.
Turun kliininen tohtoriohjelma
Marraskuu 2020

TIIVISTELMÄ

Unenaikaista hengityshäiriötä sairastavien määrä on kasvussa, ja erityisesti obstruktiivista uniapneaa sairastavia potilaita on vuosi vuodelta enemmän. Uniapneaa hoidetaan usein ylipainehengityslaitteella (continuous positive airway pressure, CPAP). Unenaikainen hengityshäiriö on sateenvarjotermi, jonka alta löytyy eri alatyyppejä, joita yhdistävät unenaikaiset hengityskatkokset, mutta niiden syntymekanismit ja riskiprofiili vaihtelevat. Tulevaisuudessa siirryttäneenkin yksilöllisempään hoitoon, jolloin CPAP ei ole ensisijainen hoitomuoto kaikille. Tämän vuoksi lisätieto CPAP-hoidon pitkäaikaisvaikutuksista on erityisen tärkeää.

Tutkiaksemme elintapoja, painon muutosta sekä leptiinin ja insuliinikaltaisen kasvutekijä 1:n (IGF-1) pitoisuuksia pitkäaikaisen CPAP-hoidon aikana, Turun yliopistollisen keskussairaalan keuhkoklinikalle uniapneaepäilyn vuoksi lähetetyille 223 potilaalle annettiin kyselylomakkeita, joissa kysyttiin unen pituudesta ja laadusta, uneliaisuudesta, masennus- tai ahdistusoireista, erilaisten ruokien mieliteoista sekä liikuntatottumuksista. Lisäksi heille tehtiin yöpolygrafia ja otettiin paastoverinäyte. Potilaat jaettiin kolmen vuoden seuranta-ajan jälkeen CPAP-käyttäjiin (n=76) ja ei-käyttäjiin (n=73) ja heille tehtiin yöpolygrafiaa lukuun ottamatta samat tutkimukset. Lääkkeiden käyttöä tutkittiin Paimion sairaalaan v. 1994-1998 uniapneaepäilyn vuoksi unipatjatutkimukseen tulleiden naisten avulla (n=601). Lääkekäyttötiedot Kelalta pyydettiin kolme vuotta ennen ja kolme vuotta laitehoidon aloituksen tai rekisteröintipäivän jälkeen. Naiset jaettiin joko CPAP-käyttäjiin (n=66) tai verrokkeihin (n=122). Myös unenaikaisen hengityshäiriön tyyppi otettiin huomioon.

Tutkimuksessamme pitkäaikainen CPAP-hoito lievitti tehokkaasti unenaikaisen hengityshäiriön oireita sekä masennus- ja ahdistuneisuusoireita. Hoidolla ei ollut vaikutusta potilaiden elintapoihin, eivätkä potilaat laihtuneet. Painon nousu oli yhteydessä tehokkaaseen CPAP-laitteen käyttöön. Naisilla leptiinipitoisuudet nousivat hoidon aikana, erityisesti jos he käyttivät CPAP-laitetta. Insuliininkaltaisen kasvutekijä 1:n-pitoisuudet eivät muuttuneet. Liitännäissairauksien lääkekäyttö jatkoi nousuaan CPAP-hoidosta huolimatta, ja CPAP:n käyttäjillä oli jo alkuvaiheessa enemmän sairauksia kuin verrokeilla. Lääkekäytön lisääntyminen ei eronnut CPAP-hoitoa käyttävillä ja ei-käyttäjillä. Unenaikaisen hengityshäiriön tyypillä ei ollut vaikutusta lääkekäyttöön.

Tulostemme valossa ehdotamme, että uniapneaa sairastaville tulisi CPAP-hoidon lisäksi tarjota tehokasta elintapavalmennusta. CPAP-hoito ei automaattisesti vähennä lääkekulutusta. Varhaisempi uniapnean diagnosointi ja hoito saattaisi estää liitännäissairauksien kehittymistä ja säästää terveydenhuollon kuluja. Lisäksi naisten erilainen taudinkuva tulisi muistaa.

AVAINSANAT: CPAP, unenaikainen hengityshäiriö, obstruktiivinen uniapnea, elintavat, leptiini, lääkkeiden käyttö, liitännäissairaudet

TABLE OF CONTENTS

ABBREVIATIONS

ACS	Acute coronary syndrome
AF	Atrial fibrillation
AHI	Apnoea-hypopnea index
BBB	Blood-brain barrier
BMI	Body mass index
CB	Carotid body
CGRP	Calcitonin gene-related peptide
CNS	Central nervous system
COMISA	Comorbid insomnia and OSA
COPD	Chronic obstructive pulmonary disease
CPAP	Continuous positive airway pressure
CSA	Central sleep apnoea
CSN	Carotid sinus nerve
CV(D)	Cardiovascular (disease)
DDD	Defined daily dose
DEPS	Depressive symptom scale
ECG	Electrocardiography
EDS	Excessive daytime sleepiness
EEG	Electroencephalography
EMG	Electromyography
EOG	Electrooculography
ESS	Epworth Sleepiness Scale
GHQ-12	General Health Questionnaire
HADS	Hospital Anxiety and Depression Scale
HNS	Hypoglossal nerve stimulation
HVR	Hypoxic ventilatory response
IGF-1	Insulin-like growth factor-1
IRR	Increased respiratory resistance
MAD	Mandibular advancement device
MMA	Maxillomandibular Advancement
MSLT	Multiple Sleep Latency Test

MWT	Maintenance of Wakefulness Test
NREM	Non-REM sleep stage
NTS	Nucleus of the solitary tract
ODI	Oxygen desaturation index
OSA(S)	Obstructive sleep apnoea (syndrome)
Pcrit	Critical closing pressure of the airway
PG	Cardiorespiratory polygraphy
PLMS	Periodic leg movement syndrome
POSA	Positional obstructive sleep apnoea
PSG	Polysomnography
PSQI	Pittsburgh Sleep Quality Index
$PtcCO_2$	Transcutaneous carbon dioxide
QoL	Quality of life
REM	Rapid Eye Movement
RERA	Respiratory effort related arousals
RIP	Respiratory inductive plethysmography
SaO_2	Arterial oxyhaemoglobin saturation
SCSB	Static-charge-sensitive bed
SDB	Sleep-disordered breathing
STAI	State-trait anxiety inventory
TIA	Transient ischemic attack
TIB	Time in bed
TSH	Thyroid stimulating hormone
UAO	Upper airway obstruction
UPPP	Uvulopalatopharyngoplasty
VAS	Visual analogue scale
WHR	Waist hip ratio

LIST OF ORIGINAL PUBLICATIONS

This dissertation is based on the following original publications, which are referred to in the text by their Roman numerals:

I Aro M, Anttalainen U, Polo O, Saaresranta T. Mood, sleepiness, and weight gain after three years on CPAP therapy for sleep-disordered breathing. *Submitted.*

II Aro M, Anttalainen U, Kurki S, Polo O, Irjala K, Saaresranta T. Gender-specific change in leptin concentrations during long-term CPAP therapy. *Sleep Breath.* 2020; 24(1): 191–99. https://doi.org/10.1007/s11325-019-01846-y

III Aro M, Saaresranta T, Vahlberg T, Anttalainen U. Medication of comorbidities in females with sleep-disordered breathing during long-term CPAP therapy. *Respiratory Medicine*. 2020; Vol 169:106014. https://doi.org/10.1016/j.rmed.2020.106014.

1 INTRODUCTION

The prevalence of sleep-disordered breathing (SDB) is rising, largely due to the increase in obesity (Heinzer et al. 2015). Continuous positive airway pressure (CPAP) therapy is the gold standard for treating patients who have moderate-to-severe obstructive sleep apnoea (OSA) (Sullivan et al. 1981). As CPAP therapy has become more common, the positive and negative effects of long-term therapy have drawn additional attention. The rising population who have OSA is creating increased healthcare costs including increased medication cost, more sick leave, and more hospitalisations. The cost-effectiveness of CPAP therapy needs more research, especially regarding long-term treatment (Jennum & Kjellberg 2011). At the same time, the knowledge of SDB has increased, and thus, currently we know that SDB is merely an umbrella term for different conditions with different risks and pathophysiology, sharing the characteristic of disturbed nocturnal breathing (Zinchuk & Yaggi 2019). Therefore, in the future, not all patients will be treated with CPAP and gaining more data on who benefits the most, is highly encouraged.

The most common risk factor for SDB is obesity (Young et al. 1993). Thus, it has been assumed that initiating CPAP therapy will alleviate SDB symptoms such as sleepiness and poor sleep quality, thereby leading to more daytime activity, and healthier food choices resulting in weight loss. The data on these long-term effects have been controversial, and the studies have consisted mainly of men with OSA. The consensus in short-term CPAP use is that it may or may not promote weight gain (Drager et al. 2015). These changes in lifestyle and food consumption, however, have not been thoroughly studied, even if they are viewed as important factors in achieving weight change.

The effect of gender on SDB has been recognised in the shift of the millennium (Bixler et al. 2001). Clinical presentation of SDB differs between genders, but the data on the effects of CPAP have been collected primarily on male cohorts. The data on female SDB are, however, delightfully increasing and in the near future will likely result in a more detailed evaluation of gender differences. Currently we know that female SDB is under-diagnosed and under-treated, and the symptoms and risks for SDB also appear to differ from those for men (Bonsignore et al. 2019b).

This thesis thus evaluated multiple factors to find clear predictors of weight gain for patients receiving long-term CPAP therapy. Our goal was to investigate whether CPAP therapy alleviates SDB symptoms and leads to healthier lifestyle. In addition, the differences between the genders were of clear interest. Leptin and Insulin-like Growth Factor 1 (IGF-1) could perhaps play an important role in weight reduction, and thus they were controlled, separately for both genders. Finally, the cost-effectiveness of CPAP therapy in women with both overall medication and different medication subgroups were evaluated. SDB type was also included in these analyses.

2 REVIEW OF THE LITERATURE

Sleep-disordered breathing (SDB) is a medical condition, where pharyngeal space is narrowed or obstructed during sleep, leading to repetitive pauses in breathing, sleep fragmentation, and oxygen desaturation events (Malhotra & White 2002). The variations in SDB range from increased upper-airway resistance to obstructive sleep apnoea syndrome (OSAS), where in addition to complete collapse (apnoea) and partial collapse (hypopnoea) of airways, patients suffer from a broad spectrum of daytime symptoms (Malhotra & White 2002). SDB is an umbrella term, and as such, it includes obstructive sleep apnoea (OSA), central sleep apnoea (CSA), sleep-related hypoventilation disorders, and sleep-related hypoxemia disorder (Sateia 2014), with OSA being the most common.

2.1 Epidemiology

In Western countries, the prevalence of SDB is currently rising. In the 1990's the Sleep Heart Health Study estimated that 24 % of men and 9 % of women suffered from OSA in middle age, and 4 % of men and 2 % of women had OSAS (Young et al. 1993). Peppard et al. updated prevalence two decades later in the Wisconsin Sleep Study Cohort, suggesting that 27 % of men and 12 % of women age 30-70 suffered from moderate to severe OSA (Peppard et al. 2013). Along with improvement in and an increased sensitivity of technology, the diagnostic criteria for OSA changed in 2012, leading to even more increased SDB prevalence (Berry et al. 2012).

One of the first studies that commenced after the changed criteria, was the HypnoLaus study, where the prevalence of moderate to severe OSA was as high as 49.7 % in men and 23.4 % in women, aged 40-85 years (Heinzer et al. 2015). The changed criteria, and this unforeseen increase in the number of OSA patients, craved further and more profound prevalence investigation. In a recent review, SDB prevalence ranges from 24 to 83.8 % in men and from 9 to 76.6 % in women, and moderate-to-severe SDB from 7.2 to 67.2 % in men and 4 to 50.9 % in women (Matsumoto & Chin 2019).

The results before and after the change in diagnostic criteria are challenging to compare, hence the actual increase remains unclear. Moreover, the studies are difficult to compare due to varying patient selection and possible bias regarding

certain medical comorbidities, that are of particular and related interest. The extremely high prevalence estimates also raise the question of whether part of the OSA is just a physiologic or compensatory phenomenon that does not require treatment (Dempsey et al. 2010). The high prevalence rates call for more research on who should be treated and how to be treated, and how OSA can be prevented.

In terms of ethnicity, the African American population and the Hispanic population develops more OSA than the Caucasian population does (Foldvary-Schaefer & Waters 2017). Elderly have more OSA than younger controls, and in the Osteoporotic Fractures in Men Sleep Study, moderate-to-severe OSA was found in 26.5 % of men over 65, and that prevalence increased with age, leading to 30.1 % of patients over 80 years in age being affected (Mehra et al. 2007). It has also been suggested that with age, the prevalence of REM (rapid eye movement) related SDB increases, and indeed, in one study, the prevalence was 42.8 % in men over 65 (Khan et al. 2013). Increased risk of OSA with age could also be associated with a reduction in slow wave sleep, which is thought to protect from SDB and airway collapse, combined with the natural age-related tissue loosening. (Van Cauter et al. 2000). Older men are also less symptomatic and report less daytime sleepiness and fatigue (Mehra et al. 2007). Premenopausal women have less SDB than men, but after menopause, prevalence increases significantly, and approaches that seen in men (Anttalainen et al. 2006; Bixler et al. 2001).

2.2 Pathophysiology

2.2.1 Anatomical factors

Anatomical features play an important role in the development of SDB. Nocturnal pauses in breathing are a result of the anatomical collapse of pharyngeal structures, and alterations in the function of the upper airway muscles (Patil et al. 2007). The upper airway is composed of soft tissue between the larynx and the hard palate. The soft palate has five pairs of muscles (Table 1), and their function is to maintain patency during breathing. They are the most important determinants of proper pharyngeal space.

Most patients who are suffering from SDB are obese; however, over 30 % of SDB patients are lean (Malhotra & White 2002). Obesity increases the incidence of SDB, and any increase in weight by 10 % increases the incidence of SDB six-fold, and AHI by 30 % (Peppard et al. 2000). Airway size is affected by obesity via several mechanisms, but the accumulation of fat narrows the pharyngeal tube mechanically and offsets the dilatory function in the neck muscles, resulting in an increased neck circumference (Davies & Stradling 1990). Tongue fat and tongue weight correlate to the degree of obesity (Nashi et al. 2007), and patients with OSA are shown to have

increased retroglossal fat deposition compared to controls, even after adjustment for gender, age, race, and BMI. In addition, tongue fat volume correlates with AHI and BMI (Kim et al. 2014).

Upper airway muscle activation is more strongly related to airway collapsibility than it is to body mass index (BMI), suggesting that obesity is merely one factor that can cause the narrowing of the pharyngeal space (Pierce et al. 2007). Other craniofacial features can include congenital anomalies of the upper airway, such as narrow airways or maxilla, and the size and position of the cranial bones, for example a reduced length of the mandibular body, a low hyoid bone, and retro positioning of the jaw (Pierce et al. 2007). In addition, traumatic incidents affecting the upper airways or the palate and micrognathia can narrow the upper respiratory lumen via incorrect placement of mandibula (Watanabe et al. 2002). Further still, increased upper airway length is associated with airway collapse (Eckert 2018).

Table 1. Muscles of pharynx and their function.

Muscle	Function
Genioglossus (left and right)	Protrusion of the tongue and deviation towards the opposite side. Together depress the center of the tongue at its back
Tensor veli palatini	Tightening of the soft palate and opening auditory tube
Levator veli palatini	Elevation of soft palate and opening of auditory tube
Palatoglossus	Elevation of tongue
Palatopharyngeus	Pulling the laryngeal and pharyngeal walls upwards during swallowing
Musculus uvulae	Shortening and raising the uvula

Pharyngeal critical closing pressure (Pcrit) is the gold standard for measuring upper airway collapsibility. It defines the minimal intraluminal airway pressure that is necessary to keep the airway open and higher Pcrit values indicate greater collapsibility (Carberry et al. 2016). Pcrit is measured with the help of CPAP, in order to minimise pharyngeal muscle activity. The holding pressure is rapidly reduced to varying levels to induce upper airway collapse and airflow limitation. The value is the estimated pressure at which the upper airway collapses and airflow ceases (Smith et al. 1988; Wellman et al. 2011).

2.2.2 Control of breathing

The physiology of breathing is complex, and anatomical factors form only part of the intricate cascade that leads to the formation of SDB as seen in Figure 1 (Figure drawn based on data in the article of Wellman et al. 2011). Recently, it has been discovered that the physiological mechanisms underlying SDB vary between patients, and we have moved toward phenotypic traits, or treatable traits, dependent of the underlying problem. Clustering patients is still under investigation, and mostly if not directly applicable to clinical practice as yet, but the future of treating SDB is heading toward personalised approach, and the focus of diagnosis and treatment is moving beyond apnoea-hypopnoea index (AHI) toward more broader evaluation (Zinchuk & Yaggi 2019).

There are several compensatory mechanisms in our body that are involved in hypoxia. Hypoxic ventilatory response (HVR) is complex, involving peripheral sensing of hypoxia, mainly in the carotid bodies (CB) located in the carotid artery bifurcation. Information is conducted via the carotid sinus nerve (CSN) to the nucleus of the solitary tract (NTS) and then to the brainstem. Abnormal HVR plays an important role in the pathogenesis of SDB, as HVR increases due to intermittent hypoxia in SDB; however, the mechanisms are not yet fully understood (Teppema & Dahan 2010).

Pauses in breathing can be the result of different traits. First, anatomical features and the collapsibility of airways can be the main factors causing the apnoeas (Isono et al. 1997; Remmers et al. 1978). Second, pauses can be caused by a hypersensitive ventilatory control system, often referred to as a system with a high loop gain. Loop gain is the ability to compensate for the disturbances in breathing with an increase in ventilatory drive. The higher the ratio between these factors, the higher will be the loop gain as presented in Figure 2 (Wellman et al. 2011; Deacon & Catcheside 2015). Third, upper airway muscles, especially the genioglossus muscle, can have poor ability to respond to an increased ventilatory drive, due to the repetitive pauses in breathing. This circumstance results in decreased Pcrit (Loewen et al. 2011). Finally, a low respiratory arousal threshold can cause a patient to arouse from sleep for very small increases in respiratory drive (Berry & Gleeson 1997). In one study, it was estimated, that 56 % of OSA patients had a significant anatomic factor influencing their condition, 36 % had high loop gain, 36 % had low a genioglossus response to increased ventilatory drive, and 37 % had low a arousal threshold (Eckert et al. 2013).

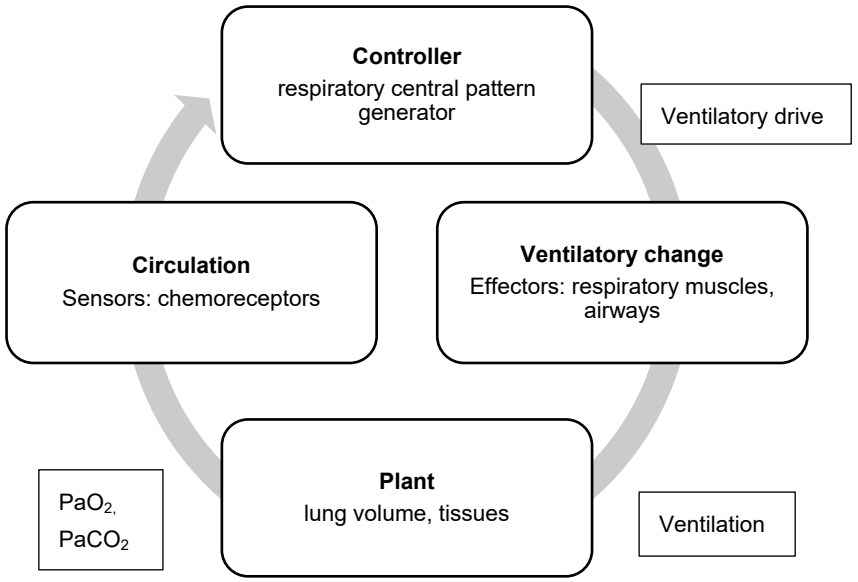

Figure 1. Control of breathing. PaO_2 represents the partial pressure of oxygen in arterial blood and $PaCO_2$ represents the partial pressure of carbon dioxide in arterial blood.

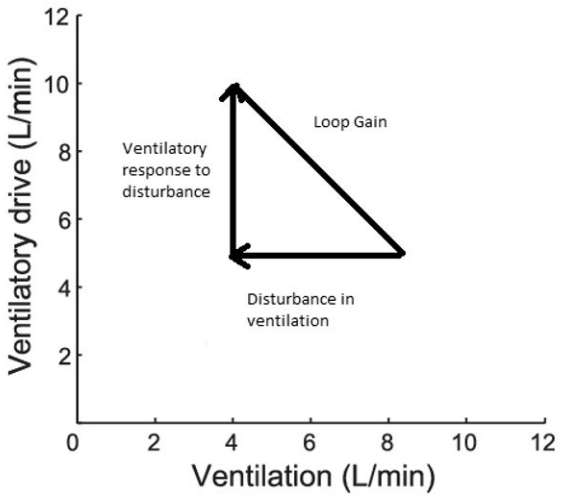

Figure 2. Loop gain is a disturbance in ventilation divided by ventilatory response. Modified from Wellman et al 2011.

2.2.3 Comorbidities in SDB

From the early days of OSAS, it was discovered that patients have a higher risk of cardiovascular comorbidities (Wolk et al. 2003), but the large presence of confounders, especially obesity, have complicated research. In recent years, the true burden and risks of various comorbidities in OSA have been discovered, leading to ever growing research and a vast pool of data, which are impossible to go through in detail briefly (Bonsignore et al. 2019a). In the face of the mounting data, a score for the risk of comorbidities has been suggested. The researchers have identified 10 comorbidities that increase OSAS patient morbidity, and after adjusting for the risk associated with each disease state, and the number of comorbidities, a score can be calculated. This process may be a positive step toward offering more effective treatment, when the focus can be turned toward the most detrimental comorbidities (Chiang et al. 2017).

The most dangerous comorbidities are considered to be cardiovascular diseases (CVD) such as systemic hypertension, coronary artery disease, arrhythmias, and ischemic stroke and metabolic disorders, the most important being diabetes mellitus; and respiratory diseases including chronic obstructive pulmonary disease (COPD) and asthma. Many other disorders have also been identified, including anxiety, insomnia, depression, and gastrointestinal diseases (Bonsignore et al. 2019a). Psychiatric disorders are discussed later in the symptoms section.

2.2.3.1 Cardiovascular diseases (CVD)

OSA may increase cardiovascular risk through multiple mechanisms, including high sympathetic nervous activity, oxidative stress, systemic hypertension, intermittent hypoxia, inflammation, and endothelial cell dysfunction (Lévy et al. 2015).

Repetitive pauses in breathing result in increased respiratory effort, which in turn leads to increased intrathoracic pressure. Due to this action, the filling mechanisms of the left side of the heart change, resulting in impaired cardiac functioning, inducing vasoconstriction, and eventually leading to atrial and aortic enlargement. Moreover, hypoxemia, hypercapnia, and arousal afflict the sympathetic nervous system overdrive and the autonomic regulation changes in blood pressure (Figure 3) (May et al. 2017).

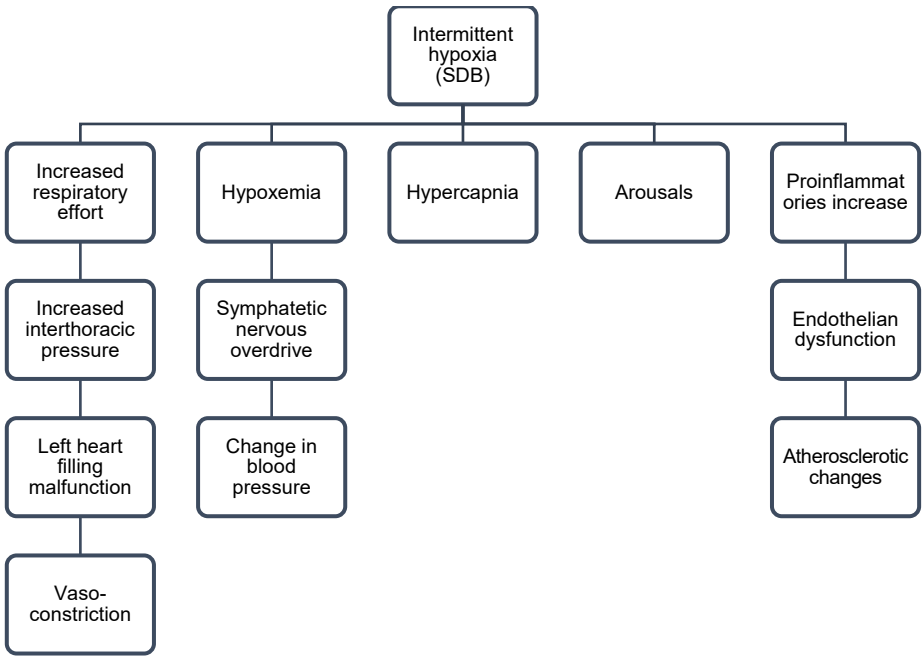

Figure 3. The mechanisms influencing on cardiovascular morbidity in SDB.

Patients with CVD have a high prevalence of SDB as seen in Table 2 (Rundo, 2019).

Table 2. The prevalence of obstructive sleep apnoea (OSA) in patients with cardiovascular disease (Rundo et al 2019).

Disease	Mild OSA (%)	Moderate-to-severe OSA (%)
Hypertension	83	30
Heart failure	55	12
Arrhythmias	50	20
Stroke	75	57
Coronary heart disease	65	38

The most common, and most studied cardiovascular comorbidity is hypertension (Bonsignore et al. 2019a). There is also a relationship between the severity of OSAS and hypertension (Xia et al. 2018). Resistant hypertension is common among OSAS patients despite taking three antihypertensive medicines (Bonsignore et al. 2019a). Hypertension can occur during the night, daytime, or both. Therefore, 24-hour measurement of blood pressure is advised on OSAS patients (Parati et al. 2013).

Other significant comorbidities include arteriosclerosis and cardiac arrhythmias (Bonsignore et al. 2019a).

It has been estimated that 25 % of patients with acute coronary syndrome (ACS) also have severe OSA (Huang et al. 2017). When atrial fibrillation (AF) is considered, studies have shown that SDB doubles the risk. In patients with both OSA and heart failure, the risk of AF is two to four times higher than for those without either condition (May et al. 2017). In addition, patients with peripheral arterial disease have surprisingly high prevalence of OSA (Utriainen et al. 2013) and they have poorer prognosis after revascularisation (Utriainen et al. 2014). SDB is common in patients with heart failure, but they generally do not have EDS. However, large cohort studies in the United States have indicated that SDB with heart failure is associated with more hospitalisations, increased medical costs, and excess mortality (Javaheri et al. 2020). Moreover, SDB is common in both, stroke patients and in ischemic stroke patients and SDB is also an independent risk factor for a stroke, even when other risk factors such as hypertension, diabetes mellitus, hyperlipidaemia, and AF are controlled. Therefore, all patients hospitalised for stroke or transient ischemic attack (TIA) should be screened for SDB (Jehan et al. 2018).

2.2.3.2 Metabolic diseases

The majority of patients with SDB, especially OSAS, additionally have obesity (Malhotra & White 2002). Obesity is known to interfere with energy balance and also affect adipose tissue inflammation (Schenk et al. 2008). In addition, OSA and obesity have a bilateral and complex relationship via multiple mechanisms, making it merely impossible to consider these two conditions separately (Bonsignore et al. 2012). On the other hand, OSA causes sleep fragmentation and hypoxia that can influence glucose metabolism, making OSA an independent risk factor for diabetes as well (Reutrakul & Mokhlesi 2017). In diabetic patients with OSA, the prevalence of neuropathy, nephropathy, retinopathy and peripheral arterial disease increase (Bonsignore et al. 2019a), making it essential to take OSA into consideration when treating diabetic patients.

2.2.3.3 Respiratory diseases

COPD is known to coincide with OSA (Flenley 1985; Owens et al. 2017) and asthma and OSA is also thought to have a causal link (Kong et al. 2017). The prevalence of a OSA-COPD overlap syndrome has been reported to range from 1 to 3.6 % in the general population, 8-56 % in OSA patients, and 3-66 % in COPD patients (Shawon et al. 2017). SDB in COPD patients in mainly seen in REM phase of sleep, due to

reduced intercostal muscle activity and chest wall mobility (Johnson & Remmers 1984). Moreover, patients with overlap syndrome have been reported to have a poorer health related quality of life (QoL), in part related to sleep disruption and worse nocturnal oxygenation. Overlap syndrome is considered to cause rising health care costs, as SDB has been shown to increase the rate of COPD exacerbation, hospitalisation, and even mortality when compared to COPD-only patients (Shawon et al. 2017). In addition, overlap syndrome has been associated with pulmonary hypertension and respiratory failure (Singh et al. 2018).

The results of the link between asthma and OSA severity are controversial (Julien et al. 2009; Tveit et al. 2018). It has been suggested, that especially women with obesity have a higher prevalence of asthma (Bonsignore et al. 2018). In patients who have difficult-to-treat asthma, mild to moderate OSA was found in 49 % (Taillé et al. 2016). Patients who have severe asthma, can experience similar symptoms as those for SDB, such as poor sleep quality and daytime sleepiness, making differential diagnosis challenging (Julien et al. 2009). In part, the underlying inflammatory mechanism can be similar in both conditions, as it has been shown that upper airways are smaller in size in both SDB and asthma patients (Dultra et al. 2017). In patients with both asthma and SDB, the main type of respiratory event has proven to be hypopnoea (Julien et al. 2009).

2.3 Symptoms of SDB

2.3.1 Sleepiness

The most detrimental symptom of SDB is excessive daytime sleepiness (EDS) (Ramar & Guilleminault 2006; Stepanski et al. 1984). It is a highly subjective symptom, but there are a range of questionnaires that have been developed for evaluating EDS with the Epworth Sleepiness Scale (ESS) being the most common (Johns 1991). In addition, EDS is widely present in the general population, the estimate being 12 % (Hyon & Young 2005) and there are evaluations that indicate EDS may be more strongly associated with depression and metabolic factors than with SDB, and that EDS is more common in people under 30 years or over 70 years in age (Bixler et al. 2005).

There are no standard description for EDS, but it is often described as the inability to stay awake and alert during the day when the circadian sleep drive promotes alertness (Arand et al. 2005). Sleepiness is associated with an increased risk for traffic accidents (Sanna 2012; Tregear et al. 2009), increased medical expenses (Guest et al. 2008; Jennum & Kjellberg 2011), and more sick leave (Jennum & Kjellberg, 2011).

EDS among OSA patients is estimated to vary from 19 to 87.2 % (Garbarino et al. 2018b). However, ESS poorly correlates with objective tests of vigilance such as multiple sleep latency test (MSLT) or the maintenance of wakefulness test (MWT), their sensitivity ranging from poor-to-moderate (Johns 2000). Moreover, EDS is not a symptom specific to SDB, but rather the wide range of other comorbidities that often occur in the same patients (Saaresranta et al. 2016). However, the recent clustering analysis of the phenotypes of SDB, the traditional sleepy-type OSA patient was not the most common phenotype. Surprisingly, the non-sleepy clusters, had a higher risk for CVD than did patients with EDS (Anttalainen et al. 2019; Ye et al. 2014).

2.3.2 Depression

The estimations of the prevalence of depressive symptoms among patients with SDB do vary in studies and range from 7 % to 63 % (Saunamäki & Jehkonen 2007). In addition, people with major depressive disorders are five times more likely to have SDB than are the controls (Ohayon 2003). Depressive symptoms are also present especially among women with SDB. In one study, women had more depressive symptoms than men, regardless of their SDB severity. The more severe the SDB was, the more depressive symptoms they had (Pillar & Lavie 1998).

Surprisingly, women who only snored, had more depressive symptoms than the women with mild OSA, in all age groups, perhaps referring to prolonged upper airway resistance (Pillar & Lavie 1998). Symptoms of true depression overlap with SDB especially in women, and can be mistaken as mental illness (Pillar & Lavie 1998). Depressive symptoms can be evaluated using numerous questionnaires; DEPS (Salokangas et al. 1995) widely used in Finland, and Beck Depression Inventory (BDI)(Beck et al. 1996) used worldwide. Earlier studies on the correlation between the severity of SDB and depressive symptoms have been contradictory (Muñoz et al. 2000; Sánchez et al. 2001). However, a recent study suggested, that mild SDB correlated with more depressive symptoms, and additionally, depressive symptoms were associated with EDS (Lee et al. 2019).

2.3.3 Anxiety

Anxiety related to SDB is not as thoroughly investigated as are depressive symptoms. Currently it is estimated, that approximately half of the patients with SDB also suffer from anxiety (Lee et al. 2019; Rezaeitalab et al. 2014), and tend to have more anxiety than the general population (Rezaeitalab et al. 2014). However, it has been suggested that anxiety is more often present in patients with less severe SDB (Lee et al. 2019). Moreover, if female patients have both insomnia and SDB, they are also more likely to have anxiety (Foster et al. 2017).

2.3.4 Nocturnal symptoms

The most characteristic symptom of OSA is snoring, which occur in 70 -95 % of SDB patients (Guilleminault & Bassiri 2005) and 75 % of patients report pauses in breathing during sleep (Guilleminault et al. 1977; Guilleminault & Bassiri 2005). Other nocturnal symptoms include nocturia in 28 % of patients (Guilleminault & Bassiri 2005; Miyazaki et al. 2015), waking up with the sensation of choking for 18-31 %, restless sleep or sweating in 50 % and dryness of mouth in 74 % of patients (Guilleminault & Bassiri 2005; Rundo 2019).

2.3.5 Insomnia

Insomnia is a common sleep disorder that is estimated to affect 4 to 35 % of the population depending on the criteria used (Kay-Stacey &Attarian 2016). Further, co-morbid OSA and insomnia (COMISA) prevalence estimates range from 6.7 (Lang et al. 2017) to 27-85 % (Sweetman et al. 2017). Insomnia is usually characterised as having difficulty initiating sleep, maintaining sleep, or waking up too early or being unable to return to sleep (Sateia 2014). In recent studies, COMISA has emerged as a significant cluster of OSA, usually associated with the female gender (Sweetman et al. 2017).

The COMISA cluster has been linked to a higher risk of CVD, pulmonary diseases, and psychiatric comorbidities (Anttalainen et al. 2019; Saaresranta et al. 2016). It is also associated with significant daytime functional, social, and occupational impairments, and a reduced quality of life (Morin et al. 2006). Recent research further indicates that patients with COMISA are less likely to accept and use CPAP therapy compared to those patients without insomnia (Eysteinsdottir et al. 2017; Wickwire et al. 2010). Therefore, it has been suggested, that in COMISA, patient's insomnia should be treated first, in order to increase patient acceptance of CPAP therapy (Luyster et al. 2010; Sweetman et al. 2017).

2.3.6 The effects of gender

Women do report different symptoms of SDB than men do, and women also often suffer from daytime fatigue, anxiety or depressive symptoms, lack of energy, insomnia, and morning headaches (Kapsimalis & Kryger 2002). In addition, women with SDB have lower AHI, less severe hypoxemia, and a greater peripheral fat mass than men (Sforza et al. 2011). The diagnosis of SDB is often delayed in women, partially because of the different variation in symptoms compared to those in men (Lindberg et al. 2017; Young et al. 1996). Even though women have lower AHI, they do appear to be more symptomatic at lower levels of AHI when compared to men (Young et al. 1996).

In part, this difference could be explained by the fact that women have more prolonged partial upper airway obstruction (UAO), which is not implemented in AHI value, but can cause symptoms similar to OSA (Anttalainen et al. 2016; Mohsenin 2001; Saaresranta et al. 2015). Prolonged partial upper airway obstruction is now considered to be a relevant part of the SDB family, and recent research is implying that prolonged UAO is more than just mild OSA (Anttalainen et al. 2016). To emphasise the different phenotype for female SDB, women also have more REM related SDB (Kapsimalis & Kryger 2002), and their prevalence of positional obstructive sleep apnoea (POSA) may differ from that in men.

Some studies also indicate that women have less POSA than men (Basoglu & Tasbakan 2018), whereas other studies suggest that POSA in women is more common regardless of SDB severity (Heinzer et al. 2018). Women have less SDB than men, but after menopause the prevalence of SDB doubles (Anttalainen et al. 2006; Bixler et al. 2001). In menopause, women go through an array of changes, including hormonal decline in oestrogen and progesterone levels, leading to vasomotor changes, mood alterations, and often also sleep disturbances (Takahashi & Johnson 2015). Not only SDB prevalence, but also the prevalence of other sleep disturbances, such as restless legs syndrome and insomnia, increases after menopause (Baker et al. 2018). The definite underlying mechanisms are not fully understood, but studies have indicated that it is an complex interaction that involve aging, hormonal changes, visceral fat redistribution, and pharyngeal collapsibility (Perger et al. 2019).

2.4 Diagnosis

The diagnosis of SDB is based on thorough clinical examination, involvement of appropriate symptoms in patient history, and most importantly, polysomnography (PSG) or cardiorespiratory polygraphy (PG) (Kapur et al. 2017). Several questionnaires have been developed for screening SDB, and if the possibility is high, then PG or PSG should be performed. PSG and PG are expensive tests, and the workload is substantial, therefore screening is advised (Kapur et al. 2017). The most common questionnaire for screening is STOP-BANG, which includes four subjective elements (STOP: Snoring, Tiredness, Observed apnoea and high blood Pressure) and four demographic items (BANG: BMI, Age, Neck circumference, Gender). It is well validated for determining the possibility of moderate-to-severe OSA (Nagappa et al. 2015).

2.4.1 Cardiorespiratory polygraphy

Cardiorespiratory polygraphy (PG) is the most common examination utilised for determining SDB in Nordic countries, whereas in most other parts of the world

polysomnography (PSG) is the most applied method. In PG, sleep stages cannot be determined, as the set-up does not include an electroencephalogram (EEG). PG usually includes measurements of electrocardiography (ECG), inspiratory flow pressure with differential pressure sensor connected to nasal prongs, abdominal and thoracic movement analysis with belts with respiratory inductive plethysmography (RIP), and determination of sleeping position. In addition, electromyographic (EMG) sensors may be connected to both the patient's legs to m. tibialis anterior to determine sleep-related movement disorders. If PG is performed in a hospital ward, transcutaneous carbon dioxide partial pressure can be measured based on the diffusion of carbon dioxide through tissue and skin, with the help of a heated electrode. Video recording can also be included.

Arterial oxyhaemoglobin saturation (SaO_2) is measured with a finger probe pulse oximetry. The advantage of preferring PG is the possibility to perform the study as ambulatory and to decrease the costs and workload of the analysis. Basic PG is usually sufficient to diagnose SDB in adults (Kapur et al. 2017). In addition, in PG, the AHI values are approximately 30 % lower than in PSG due to a partly different scoring criteria and missing data on sleep staging. Hence wake time is included in PG (Escourrou et al. 2015; Hedner et al. 2011).

2.4.2 Polysomnography

The set-up of PSG includes the same measurements as PG, with sensors added to determine sleep stages. This process allows a more detailed diagnosis of a wider range of sleep disorders. In PSG, at least three electroencephalography (EEG) leads, two electrooculography (EOG) leads, and an EMG lead for the m. submentalis are attached. PSG allows an evaluation of wake, arousals, and sleep stages, usually in 30-second epochs, and the breathing patterns associated with each of them. In addition, with the help of EMG leads, bruxism can be detected. Video recording is often included in the PSG set-up.

2.5 Subtypes of SDB

2.5.1 Obstructive sleep apnoea

The most common type of SDB is obstructive sleep apnoea, characterised by episodes of total or partial pharyngeal collapse during sleep leading to pauses in breathing. This obstruction results in desaturations of blood oxygen concentration, and sleep fragmentation. The diagnosis is made using either PSG or PG (Kapur et al. 2017). In PG, apnoea is defined as a decrease in breathing amplitude of 90 % for 10 seconds, while attempts to breathe continue. Efforts of breathing are detected as

movements in thoracic and abdominal belts. In addition, desaturation of 3 % or more from the baseline level in arterial oxyhaemoglobin saturation must be present for the event to be considered as apnoea. Hypopnoea is defined as a decrease in breathing amplitude by 30 % or more from the normal stable level and combined with a desaturation of 3 % in arterial oxyhaemoglobin saturation. The sleeping time is divided by the sum of these two events, giving a total AHI. The patient is diagnosed with obstructive sleep apnoea if AHI >5/h. OSA is considered as mild if AHI<15/h. Values of 15-29/h result in moderate OSA, and values ≥30/h are considered as severe OSA. If the patient has daytime symptoms, then the condition is called obstructive sleep apnoea syndrome (OSAS) (Berry et al. 2012).

2.5.2 Prolonged partial upper airway obstruction

In prolonged partial upper airway obstruction, the airways do not collapse completely, but the air stream is affected and diminished for at least 1-3 minutes, but it can persist as long as 60 minutes, resulting in similar symptoms as in OSA. In polygraphy, the air flow in the respiratory channel is flattened as seen in Figure 4. In addition, it has been shown that during prolonged UAO, transcutaneous carbon dioxide ($PtcCO_2$) levels increase higher than in other SDB forms or during steady breathing (Figure 5) (Rimpilä et al. 2015). Upper airway obstruction is more common in women than it is in men, and it is often disregarded when determining treatment considerations (Anttalainen et al. 2016; Polo-Kantola et al. 2003; Tenhunen et al. 2013). It has been estimated, that 17.7 % of subjectively healthy postmenopausal women suffer from UAO (Polo-Kantola et al. 2003), and from a clinical cohort of females with suspected SDB, UAO was found in 66.1 % of postmenopausal and 50.9 % of premenopausal women (Anttalainen et al. 2006).

Only recently, has the significance of this phenomenon been understood, and recent studies have shown that clinically, the future risks of UAO may be as high as other SDB (Saaresranta et al. 2015). The consensus of the reference values or clinical practice is still under investigation, but recent studies do point in the direction that this issue should be taken as seriously as other SDBs and treated just as efficiently (Anttalainen et al. 2010a; Saaresranta et al. 2015).

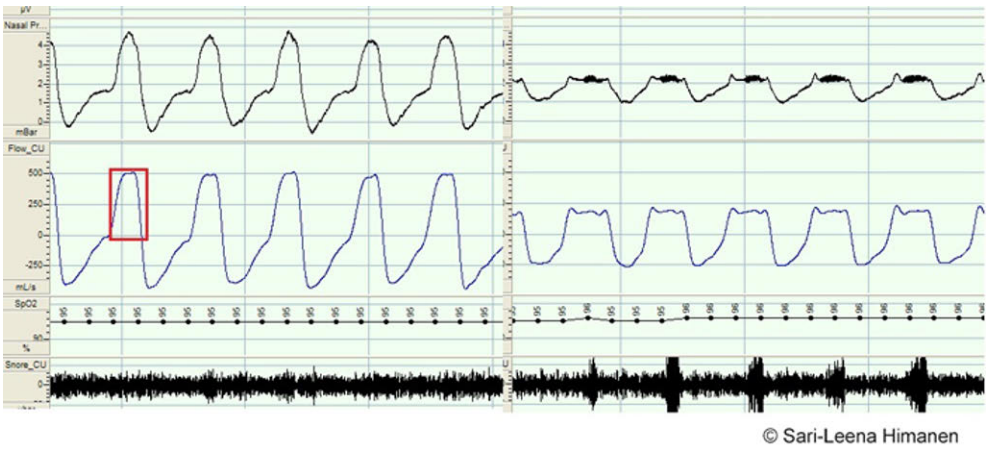

Figure 4. Prolonged upper airway resistance in polygraphy. The red square shows normal breathing pattern and flow amplitude which is flattened in the latter patterns that illustrate upper airway resistance. Reprinted with a permission of Sari-Leena Himanen.

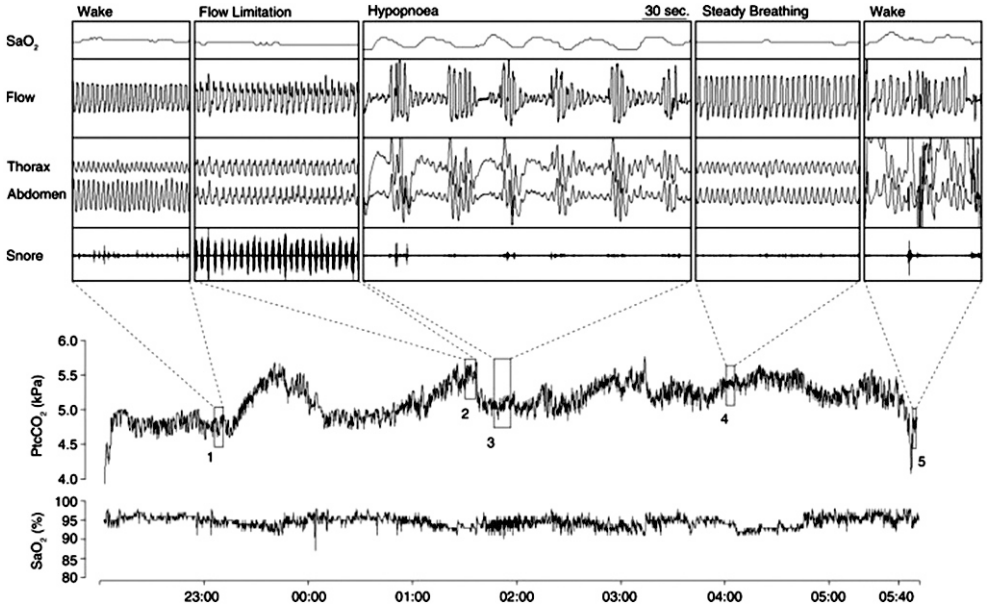

Figure 5. Example of polygraphy (PG) profile during wake, upper airway obstruction (UAO) illustrated with flow limitation, hypopnoea, normal breathing and wake. The numbers 1-5 illustrate different types of breathing and the typical level of transcutaneous carbon dioxide ($PtcCO_2$) during them. Arterial oxyhaemoglobin (SaO_2) concentrations are illustrated at the bottom. Reprinted from Rimpilä et al. 2015 with a permission of Respiratory Physiology & Neurobiology.

2.5.3 Mild sleep apnoea

Traditionally, mild sleep apnoea is diagnosed, if AHI is 6-14/h (Berry et al. 2012). In the HypnoLaus study, the prevalence of mild symptomatic sleep apnoea varied according to gender and age. In men under 60, the prevalence was approximately 40 % and in women the same age, it was over 30 %. In men over 60, the prevalence was approximately 25 % and in women, it was over 40 % (Heinzer et al. 2015). In addition, especially for mild sleep apnoea measured with portable home monitoring, the night-to-night variation in AHI was high (Prasad et al. 2016; Stöberl et al. 2017). Mild obstructive sleep apnoea is thought to have less of an impact on comorbidities or other risks, and it is usually left untreated or treated with lifestyle changes, positional treatment, or a mandibular device (Tingting et al. 2018).

However, recent studies have discovered, that patients with mild sleep apnoea have the same risks for comorbidities as do patients with a more severe condition (Anttalainen et al. 2010a; Saaresranta et al. 2015). It is currently discussed whether mild sleep apnoea should be treated as efficiently as more severe conditions, in order to prevent the comorbidities and rising costs that come with the condition. As we have broadened our perspective of sleep apnoea with more knowledge of different phenotypes being included in this umbrella term, the importance of AHI is going to diminish in the future. Patients previously destined to fall into a "mild" category, regardless of detrimental symptoms and hence left untreated, can be evaluated more sufficiently using this tailored approach. One innovative suggestion is to use the PALM scale (Pcrit, Arousal threshold, Loop gain and Muscle responsiveness scale) (Eckert 2018), but it has been criticised for demanding excessive amount of data and measurements that cannot be performed in wide clinical settings (Bonsignore et al. 2017).

2.5.4 SDB related to REM sleep

SDB related to rapid eye movement (REM) sleep can be diagnosed with PSG, where respiratory events can be seen along with their association to the REM stage of sleep. If the sleep study is performed with PG, sleep stages are not visible due to a lack of EEG. With PG, REM related SDB can be diagnosed only by using the assumption, that apnoeas are seen during the hours fit for REM sleep (Berry et al. 2012). The REM stage of sleep occurs mainly in the early hours of morning at the end of a night. If the scorer does not recognise these stages, then the condition can be masked, due to the fact, that AHI dilutes when the value is calculated by using the entire time in bed (Berry & Gleeson 1997).

REM OSA is common, evaluations being 10–40.8 % of patients referred to investigations for suspected sleep apnoea (Acosta-Castro et al. 2018; Nisha Aurora et al. 2018). In REM sleep, genioglossus muscle activity and pharyngeal dilator muscle control are decreased due to changes in the neurotransmitters, leading to an

increased possibility of upper airway collapse (Grace et al. 2013). Moreover, REM sleep is related to haemodynamic variability and an increase in sympathetic activity and myocardial demand. Therefore respiratory events during REM sleep are thought to be longer and more frequent, leading to deeper oxyhaemoglobin desaturation than events during non-REM (NREM) sleep (Penzel et al. 2016; Somers et al. 1993). Based on the aforementioned, REM OSA has thus been associated with hypertension (Appleton et al. 2016), impairments in glucose metabolism (Acosta-Castro et al. 2018; Chami et al. 2015), and cardiovascular disease (Acosta-Castro et al. 2018; Aurora et al. 2018; Aurora &Punjabi 2013).

REM OSA is more common in women than in men (O'Connor et al. 2000), leading to women being under-treated for OSA based on the total AHI. Traditional AHI reflects NREM-AHI, which is predominant in men, but it disregards REM-AHI. Under-treatment of OSA, therefore, may contribute to an increase in risk for cardiovascular disease in women. In addition, the standard use of NREM-AHI emphasises the importance of using CPAP throughout the entire night to cover the apnoeas related to REM sleep, which is present in the latter part of the night (Won et al. 2019).

2.5.5 Central sleep apnoea

Central sleep apnoea (CSA) does not originate from obstruction of the airways, but from the central control of breathing. The prevalence is estimated to be 0.9-4 % of population level (Donovan & Kapur 2016; Heinzer et al. 2015). Central events are currently thought to represent an instability of the breathing pattern and it may provoke obstructive events (Dempsey et al. 2014). In CSA, high loop gain is present, resulting in CO_2 concentrations' decreasing beyond the apnoeic threshold, resulting in the apnoea persisting until the CO_2 concentration has elevated to a normal level (Naughton 2010; White 2005; Younes et al. 2001). In PSG or PG, central apnoeas are seen as a flat line in the respiratory channel, but contrary to OSA, there are no efforts of breathing visible in the abdominal or thoracic belts (Randerath et al. 2017). CSA can be a result of cardiovascular (Arzt et al. 2016), internal or neurological disorders (Lipford et al. 2014; Nachtmann et al. 1995; Perks et al. 1980), or it can emerge under CPAP therapy (Morgenthaler et al. 2006) or during opioid use (Guilleminault et al. 2010), or at high altitudes (Bloch et al. 2015).

2.6 Treatment of SDB

In the imminent future, the treatment of SDB is most likely going to change. Nowadays, the gold standard of treatment is CPAP therapy, and it is commenced in all patients who have moderate to severe sleep apnoea (AHI>15/h) (Kapur et al.

2017; Sateia 2014), and for patients with mild sleep apnoea if they have severe symptoms or are not candidates for a mandibular device. However, there are still other treatments that can be used if CPAP therapy is unsuccessful or if the SDB is mild (Tingting et al. 2018). In the future, the phenotype for patient suffering from SDB, will dictate the right treatable trait, and those patients can then be treated accordingly (Bonsignore et al. 2017; Saaresranta et al. 2016).

2.6.1 Continuous positive airway pressure (CPAP) treatment

Nasal CPAP was invented in 1981 by the Australian physician, Colin Sullivan, and his co-workers (Sullivan et al. 1981). Since that invention, CPAP has been the gold standard for treating SDB, especially obstructive sleep apnoea (Sullivan et al. 1981). CPAP is used during sleep, and it supports the patient's breathing by delivering a constant airflow into the airways, creating a pillar of air, that then mechanically keeps the upper airways open. The air is delivered via a nasal mask, which is linked to the actual CPAP device via a long flexible tube (Sullivan et al. 1981).

CPAP therapy reverses SDB and normalises the metabolic factors that influence breathing. The treatment is efficient, but adherence remains a problem and is the most important factor that results in discontinuing the therapy. In twenty years, the adherence has not improved, and non-adherence continues to remain in 34 % of patients (Rotenberg et al. 2016). A lot of technical efforts have been undertaken to improve adherence. Masks have improved in recent years, along with advances in CPAP device technology that have enabled smaller, quieter, and more convenient devices being available for patients (Patil et al. 2019).

The positive effects of CPAP therapy have been demonstrated in numerous studies over thirty years (Gay et al. 2006), but the adverse effects continue to be vigorously studied to this day. There are mixed results, both positive and negative, for the countless variables (Bonsignore et al. 2019a; Jennum & Kjellberg 2011). All in all, the results have been sustained more on the positive side, and CPAP therapy still remains the best choice today, along with lifestyle changes, for treating patients with moderate to severe SDB.

2.6.2 Non-CPAP treatment

CPAP therapy remains to be the most efficient treatment for moderate-to-severe OSA, but there are other treatments that can be used along with CPAP therapy, or if CPAP therapy is unsuccessful. Especially lifestyle counselling should be offered to all SDB patients regardless of other treatments.

2.6.2.1 Weight loss

It has been estimated that 70 % of patients with SDB are obese (Young et al. 1993) Obesity and OSA have a complex bidirectional alliance (Peppard et al. 2000) described in Figure 6.

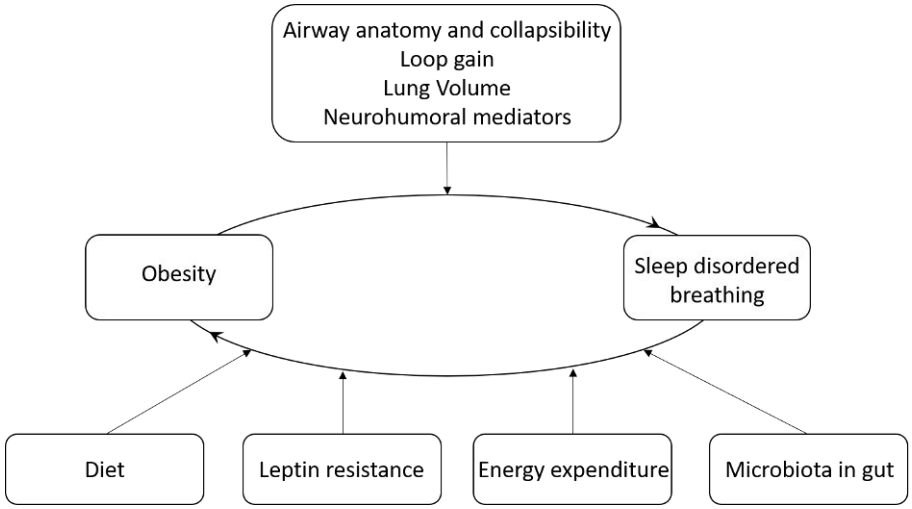

Figure 6. The bidirectional alliance of SDB and obesity

Previously, it was thought that treating sleep deprivation in SDB patients resulted in a more reasonable diet, greater physical activity, and finally, weight loss. Unfortunately, this seems not to be the case overall (Joosten et al. 2017; Tachikawa et al. 2016). Over the course of long-term CPAP therapy, weight tends to remain the same or even increase, especially in young obese OSA patients and in women (Myllylä et al. 2016; Redenius et al. 2008). Yet weight loss has been proven to influence SDB positively and in some cases even cure OSA (Joosten et al. 2017; Tuomilehto et al. 2009). In addition, weight loss leads to improvement in overall cardiovascular risk and may lead to additional benefits for SDB symptoms (Chirinos et al. 2014). Even small reduction in weight is associated with improvement of OSA; 10 % reduction in body weight results in an approximate decrease of 26/h to 32/h in AHI (Peppard et al. 2000). Therefore, all efforts to manage OSA must involve lifestyle counselling and support for weight loss along with ongoing CPAP therapy (Joosten et al. 2017).

2.6.2.2 Lifestyle changes: Smoking, alcohol, and exercise

Lifestyle changes are a key factor when treating SDB as noted above (Joosten et al. 2017). The prevalence of smoking is high among patients with OSA, even reaching 35 %, when in the overall population, only 18 % smoke. In addition, smokers are 2.5 times more likely to have OSAS (Kashyap et al. 2001). Male patients smoke more than female OSA patients do (Varol et al. 2015), and further, both OSA and smoking are well-known risk factors for metabolic disorders (Craig et al. 1989; Zhu et al. 2017). Various compounds in cigarette smoke increase oxidative stress and systemic inflammation, thus contributing to the formation of metabolic disorders (Ambrose & Barua 2004). Smoking also causes swelling of the mucosa possibly due to increased calcitonin gene-related peptide (CGRP) related to neurogenic inflammation, and exacerbation of any upper airway collapse at the level of the uvula, resulting in a worsening of UAO (Kim et al. 2012). Therefore, smoking cessation for these patients or those at risk for OSA is essential.

Kolla et al stated in their own meta-analysis that given alcohol consumption, AHI increased, mean SaO_2 reduced, and there was an increase in respiratory event duration, and a decrease in nadir SaO_2 following two or three standardised drinks (Kolla et al. 2018). Alcohol consumption should be kept to a minimum in patients with SDB.

Exercising affects SDB, even if it does not affect weight (Carneiro-Barrera et al. 2019). In the Wisconsin Sleep Cohort Study, hours of exercise were associated with a reduced incidence of mild and moderate OSA, independent of other confounders such as BMI (Awad et al. 2012). One hypothesis suggests that moderate exercise reduces fluid accumulation in the legs, thereby decreasing nocturnal fluid shift. When lying down, fluid redistributes to the neck which may lead to increased pressure in tissues surrounding the upper airway, reducing its size and increasing its collapsibility (Redolfi et al. 2015).

2.6.2.3 Mandibular advancement device

Mild SDB can be treated with a mandibular advancement device (MAD), constructed by a dentist. A wide variety of devices are available, but all MADs are worn intraorally during the night. They prevent upper airway collapse by holding the mandible and tongue forward and increasing the antero-posterior dimensions of the oropharynx (Cistulli et al. 2004). In addition, it is assumed, that the effect of MAD is also associated with an increase in lateral dimensions, i.e., the lateral displacement of the parapharyngeal fat pads from the airway, an increase in lower anterior facial height, a raised position of the hyoid, and anterior positioning of the base of tongue muscles (Chan et al. 2010). For patients who are intolerant of CPAP therapy, MAD can be effective in reducing the AHI compared to non-treatment.

In patients with only mild OSA, CPAP and MAD are similarly effective therapy options. There is a significant heterogeneity between patients in their response to MAD therapy, which can, in part, be explained by the severity of OSA at baseline (Sharples et al. 2014). OSA patients usually prefer MAD over CPAP, but more than one-third of the patients will have minimal or no major reduction in AHI with MAD. Based on a recent meta-analysis, the responders had lower age, lower BMI, smaller neck circumference, lower AHI, an anatomic variation such as a retracted maxilla and mandible, a narrower airway or a shorter soft palate than non-responders (Chen et al. 2020).

2.6.2.4 Surgical interventions

When a patient suffers from SDB as a result of anatomical abnormalities, surgical interventions can be successful. Surgical options for the treatment of OSA include tonsillectomy and adenoidectomy, uvulopalatopharyngoplasty (UPPP), radiofrequency ablation, and maxillomandibular advancement (MMA) (Wray & Thaler 2016). The past decade, MMA has been revealed to be the most popular and effective surgical therapy, and offer the most active research (Awad et al. 2019). UPPP has been reported to reduce AHI by approximately 33% twelve months after surgery, but still, it is primarily indicated for those patients with an anatomic basis for obstruction (Strollo et al. 2015).

In morbidly obese patients, gastric bypass surgery is considered as a valid treatment of SDB, but the research evidence remains limited (De Raaff et al. 2018). Hypoglossal nerve stimulation (HNS) was already successfully reported in 2001 (Schwartz et al. 2001). The target of the stimulation is activating the genioglossus muscle and thus improve nocturnal breathing in OSA patients. The stimulator is a pacemaker-like pulse-generator with two parts: The generator is implanted to detect ventilator effort, and a stimulation lead stimulates the branches of the hypoglossal nerve, predominantly the genioglossus muscle (Wray & Thaler 2016). Therapy has been proven to be effective, however, only a well selected OSA patients; hence broader clinical use still remains to be seen (Wray & Thaler 2016).

2.6.3 Effects of CPAP therapy

2.6.3.1 Weight

It has been revealed in recent years that treating SDB with CPAP therapy does not result in weight loss (Myllylä et al. 2016; Redenius et al. 2008) nor increase a patient's physical activity during the day (Bamberga et al. 2015). The assumption, therefore, today is that patients using CPAP therapy remain the same weight or even

gain weight, especially the young and women (Drager et al. 2015; Ou et al. 2019). The regulation of energy balance in OSA is complex and multifactorial, involving hormonal regulation of hunger, food intake, and energy expenditure that affects the metabolism and physical activity. CPAP therapy may reduce energy expenditure, but it does not result in any compensatory increase in physical activity (Shechter 2016). The toning down of sympathetic overdrive during the night in SDB results in less energy consumption and, therefore, a weight gain (Bamberga et al. 2015). Tachikawa et al. discovered that three months of CPAP therapy reduced the basal metabolic rate thereby favouring a positive energy balance in terms of energy expenditure (Tachikawa et al., 2016). Exercising habits and food consumption seem to remain similar compared to those before CPAP therapy, although in women a modest increase in recreational activity during CPAP therapy has been reported (Batool-Anwar et al., 2014).

2.6.3.2 Mood

SDB causes a variety of mental symptoms (Garbarino et al. 2018a). Especially in women, these symptoms can be severe, and initially, they can be mistaken for and thus treated as mental illnesses. Depressive symptoms are present in a quarter of patients suffering from SDB (Ramar & Guilleminault 2006) and it has been suggested in many studies that treating SDB with CPAP alleviates these symptoms dramatically (Lang et al. 2017; Millman et al. 1989; Sánchez et al. 2001). In addition, anxiety is commonly present, but the effects of CPAP therapy on anxiety have not been studied as thoroughly as the depressive symptoms.

There are, however, some indications that CPAP therapy alleviates anxiety (Sánchez et al. 2001); yet, in a recent meta-analysis, there was no significant improvement in anxiety with CPAP therapy (Zheng et al. 2019). SDB is overrepresented in the population with severe mental illnesses (Nikolakaros et al. 2015). Of patients with schizophrenia, 15–48 % have SDB (Kalucy et al. 2013), and these symptoms are often discarded. CPAP therapy seems to improve the cognitive impairment of schizophrenia (Myles et al. 2019), and alleviate both the symptoms of SDB and the psychiatric disorder (Gupta & Simpson 2015). Bipolar disorder, however, has been described to worsen during CPAP therapy, and therefore, these patients should be treated with greater caution (Aggarwal et al. 2013).

2.6.3.3 Leptin

Leptin is an adipocyte-secreted hormone that controls food intake and stimulates energy expenditure mainly through the neuronal pathways in the brain (Auwerx & Staels 1998). Leptin crosses the blood–brain barrier (BBB) via a receptor-mediated

endocytosis mechanism as illustrated in Figure 7. The signalling interactions have been revealed to be complex. In addition, leptin is produced in various organs. Circulating leptin concentrations are correlated with the amount of body fat and are thought to reflect energy status (Auwerx & Staels 1998).

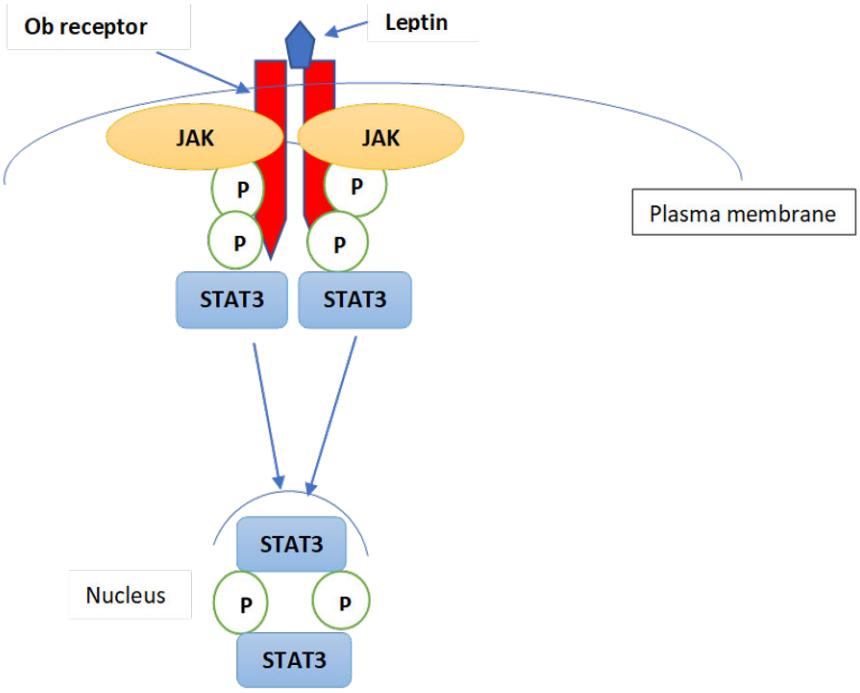

Figure 7. Activation of Janus Kinase (JAK) occurs by transphosphorylation (green circles) and subsequent phosphorylation of tyrosine residues in the cytoplasmic region of the Ob-receptor. Phosphorylation of JAK leads to phosphorylation of signal transducers and activators of transcription (STAT's), which allows their dissociation from the receptor. Active STAT's translocate to the nucleus to regulate gene expression.

If gene controlling leptin production is absent or violated, the result is excessive eating and morbid obesity, as has been observed in ob/ob knock-out mice, who lack the gene that enables leptin formation, resulting in leptin deficiency (Zhang et al. 1994). The mice become obese and develop multiple comorbidities, such as diabetes, and thus that species is widely used in research (Münzberg & Morrison 2015). In humans, the lack of an ob gene is extremely rare, but as humans gain weight, or get older, leptin resistance emerges and the feelings of satiety demand escalating leptin concentrations (Zhou & Rui 2014).

The precise underlying mechanism of leptin resistance is still unknown, but it might be the result of changes in the leptin receptors in the hypothalamic area, resulting in leptin being unable to penetrate the BBB (Myers et al. 2008). Resistance

at the BBB level seems to be multifactorial and according to yet another theory leptin transporters are increasingly saturated during obesity, and the transporters reach full capacity at a leptin concentration 40 ng/ml, thereby blocking the access of leptin to the central nervous system (CNS), resulting in continuous weight gain (Banks et al. 2000).

In patients who are suffering from OSA, leptin concentrations are higher than in the controls, regardless of age or BMI (Considine et al. 1996; Thomas et al. 2000). This circumstance is thought to be a result of hypoxia during sleep or sleep fragmentation, both of which have been shown to elevate leptin concentrations in mice (Harsch et al. 2003; Taheri et al. 2004). This result could be associated with the fact that leptin is a powerful ventilatory stimulant, independent of its metabolic effects. It increases ventilation through receptors in CB (Caballero-Eraso et al. 2019; O'Donnell et al. 1999) and acts in the medullary centres that regulate the responses to hypercapnia (O'Donnell et al. 1999).

The effect of CPAP therapy on leptin concentrations has been broadly studied, leading to rather conflicting results. Most studies reported a decrease in leptin concentrations during CPAP therapy (Pan & Kastin 2014). However, these study samples were rather small and consisted primarily of men. It is also known that leptin concentrations are gender related (Akilli et al. 2014); therefore, the results for men should not be generalised to women. The results in some of the previous studies on the CPAP effect are presented in Table 3.

Table 3. Some previous studies of CPAP therapy and change in leptin concentrations.

Author	Year	N	Gender	Duration (months)	Result
Chin	1999	10	All male	6	Decreased
Ip	2000	30	M 27, F 3	6	Decreased
Harsch	2004	30	All male	2	Decreased
Sanner	2004	86	M 69, F 17	6	Decreased among high adherence patients
Yee	2006	14	M 11, F 3	18–36	Decreased
Drummond	2008	98	All male	6	First decreased, then increased
Dorkova	2008	32	M 27, F 5	2	No change
Cuhadaroglu	2009	31	All male	2	Decreased
Macrea	2010	10	All male	11–39	No change
Sanchez	2012	36	All male	3	Decreased
Yosukaya	2015	31	All male	3	No change

2.6.3.4 Insulin-like Growth Factor 1 (IGF-1)

IGF-1 is expressed mainly in the liver, but it can also be produced in almost every tissue of the body (Ohlsson et al. 2009). The secretion of IGF-1 is dependent on pulsatile growth hormone production from the anterior pituitary gland and portal insulin exposure (Münzer et al. 2010). It is considered to be an important growth factor. OSA is thought to be associated with a significant decrease in serum IGF-1 concentrations (McArdle et al. 2007; Ursavas et al. 2007). A growing body of evidence from the clinical research indicates that CPAP therapy appears to increase IGF-1 levels in OSA patients (Chen et al. 2015). Some of the previous studies and their results are presented in the following Table 4.

Table 4. Previous studies on CPAP therapy and IGF-1 concentrations. Modified from Chen et al. 2015.

Author	Year	N	Gender	Duration (Months)	Result
Grunstein	1989	43	All male	3	Increased
Brooks	1994	9	M 7	4	No change
Meston	2003	52	All male	1	Small increase
Lindberg	2006	11	All male	6	Increase
Barcelo (EDS)	2008	20	All male	3	Increase
Barcelo (NON-EDS)	2008	15	All male	3	Increase
Makino	2012	18	All male	17.5	Increase

2.6.3.5 Comorbidities and medication

The effects of OSA treatment on various comorbidities has been broadly studied, but mainly as comorbidity prevalence before and after therapy initiation. Principally the treatment for the comorbid patient group has been CPAP, as comorbidities are seen as an increased risk of overall morbidity, thus leading to choosing the most effective therapy for patients who have multiple comorbidities (Bonsignore et al. 2019a). Along with these comorbidities come increased expenses for medication, so therefore, the effects of CPAP therapy have been of particular interest.

2.6.3.6 Cardiovascular comorbidities

The effects of CPAP on cardiovascular comorbidities is widely studied. The effect of CPAP therapy on hypertension has been studied the most and by using various methods, but as the knowledge has mounted, the conclusion is that the effect is

positive, although minor (Pengo et al. 2020). However, these results have possibly been controversial due to their effect being dependent on adherence to CPAP, the severity of SDB, and the baseline values of blood pressure (Haentjens et al. 2007). The same confounders have been discovered to influence more detrimental cardiovascular outcomes such as myocardial infarction, stroke and cardiovascular mortality (Hudgel 2018).

Some studies also have indicated that cardiovascular morbidity and mortality are normalised with CPAP therapy (Marin et al. 2010; Myllylä et al. 2019), while others have reached the conclusion that CPAP has no protective effect (Yu et al. 2017). In one recent review, there were no indications that CPAP therapy could improve CV outcomes (Labarca et al. 2020). However, in another review, CPAP was found to have a minor effect on CV outcomes for patients with coronary artery disease in small studies, but not in randomised controlled trials (Wang et al. 2018). Arrhythmias are common among patients with SDB, and CPAP therapy seems to decrease recurrent arrhythmias (Deng et al. 2018). Patients with heart failure and OSA have also been shown to benefit from CPAP therapy. Treatment reduced rates of hospitalisations, but again, the effect depended on adherence (Kasai et al. 2008).

2.6.3.7 Metabolic comorbidities

As discussed earlier, metabolic comorbidities arise from the union of obesity and SDB. Therefore, treating SDB with CPAP therapy should at least in part have positive effects. Yet, on the other hand, CPAP therapy alone does not influence the visceral adipose tissue (Chen et al. 2020) and the metabolic instabilities that obesity creates (Sivam et al. 2012). Still, there are indications that CPAP therapy can have a positive influence on metabolic disturbances in patients with insulin resistance (Abud et al. 2019). However, diabetes and OSA have a bidirectional link. Thus, treating patients with OSA and diabetes with CPAP, has been proven to reduce such consequences, as neuropathy, nephropathy, and retinopathy, while the glycaemic blood concentrations are not affected (Zhu et al. 2018). This finding has led to a discussion on screening SDB of patients with diabetes to prevent severe complications.

2.6.3.8 Respiratory comorbidities

Recent studies indicate that CPAP therapy has a protective effect on patients with COPD and OSA overlap syndrome (Marin et al. 2010; Stanchina et al. 2013), but that knowledge is still scarce. Phenotyping of SDB patients is thought to bring about better understanding and more knowledge of when to treat overlap patients. Similar situation exists with asthma and SDB patients. There are studies both in favour of

(Kauppi et al. 2016) and against (Ng et al. 2018) the positive effect of CPAP therapy on asthma symptoms, but it is still thought that in severe or poorly controlled asthma, CPAP therapy can be beneficial (Davies et al. 2018).

2.6.3.9 Medication

Patients with SDB, especially OSAS, have a higher risk of comorbidities (Somers et al. 2008) leading to an increased use of health care as early as seven years before the diagnosis (Jennum et al. 2014). In one study, risk of lost work days was higher as early as five years before SDB diagnosis in women and one year in men, thus increasing health care costs (Sjösten et al. 2009). In addition, all-cause mortality is shown to be higher in patients with OSA, and CPAP therapy seems to reduce that risk in men, but not in women (Jennum et al. 2015).

Medication use is higher in patients with OSA (Jennum & Kjellberg 2011), perhaps due to a greater number of comorbidities, but the effect of CPAP on medication use remains controversial. Some studies have shown that the overall costs of medication are reduced with CPAP (Tan & Marra 2006), while others have failed to show any reduction, and instead an increase in medication costs (Jennum & Kjellberg 2011).

3 AIMS OF THE STUDY

This study sought to evaluate the effects of long-term CPAP therapy on various factors, especially those that influence weight and medication use. In addition, the study wants to find the predictors of changes in weight and the effects of gender on these issues. The following three specific objectives thus were:

1. Evaluate whether long-term CPAP therapy for SDB can alleviate patients' SDB symptoms, leading to a healthier lifestyle and better weight reduction.
2. Evaluate the effect of long-term CPAP therapy on weight, leptin, and IGF-1 concentrations in obstructive sleep apnoea.
3. Evaluate the effects of long-term CPAP therapy on medication use for comorbidities in females who have sleep apnoea or prolonged partial upper airway obstruction.

4 PARTICIPANTS AND METHODS

4.1 Participants

4.1.1 Study I and II

Participants in Studies I and II were consecutive patients who were referred to the Department of Pulmonary Diseases at the Turku University Hospital to confirm or rule out their instance of SDB. The cohort was prospectively collected from March 2004 to October 2006, and totalled 223 patients, of which 101 were men (45.3 %), and 122 were women (54.7 %). After three years of follow-up, the study population was divided into two groups: 1) CPAP users, who had used CPAP therapy for three years at least four hours per day and 2) non-users, who did not commence CPAP at the beginning or had discontinued the use before their three-year follow-up visit. Among the non-users, there were 20 patients (11 males, 9 females) who had AHI< 5/h; however, all had symptoms suggesting OSAS. Of the cohort, 149 patients (66.8 %; 65 males, 84 females) participated in the follow-up visit. Out of those who participated, 76 patients (51.0 %; 32 males, 44 females) were categorised as CPAP users and the rest as non-users (n=73; 33 males, 40 females).

Among the non-users, 20 patients had AHI < 5/h and CPAP therapy was not suggested. Further, 29 patients refused to commence CPAP treatment despite the pulmonologist's recommendation. Additionally, seven patients started the therapy, but used it for less than three months, five patients used CPAP for 3-11 months, and nine used it for 12-24 months. There were some missing values in the questionnaires and blood values; therefore, the number of participants differed in Studies I and II, as explained later in detail. The flowchart for the patient selection is described in Figure 8.

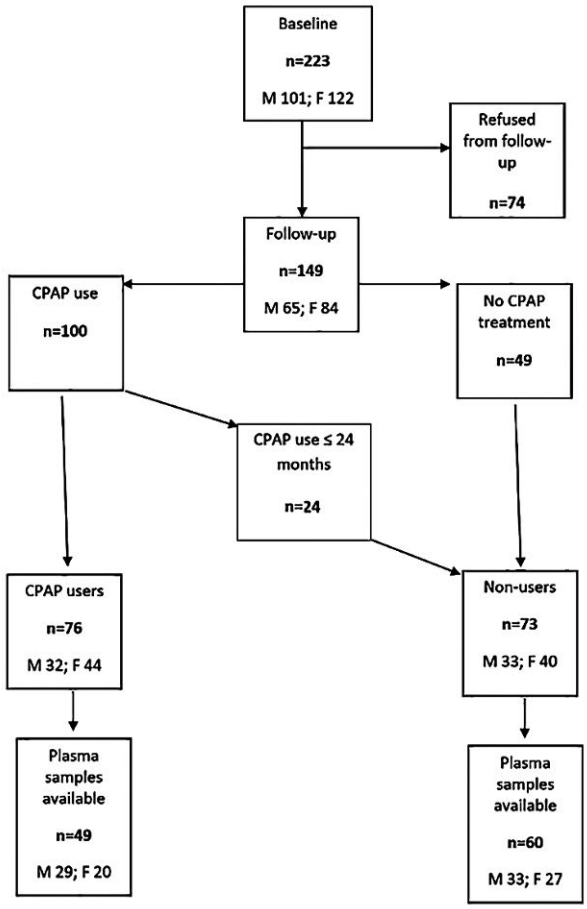

Figure 8. Flow chart of the study population in study I and II. Reprinted from original publication II with permission of Sleep and Breathing.

4.1.2 Study III

In this retrospective study, only females were included. Patients were selected from the pulmonary clinic database of 601 consecutive females who were referred to the Department of Pulmonary Diseases in Turku University Hospital from 1994 to 1998 for suspected SDB. They all had symptoms suggesting sleep disordered breathing, such as snoring, daytime sleepiness, or apnoeas witnessed during sleep.

From these 601 patients, Static-Charge-Sensitive bed (SCSB) recordings were available for 469 (78 %) patients and SDB was found in 368 patients (65 %). CPAP therapy was initiated with 137 women, and 231 women were considered as the controls, as they did not initiate CPAP. Hospital records were retrospectively screened for information on age, BMI, neck circumference, and smoking status. This

information was available from 587 (97.7 %) of the original patients. Data on CPAP use were derived from the hospital records at the time of the sleep study, and then after one or two years of CPAP use. If the patient had used CPAP for more than four hours per night, she was considered a CPAP user. The controls did not start CPAP therapy or discontinued therapy within one year of treatment. National Social Insurance Institution medication data were available from 1993 onwards. Therefore, only those patients, whose sleep study was undertaken in 1996-1998 were included in the study to allow for use of medication data three years before CPAP initiation or the sleep study. This criterion resulted in 66 CPAP users and 122 controls as seen in Figure 9.

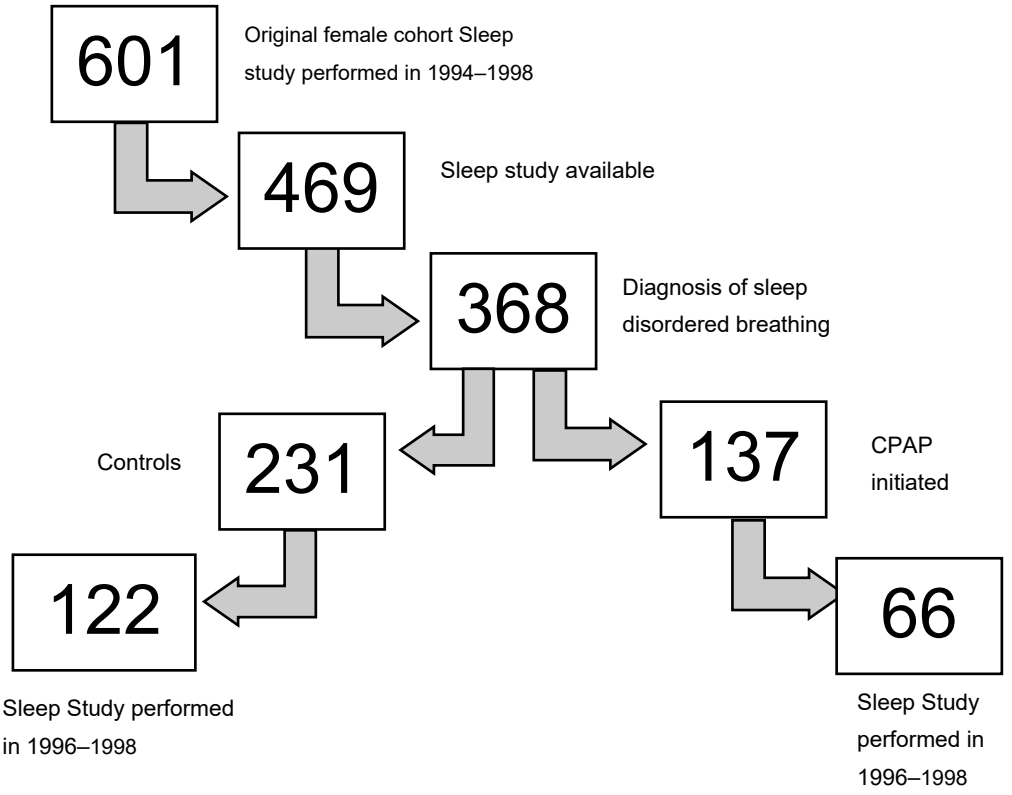

Figure 9. Flow chart of patient selection in study III. Modified from Original Publication III.

4.2 Methods

In Studies I and II, during the baseline study at the ward, patients filled in questionnaires in the evening, after a standardised hospital meal. During the night, they underwent an overnight PG, and in the morning their blood was drawn after an overnight fast. In addition, their height and weight were measured by a nurse, and the BMI calculated. Questionnaires, blood samples, and measurements of BMI were repeated after three years, but the PG was not repeated. In addition, some patients had their waist and hip circumference measured in order to evaluate visceral fat.

4.2.1 The sleep study

4.2.1.1 Cardiorespiratory polygraphy (Studies I and II)

All patients who participated in Studies I and II, underwent an overnight in-hospital cardiorespiratory polygraphy in the pulmonary clinic (Embla®, Medcare Flaga hf, Medical Devices, Reykjavik, Iceland). In the PG, measurements of electrocardiography, sleeping position, inspiratory flow pressure with nasal prongs, abdominal and thoracic movements, and periodic leg movements were recorded. Respiratory flow was measured with the help of a differential pressure sensor, connected to the nasal prongs, to detect alterations in nasal pressure. Respiratory movements were measured with abdominal and thoracic belts with strain gauges. Periodic leg movements were measured using electromyographic sensors connected to the m. tibialis anterior, in both legs. In addition, transcutaneous carbon dioxide partial pressure was measured ($PTcCO_2$; TCM3, Radiometer A/S, Copenhagen, Denmark).

$PTcCO_2$ is based on measuring the diffusion of carbon dioxide through tissues and skin with the help of a heated electrode. Arterial oxyhaemoglobin saturation (SaO_2) was measured via a finger probe pulse oximeter (Oximeter Embla A10 XN, Embla, Denver, Colorado USA) to determine the episodes of arterial oxyhaemoglobin desaturation of 4% units or more per hour (oxygen desaturation index, ODI_4). Desaturations were automatically determined from a recording using Somnologica software.

An experienced scorer removed all possible artefacts and visually determined hypopnoeas and apnoeas from the recording. Apnoea-hypopnoea index (AHI) was calculated using internationally accepted criteria; the number of events expressed per hour. Electroencephalogram was not available; therefore, respiratory effort related arousals (RERA) were not scored. All the patients had symptoms that suggested OSAS, but the diagnosis of obstructive sleep apnoea was only made if the AHI was ≥5 per hour. CPAP therapy was introduced to those patients whose AHI was over 15

per hour. However, if a patient suffered from severe symptoms, CPAP therapy was also commenced with an AHI of 5-15 per hour.

4.2.1.2 Static-Charge-Sensitive bed (Study III)

All patients who were included in Study III underwent an overnight in-hospital study with a static-charge-sensitive bed (SCSB, Bio-Matt® Biorec, Turku, Finland) and simultaneous oximetry recordings (BCI-oximeter ECG-monitor, Model 3101, CAT 3101A, Waukesha, Wisconsin, USA) at baseline. This method was the most common to diagnose SDB until the millennium. SCSB is a monitoring device, that can be used underneath a regular foam mattress without any electrodes or probes being attached to the patient (Alihanka et al. 1981; Polo 1992). It has a motion sensor that monitors movements in bed via static charge layers that move with the body's movements, resulting in a potential difference and sensor charge modification. The potentials are filtered, amplified, and recorded, and then categorised according to their frequencies of three movement types: gross body movements, respiratory movements, and heartbeats. The set-up of SCSB can be seen in Figure 10.

The SCSB recordings were analysed visually by two independent scorers to detect increased respiratory resistance (IRR), which is an indicator of prolonged partial upper airway obstruction or four types of periodic breathing patterns: P1, OP-1, OP-2 or OP-3. The P-1 and OP-1 patterns reflect periodic breathing with moderate or high respiratory effort, while OP-2 and OP-3 reflect the episodes of hypopnoea and obstructive sleep apnoea (Anttalainen et al. 2016; Polo 1992). In our study, scoring was performed according to rules valid at that time. However, afterwards there has been discussion about the right classification of these breathing patterns (Tenhunen et al. 2013). In order to determine their severity, these patterns were quantified in three-minute epochs, and their frequency was expressed as a percentage of total time in bed (TIB). If the frequency was >5 % of TIB, it was considered as clinically significant.

In addition, SaO_2 was measured during the SCSB study. A recording was made with a finger probe and analysed using UniPlot software (Unesta Oy, Turku, Finland). This software reports the minimum, maximum, and median SaO_2. In addition, it reports ODI_4.

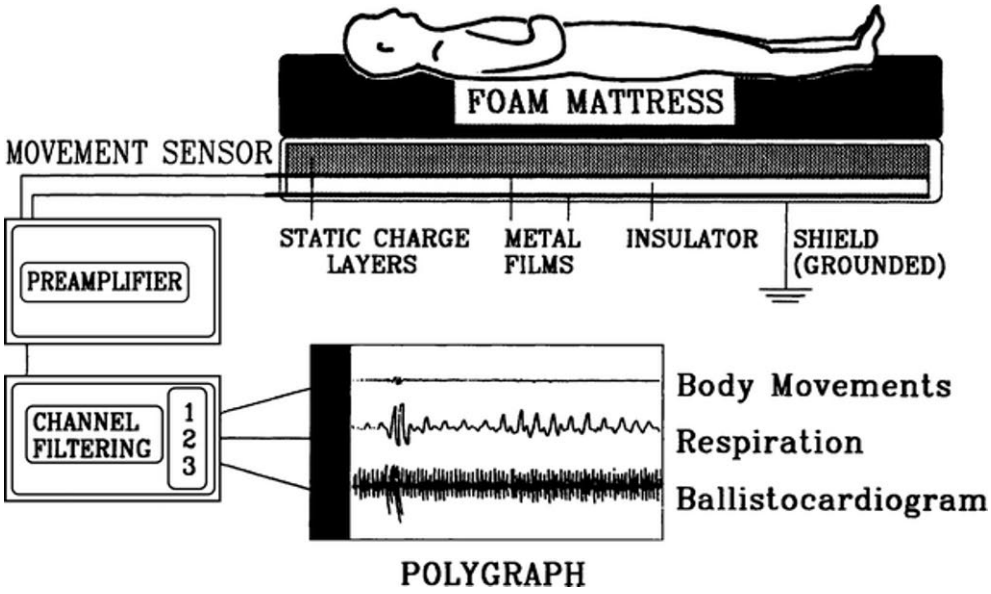

Figure 10. Static-charge-sensitive bed (SCSB) (Anttalainen et al. 2007). Reprinted with the permission of Springer Nature.

4.2.2 Questionnaires (Study I)

In the evening, following a standardised hospital meal, the participants completed a battery of questionnaires. The same questionnaires were repeated after three years in a follow-up visit. At the baseline, there were missing values for ESS (Johns 1991) in 6 patients (2.7 %), DEPS (Salokangas et al. 1995) in 7 patients (3.1 %), PSQI (Buysse et al. 1989) in 4 patients (1.8 %), and appetite-VAS and hunger-VAS (Parker et al. 2004) in 27 patients (12 %). At the follow-up visit, there were no missing values in the questionnaires.

4.2.2.1 Epworth Sleepiness Scale (ESS)

Excessive daytime sleepiness was assessed using the Epworth Sleepiness Scale (ESS) (see Appendix 1). There are eight questions in this questionnaire, and all questions had a possible score from 0 to 3. Hence, the maximum possible score is 24. Higher points indicate a more severe tendency to doze off, and a total score >10 suggests EDS. The answers are based on feelings during the two weeks before filling out the questionnaire.

4.2.2.2 Depression scale (DEPS)

Depressive symptoms were evaluated using the depression scale (DEPS) (Appendix 2). The maximum score of this questionnaire is 30 points, and more points indicate more depressive symptoms. There are 10 questions; the score for each question is 0-3. A score higher than nine indicates possible depression. The answers need to refer to the period of one month prior to filling out the questionnaire.

4.2.2.3 Pittsburgh Sleep Quality Index, (PSQI)

Insomnia symptoms and sleep quality were evaluated using the Pittsburgh Sleep Quality Index (PSQI) (Appendix 3). It is a validated method used to screen sleep disorders and quality of sleep. It has 19 questions divided into seven components. These components include subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. The total score for the questionnaire is the sum of each component score. Overall score range is 0 to 21, and more points indicate a worse quality of sleep. The questionnaire only evaluates the one-month period before a person is completing the questionnaire.

4.2.2.4 State-Trait Anxiety Inventory, (STAI)

Anxiety was screened with the help of the State-Trait Anxiety Inventory (STAI) (Spielberger et al. 1983) (Appendix 4). It has 40 questions in two groups, that evaluate separately two different kinds of anxiety, i.e., state (STAI-S) and trait (STAI-T). State anxiety measures anxiety related to an event, and trait measures anxiety as a personal characteristic. In this study, STAI-S was used. The score on STAI-S is based on the feeling at the moment one is filling out the questionnaire, and higher scores indicate greater feeling of anxiety. Usually, scores under 38 are considered “no anxiety”, scores of 38-44 are considered as “moderate anxiety” and scores over 44 are considered “high anxiety”. The maximum score on the STAI is 80 points. The scoring is different for all questions and the 4-point scale is created from answers labelled as 1) not at all, 2) somewhat, 3) moderately so, and 4) very much so. The final score on the questionnaire is the sum of all these separate scores.

4.2.2.5 Visual analogue scales

Visual analogue scales (VAS) (Appendix 5) were used to assess the participants’ hunger, thirst, appetite, food quantities, and nausea. In addition, VAS scales were used to evaluate the cravings for different food categories, which included sweet, salty, starch, fruit, vegetables, meat/fish/egg, and dairy. Participants chose a score

based on their feeling at the moment when completing the VAS scale, and a higher score indicated stronger cravings. The results of the VAS scales were reported as millimetres (score 0-100 mm).

4.2.2.6 Exercise habits and duration

Exercise habits were asked on the questionnaires with the question “How often do you exercise on average?” The answer alternatives were 1) not at all, 2) less frequently than once a week, 3) once a week, 4) twice a week, 5) three times a week, 6) four times a week, or 7) five times a week. Exercise duration was then evaluated with the question: “How long is your exercise duration?” Alternatives were 1) 0-20 minutes, 2) 20-40 minutes, 3) 40-60 minutes and 4) over 60 minutes. The final score was the number that reflected the most accurate alternative. These variables were treated as separate questions in the analysis (Appendix 6).

4.2.2.7 Medication, smoking, and alcohol consumption

Medication use by the participants was also asked on the questionnaire, and the patients provided commercial names and daily doses of medications that they used. Medications were then manually categorised by the Anatomic Therapeutic Chemical Classification (ATC) system, a drug classification system developed by the World Health Organization Collaborating Centre for Drug Statistics Methodology in Norway. In ATC, medicines are divided into groups according to the organ or system on which they act and their therapeutic, pharmacological and chemical properties (Chen et al. 2012).

Smoking was asked with the question: “Have you ever smoked 6 months or more during your life?". Choices were 1) yes or 2) no and the patients were categorised as smokers or non-smokers based on answer to this question. Alcohol consumption was categorised as 1) not at all 2) 1-6 alcohol doses per week, 3) 7-14 alcohol doses per week or 4) 15-24 alcohol doses per week. A single dose was defined as one beer (0.33 l) or 12 cl of wine or 4 cl of strong alcohol (alcohol percentage >35 %). The final score was the number, that reflected the person’s consumption most accurately (Appendix 6).

4.2.3 Blood samples (Study II)

Venous blood was drawn in the morning, after an overnight fast, to measure leptin and IGF-1 concentrations. All blood samples were stored in ice and centrifuged immediately, and then kept frozen at -70 ◦C until analysed. Leptin was assayed using the ELISA method and IGF-1 with immunoluminometric assay (DRG Instruments

GmbH®, Marburg, Germany). The reference ranges for leptin concentrations were 7.36 ± 3.73 ng/ml for women and 3.84 ± 1.79 ng/ml for men. The inter-assay coefficient of variation was 11.55 % and the control sample level 1.0 ng/ml. Reference ranges for the IGF-1 concentrations are presented in Table 5. Both baseline and follow-up leptin and IGF-1 concentrations were available from 114 patients, and 49 of these (43.0%; 29 men, 20 women) were categorised as CPAP users, and 60 as non-users (52.6%; 33 men, 27 women) as presented in Figure 8. For five of these patients, information on CPAP use was not found (4.4%; 3 men, 2 women). The data for the average hours of CPAP use were derived from 48 patients (29 men, 19 women).

Table 5. Reference range values for IGF-1 concentrations.

Age (years)	Reference range (nmol/l)
21–30	27–107
31–50	14–36
51–70	6–27
>70	8–23

4.2.4 Medication data (Study III)

To investigate the effect of CPAP therapy on medicine use, the data for medication use as daily defined doses (DDD) were collected from the National Social Insurance Institution. It maintains the reimbursement registry in Finland, for the medicines prescribed for chronic illnesses. All Finnish citizens are entitled to reimbursements if they meet the requirements, which are stricter than criteria needed for a diagnosis. Patients need a separate application and a statement from the doctor for this reimbursement. The registry has been available from year 1993 forward. In the database, medicines are categorised according to diagnosis. The data were collected on the following nine disease categories: Diabetes (both Type 1 and Type 2), hypothyroidism, severe psychosis and other severe psychiatric diseases, chronic heart failure, connective tissue diseases, chronic obstructive pulmonary disease (COPD) and asthma, hypertension, arteriosclerosis, and cardiac arrhythmias.

To compare the medicine use of participants to the medicine use of the entire Finnish female population from years 1993 to 2001 and medication data on the same disease categories as described above, were derived from the National Social Insurance Institution for women.

The DDD of medications for each above-mentioned category were collected for each patient. Medication data were retrieved three years prior and three years after the CPAP therapy was commenced or the sleep study was performed. Medication

data were available for 323 participants. Since the medication data from the National Social Insurance Institution was available from 1993–2001, only patients who had their sleep recordings gathered between 1996 and 1998 were included. Thus, the final study population included 182 patients (66 CPAP users and 116 controls) as presented in Figure 9.

4.2.5 Comorbidity (Study III)

Overall comorbidity before CPAP therapy initiation was evaluated using the data for the same categories as previously mentioned. These data were collected one year before the CPAP therapy was commenced. If the patient had purchased medicines that were included in one of the categories at least once, that patient was considered to have the specific disease. The patients were then categorised into having one, two or three comorbidities. There were no patients with more than three comorbidities. CPAP users and controls were evaluated separately.

4.2.6 Statistical Analyses

4.2.6.1 Study I

In the first study, which screened the data on questionnaires and weight, the data are presented as median with range. The associations, except for regression analysis, between the variables were analysed using SAS (Statistical software package for Windows 9.2). Correlations between the variables were evaluated with Spearman's rank correlation coefficients because of the distribution of the data. The differences between CPAP-users and non-users were evaluated with the Wilcoxon Two-Sample Test, where a p-value less than 0.05 was considered statistically significant. All the variables that differed between the CPAP users and non-users, were included in the further regression analysis for finding factors influencing on the change in BMI. Analysis of variance (ANOVA) was used to test with-in or between group variation and an ordinary least squares linear regression model was fitted. Results were presented as standardized beta estimates and 95 % confidence intervals (CI) and a p-value ≤ 0.05 was considered statistically significant. The analyses were performed separately for males and females and for both regarding CPAP use. Regression analysis were performed with IBM SPSS version 25 (IBM Corp. Released 2017.IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY:IBM Corp.)

4.2.6.2 Study II

In the second study, which evaluated the effect of CPAP therapy on leptin and IGF-concentrations, the data are presented as a median with an interquartile range or as a mean with a range. The limit of quantitation was 1.00 ng/ml in leptin, and 3.25 nmol/l in IGF-1. Therefore, leptin concentrations <1.00 ng/ml were imputed with 0.50 ng/ml, and IGF-1<3.25 ng/ml with the value of 1.63 ng/ml.

Statistical analyses were performed using IBM SPSS version 23 (IBM Corp. Released in 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp). To study the effect of covariates on a three-year change in leptin concentrations, an ordinary least squares linear regression model was fitted, separately for both genders. Conditional inference trees were used to find and visualise statistically significant interactions between the categorical covariates. Bipartite correlations between the variables were studied using Spearman's rank correlation coefficients. To compare the groups, Mann–Whitney U test was used for the continuous variables and a chi-squared test was used for the categorical variables. P-values less than 0.05 were considered to be statistically significant.

4.2.6.3 Study III

In Study III, differences between the CPAP users and controls were compared in age, BMI, and neck circumference by using the two-sample T-test. Chi-squared test was used to test the differences in smoking and the proportions of SDB patterns. Wilcoxon Signed Rank test was performed to evaluate changes in DDD of medications within CPAP and control groups, and the differences in the changes between groups with Mann-Whitney U-test. In addition, the comorbidities were evaluated with Mann-Whitney U-test. The correlations between the medication use and BMI were evaluated with Spearman´s rank correlation coefficient. Level of significance was set at <0.05. Statistical analyses were performed using the SAS 9.4 System for Windows (SAS Institute Inc., Cary, NC) and the data were expressed as mean ± standard deviation.

4.3 Designs of the studies

Studies I and II were prospective observational follow-up studies in a clinical population of suspected SDB that were referred to Turku University Hospital, Department of Pulmonary Diseases. Study III was a retrospective registry study, that used clinical cohort of 601 consecutive females with suspected SDB derived from the database for the Department of Pulmonary Diseases at Turku University Hospital.

4.4 Ethical aspects

In Studies I and II, the study protocol was approved by the Ethics Committee of the Hospital District of Southwest Finland, in Turku, Finland. All patients gave their written informed consent. In Study III, the study protocol was approved by the Joint Commission on Ethics of Turku University and Turku University Hospital, and the National Agency for Medicines. The study was a registry study, and all aspects of the registry were conducted according to the principles of Good Clinical Practice and in accordance with the Declaration of Helsinki.

5 RESULTS

5.1 Effects of CPAP

5.1.1 Weight

Change of weight was evaluated with the help of BMI. In all three studies, CPAP users had more obesity at the baseline compared to the controls (Table 6). The change in BMI during follow-up did not differ in Study I or Study II between CPAP users and the controls. In Study III, a change in BMI did not differ between the groups, and it had no effect on the medicine use.

Table 6. BMI (kg/m^2) in all study populations at baseline.

		CPAP users		**Controls**		**p-value**
	Females n, %	Median	Range	Median	Range	
Study I	122 (54.7)	34.7	23.3–56.5	28.2.	21.5–55.2	*<0.001*
Study II	49 (43)	33.7.	30.1–37.1	28.3	26.2–33.7	*<0.001*
Study III	188 (100)	36.5	34.5–38.5	31.4	30.1–32.7	*<0.001*

In addition, a waist hip ratio (WHR) was available from 41 patients (25 females and 16 men). At baseline, WHR did not differ between CPAP users and non-users when gender was considered. At follow-up, female CPAP users had higher WHR than non-users and male CPAP users had lower WHR than non-users. In both genders, the change in WHR did not differ between CPAP users and non-users (Table 7).

Table 7. Waist hip ratios of the patients and their differences.

	Female					**Male**				
	CPAP (n=10)		Controls (n=15)			CPAP (n=7)		Controls (n=9)		
	Mean	SD	Mean	SD	p-value	Mean	SD	Mean	SD	p-value
Baseline	1.0	0.06	0.97	0.060	0.181	0.89	0.086	0.90	0.047	0.632
Follow-up	0.97	0.088	0.92	0.077	*0.016*	0.99	0.066	1.17	1.416	*0.013*
Change	0.02	0.089	-0.05	0.090	0.065	0.10	0.100	0.04	0.084	0.172

In Study I, weight gain in the CPAP group was not associated with baseline severity of OSAS, depressive symptoms, sleep quality, anxiety, exercise habits or duration, or a craving for distinct food categories or food quantity. However, gaining weight was associated with a feeling of satiety after a full meal (*r= 0.36, p=0.010*) (Table 8) at the baseline for patients using CPAP. Moreover, weight gain was associated with a higher use of CPAP (*r=0.28 p=0.015*) and a craving for less sweets (*r= -0.34, p=0.011*) at the three-year follow-up. In addition, in Study II, weight gain was associated with higher compliance with CPAP use (*r= 0.29, p=0.046*), but not when males (*r=0.14, p= 0.464*) and females (*r=0.31, p=0.194)* were evaluated separately.

Table 8. Correlations between the baseline variables and change in BMI in study I.

	CPAP users n=76		**Non-users n=73**	
	r	p-value	r	p-value
AHI (#/h)	−0.133	0.353	−0.210	0.080
ODI_4 (#/h)	−0.017	0.904	−0.056	0.646
DEPS (0–30)	0.149	0.281	0.191	0.119
ESS (0–20)	−0.005	0.970	−0.160	0.192
PSQI (0–21)	−0.078	0.572	0.110	0.356
Fruit VAS (0–100)	−0.040	0.788	0.128	0.317
Protein VAS (0–100)	0.005	0.976	0.041	0.750
Dairy products VAS (0–100)	−0.038	0.797	−0.035	0.786
Salty VAS (0–100)	−0.203	0.161	0.080	0.534
Sweet VAS (0–100)	−0.202	0.174	0.006	0.961
High carbohydrate products VAS (0–100)	−0.208	0.156	0.048	0.706
Vegetables VAS (0–100)	−0.065	0.662	−0.058	0.656
Thirst VAS (0–100)	0.070	0.627	0.232	0.062
Satiety VAS (0–100)	0.359	*0.010*	−0.014	0.910
Hunger VAS (0–100)	−0.069	0.632	0.056	0.660
Nausea VAS (0–100)	0.115	0.427	−0.223	0.075
Appetite VAS (0–100)	−0.057	0.692	0.028	0.825
Food quantity VAS (0–100)	−0.107	0.458	0.137	0.278
Exercise habits (0–7)	0.176	0.203	0.020	0.872
Exercise duration (0–7)	−0.157	0.266	0.139	0.259

Values are presented as median (range). BMI body mass index (kg/m^2), AHI apnoea-hypopnoea index (events per hour), ODI_4 Oxygen desaturation index with the desaturation of 4% or more, DEPS depression scale (score), ESS Epworth sleepiness scale (score), PSQI Pittsburgh Sleep Quality Index (score), VAS visual analogue scale (millimetres).

In the regression analysis, there were no other predictors of weight gain than the sufficient use of CPAP, a higher baseline BMI, or higher depressive symptoms at the baseline. When CPAP users and non-users were analysed separately, the baseline BMI remained a predictor of weight gain in all groups, whereas baseline DEPS remained a predictor in all but those men who were using CPAP and those women who were not using CPAP (Table 9).

Table 9. Regression analysis of factors influencing weight gain during three years of follow-up

	Baseline BMI (kg/m^2)			**Baseline DEPS**		
	β	CI 95 %	p-value	β	CI 95 %	p-value
All	0.84	0.71–0.98	*<.001*	0.167	0.03–0.33	*0.017*
CPAP-users (n=76)	0.83	0.69–0.99	*<.001*	0.20	0.05–0.38	*0.01*
Male (n= 32)	0.94	0.55–0.92	*<.001*	0.11	– 0.16–0.38	0.40
Female (n=44)	0.94	0.77–1.3	*<.001*	0.26	0.07–0.47	*0.01*
Non-users (n=73)	0.90	0.77–0.95	*<.001*	0.16	0.04–0.28	0.09
Male (n=33)	0.88	0.65–0.95	*<.001*	0.30	0.08–0.53	*0.01*
Female (n=40)	0.98	0.88–1.1	*<.001*	0.05	-0.1–0.1	0.93

5.1.2 Mood

CPAP users had more depressive symptoms at baseline than the controls did (*p=0.011*), and their symptoms were alleviated more during the follow-up period, than for the controls (-3 vs. 0 points, *p=0.002*) (Figure 11).

Anxiety symptoms did not differ between the study groups at the baseline (35 in the CPAP group vs. 32.5 points in the controls, *p= 0.054*), but at the follow-up, these symptoms had alleviated more in the CPAP group (-3 points in the CPAP group vs. only by 1 in the controls, *p<0.001*.) (Figure 11).

Sleepiness did not differ between the groups at baseline (10 points for the CPAP users and 9 for the controls, *p=0.572*), but sleepiness was alleviated more in the CPAP group during the follow-up time (-3.5 points vs. -2 points, *p=0.031*) (Figure 12).

Sleep quality was the same at the baseline among the CPAP users and the controls (7 points vs. 6 points, *p=0.06*), but during the follow-up time, sleep quality improved more in the CPAP group (-1 points vs. 0 points, *p<0.001)* (Figure 12).

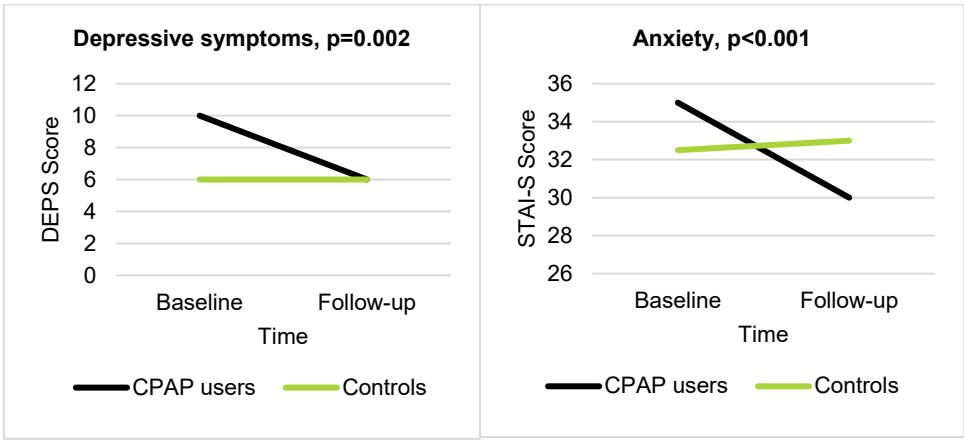

Figure 11. Change in DEPS (depressive symptoms) and STAI-S (state anxiety) scores. Higher scores in DEPS indicate higher amount of depressive symptoms and higher score in STAI-S indicate more anxiety.

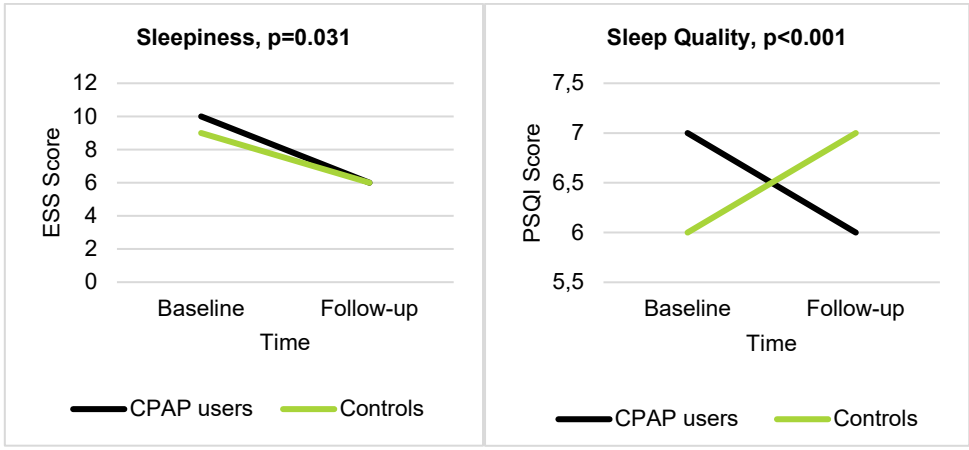

Figure 12. Change in ESS (sleepiness) and PSQI (sleep quality) score. In ESS, higher score indicates higher tendency of falling asleep. In PSQI, higher score indicates worse sleep quality.

5.1.3 Lifestyle

Exercise habits (*p=0.412*) or duration of exercise (*p=0.712*) did not differ between CPAP users and non-users at the baseline. At follow-up, neither absolute numbers, nor a change in the number of exercise sessions per week differed (*p=0.230* for change in scores in exercise habits and *p=0.484* in exercise duration).

Cravings for different food categories, satiety, hunger, and food quantity did not differ between the groups at baseline. However, the feeling of thirst was higher in CPAP users. At the follow-up, the control's thirst increased, whereas CPAP group thirst did not change as shown in Table 10.

Table 10. Lifestyle during the study and differences between the groups.

	Baseline					**Follow-up**					**Change**				
	CPAP users		Non-users			CPAP users		Non-users			CPAP users		Non-users		
	Median	**Range**	**Median**	**Range**	**p-value**	**Median**	**Range**	**Median**	**Range**	**p-value**	**Median**	**Range**	**Median**	**Range**	**p-value**
Fruit VAS (0–100)	77	0–100	81.5	1–100	0.783	80	14–100	78	0–100	0.422	1.5	47–88	0	-95–57	0.255
Protein VAS (0–100)	77	0–100	67.5	0–100	0.420	81	8–100	81	0–100	0.260	–9	-85–40	-1	-59–96	0.077
Dairy products VAS (0–100)	68	0–100	60	1–100	0.783	75	3–100	76	0–100	0.812	8	-79–90	0	-78–93	0.312
Salty VAS (0–100)	26.5	0–100	23	0–100	0.286	18	0–100	32	0–98	0.195	–3	-92–63	0	-85–88	0.063
Sweet VAS (0–100)	40	0–100	53	0–100	0.286	37	0–100	50	0–100	0.281	–1	-72–98	0	-96–82	0.910
High–carbohydrate products VAS (0–100)	57	0–100	23	0–100	0.906	70	1–100	73	0–100	0.734	1	-66–99	-3.5	-128–101	0.137
Vegetables VAS (0–100)	62	0–100	68	0–100	0.683	76	0–100	79	0–100	0.930	9	-21–94	1	-43–89	0.090
Thirst VAS (0–100)	25	0–100	15	0–97	*0.032*	32	0–100	25	0–100	0.774	0	-98–91	7.5	-65–100	*0.026*
Satiety VAS (0–100)	73	0–100	77.5	10–100	0.082	33	0–100	26	0–100	0.622	–38	-100–97	-41.5	-100–33	0.280
Hunger VAS (0–100)	6	0–100	4	0–72	0.304	15	0–100	26	0–100	0.392	3	-72–99	8.5	-41–100	0.112
Nausea VAS (0–100)	5	0–73	5	0–65	0.812	5	0–97	5	0–66	0.590	-1	-71–89	0	-45–64	0.112
Appetite VAS (0–100)	8	0–100	7	0–69	0.310	24	0–100	23	0–99	0.538	5.5	-56–99	10	-59–98	0.387

	Baseline					Follow-up					Change				
	CPAP users		Non-users			CPAP users		Non-users			CPAP users		Non-users		
	Median	**Range**	**Median**	**Range**	**p-value**	**Median**	**Range**	**Median**	**Range**	**p-value**	**Median**	**Range**	**Median**	**Range**	**p-value**
Food quantity (VAS 0–100)	13.5	0–99	10	0–100	0.422	27	0–90	29	0–98	0.147	4	-11–68	13	-71–95	0.154
Exercise habits (0–7)	4	1–7	4	1–7	0.412	4	1–7	5	1–7	0.557	0	-5–3	0	-3–4	0.230
Exercise duration (0–7)	3	1–4	2	1–4	0.712	2	1–4	3	1–4	0.273	0	-3–2	0	-2–2	0.484

VAS visual analogue scale (millimetres).

5.2 Leptin and IGF-1 concentrations

Leptin concentrations did not differ at baseline between CPAP users and non-users (17.25 ng/ml vs. 16.7 ng/ml, *p=0.870*). However, there was a difference in absolute leptin concentrations at the follow-up (26.95 ng/ml vs. 8.60 ng/ml, *p=0.002*) as well as change in leptin concentrations (9.13 ng/ml vs. -5.86 ng/ml, *p=0.007*), regardless of age or BMI. When the change in BMI was also considered, CPAP use was still a significant factor for change in the leptin concentrations. An increase in BMI by 1 kg/m^2 was associated with an increase of 2.1 ng/ml (p=0.047, 95% CI 0.03 to 4.2), and CPAP use was associated with an increase of 13.0 ng/ml (p=0.017, 95% CI 2.4 to 23.6) in leptin concentrations (Figure 13).

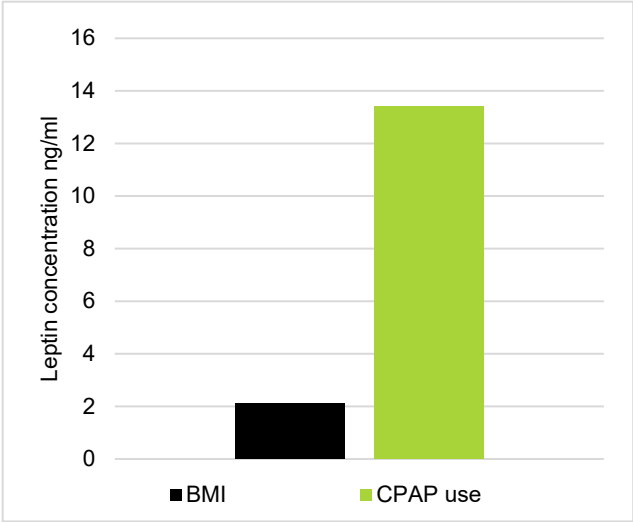

Figure 13. Effect of CPAP and BMI in leptin concentrations. When BMI increased by 1 kg/m^2, leptin concentrations increased by 2.1 ng/ml. Using CPAP increased leptin concentrations by 13.0 ng/ml

Surprisingly, when WHR was considered, in female CPAP users, when WHR elevated, their leptin concentrations decreased. However, this analysis must be interpreted with caution due to small subgroups (Table 11). The subgroups did not have sufficient statistical power for further analysis.

Table 11. Correlations between the change in leptin concentrations and change in waist hip ratio.

	r	p-value
Female (n=25)		
CPAP users	-0.60	0.07
Non-users	-0.05	0.85
Male (n=16)		
CPAP users	0.57	0.18
Non-users	-0.43	0.24

Baseline IGF-1 concentrations did not differ between CPAP users and the controls (13.6 nmol/l vs.11.8 nmol/l, *p=0.594*), nor did it differ at follow-up (15.6 nmol/l vs.15.7 nmol/l, *p=0.933*), or change during the follow-up period (2.6 nmol/l vs. 3.2 nmol/l, p=*0.775*).

In addition, fasting blood glucose and thyroid stimulating hormone (TSH) was measured, but these were not included in this analysis. There were 27 patients who had diagnosed diabetes, and 21 patients had diagnosis for hypothyroidism.

5.2.1 Effect of gender on leptin concentrations

When men and women were assessed separately, there were no differences at baseline (median male 12.4 ng/ml vs. median female 18.0 ng/ml, *p=0.578*) in the leptin concentrations. However, at the follow-up, women had higher leptin concentrations than did the men (median 32.4 ng/ml vs. median 7.*2* ng/ml *p<0.001*). In women, the median change in leptin concentration among the CPAP users was 25.97 ng/ml, and was 4.97 ng/ml among the non-users (*p=0.010*), whereas in men, the change did not differ between the CPAP users and non-users (-0.94 ng/ml vs. -8.88 ng/ml*; p=0.087*) (Figure 14).

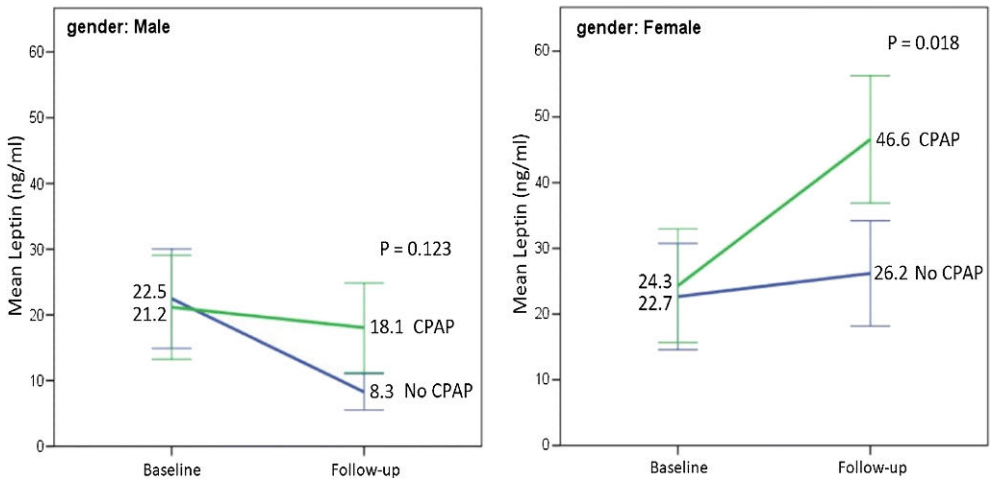

Figure 14. Leptin concentrations at baseline and at follow-up and differences between the genders according to CPAP use. Reprinted from original article II, with permission of Sleep and Breathing.

5.3 Medication use in females

There was no difference at the baseline between the female groups in terms of age, neck circumference, or smoking. The CPAP group had a greater BMI and more

illnesses than the controls did (Figure 15). Both groups had the same proportion of patients with prolonged partial upper airway obstruction and the classic form of sleep apnoea. At baseline, overall medication use was higher in the CPAP users than it was in the controls *(p= 0.036*).

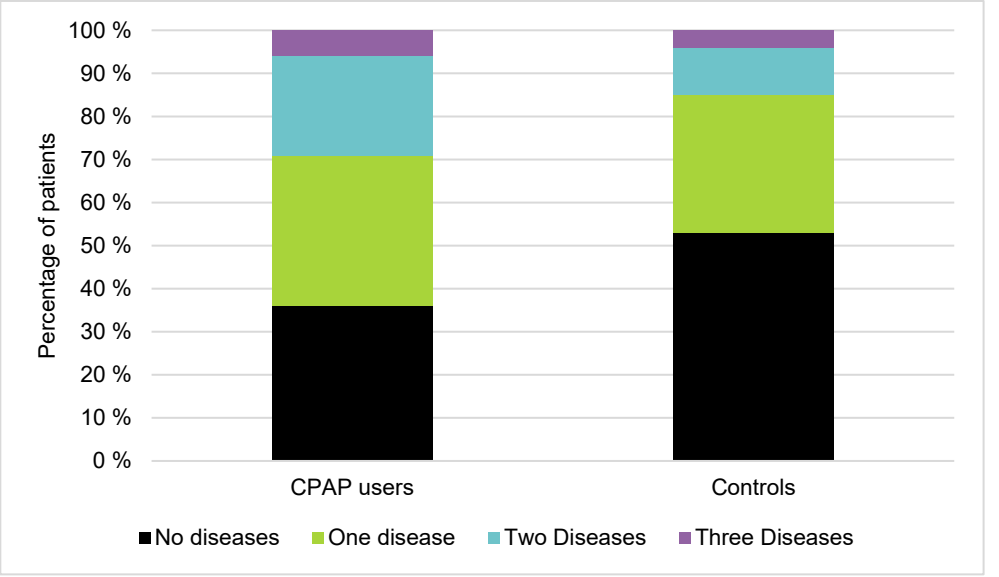

Figure 15. The number of comorbidities at baseline and the differences between the female CPAP users and controls (p= 0.017).

During the three years after CPAP initiation (CPAP users) or a diagnostic sleep study (the control group), the change in medication use did not differ (*p=0.054*). However, at the three-year follow-up point, the medication use was higher in CPAP users than in the controls (*p<0.001*). There was no difference in medicine use either in baseline, or in follow-up, or change in use when the type of SDB (prolonged upper airway obstruction or classic form of sleep apnoea) was considered (*p=0.582*). Medicine use for COPD and asthma increased during the three-year follow-up in both groups, but the rise was higher in the CPAP group (mean 203.71 vs. 113.14; *p=0.048*). The use of medicine for severe mental illnesses, such as psychosis, increased slightly in the CPAP group, whereas in the control group the use decreased (25.9 vs -23.41; *p=0.046*). There was no significant change in medication use either for diabetes, hypothyroidism, chronic heart failure, connective tissue diseases, hypertension, arteriosclerosis, or cardiac arrhythmias (Figure 16).

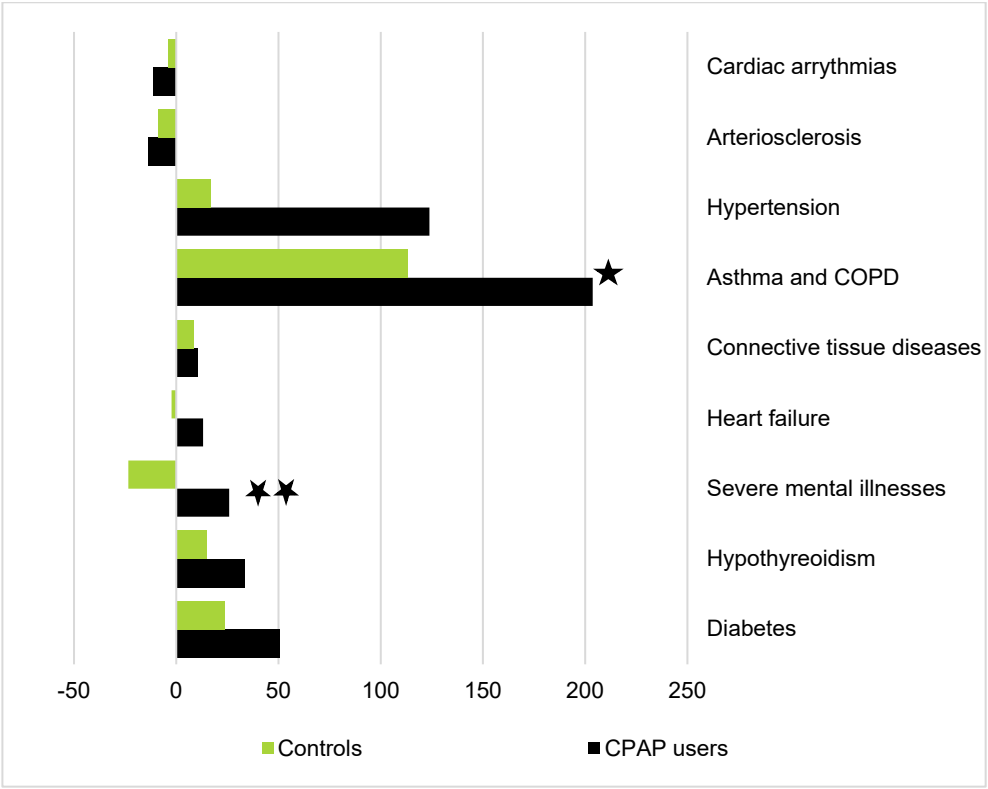

Figure 16. Change in medication use presented as defined daily dose (DDD) values, and the differences between females using CPAP and control group *p=0.048, **p=0.046. Modified from the original publication III.

In CPAP users, only the medication use for asthma and COPD increased (Table 12), and a similar increase was also found in the entire population of Finnish females. The increase in medicine use among the CPAP users in all other categories, except for the decrease in arteriosclerosis and cardiac arrhythmias demonstrated a similar trend compared to the entire Finnish female population, although it did not reach statistical significance. In the Finnish female population, between years 1993 and 2001, medication use increased in all categories. The controls demonstrated a decreasing, but still statistically non-significant, trend in medication for severe mental illnesses, chronic heart failure, arteriosclerosis, and cardiac arrhythmias.

Table 12. Use of medication in defined daily dose (DDD) in female CPAP users reprinted from original publication III with permission from Respiratory Medicine.

CPAP group (n=66)

	Before		**Follow-up**		**Change**		**p-value**
	Mean	SD	Mean	SD	Mean	SD	
Diabetes	53.5	296.7	104.2	403.9	50.7	263.8	0.188
Hypothyroidism	56.6	216	89.9	306.4	33.3	211.5	0.313
Severe mental illnesses	13.4	98.1	39.3	300.9	25.9	203.0	0.5
Heart failure	25.1	204.1	38.3	219.4	13.1	94.0	0.5
Connective tissue diseases	10.5	83.6	21.2	171.9	10.7	88.4	1
Asthma and COPD	361.6	1090.3	565.3	1061.6	203.7	614.8	*0.002*
Hypertension	751.7	1129.9	875.5	1327.5	123.8	753.4	0.111
Arteriosclerosis	76.8	347.5	63.1	272.8	-13.7	81.4	0.313

6 DISCUSSION

In recent years, the research into sleep apnoea has turned toward phenotyping patients and finding "treatable traits", such as we find in asthma. As the understanding has grown, the need for more precise research and study protocols has been needed. Phenotyping this large sector of people needs more dynamic and innovative studies and large amounts of research data in order to reveal the true phenotypes of SDB. Not all future phenotypes of SDB are candidates for solely CPAP therapy; therefore, the knowledge of the effects of long-term CPAP therapy is welcomed. This current study has concentrated on the effects of long-term CPAP therapy in order to screen those factors that influence the outcomes of SDB treatment. Women were of special interest, as most of the previous studies have consisted of mainly men.

This study can be divided into two different parts. The first part concentrates on the effect of CPAP therapy on SDB symptoms, weight, and factors that influence weight during therapy. The second part concentrates on female comorbidities, medication use, and the effect of SDB type on both. All of these efforts, however, are targeting the same goal, namely, to determine the benefits and non-benefits of long-term CPAP therapy in order to help in evaluation of the right patients who will benefit the most from CPAP therapy.

6.1 Weight

In 1981, when Dr Sullivan and his co-workers invented the CPAP machine (Sullivan et al. 1981), the assumption was that treating SDB would lead to weight reduction, and that outcome was thought to be true until the late 1990's (Loube et al. 1997). Since then, the knowledge has increased and today the consensus is that unfortunately CPAP therapy does not lead to weight reduction (Drager et al. 2015; Myllylä et al. 2016; Ou et al. 2019). The mechanisms behind this are probably multifactorial, including the toning down of sympathetic overdrive, the reduction of energy expenditure, and changes in hormonal secretion (Drager et al. 2015).

In Studies I and II, weight gain among patients was associated with a higher compliance with CPAP, and more depressive symptoms and higher BMI at the beginning of the study. The association between CPAP use and weight gain could

be explained by the factors noted previously, such as toning down of sympathetic overdrive, and it is in line with the previous studies (Drager et al. 2015). In the regression analysis, when users and non-users were analysed separately, the results of having more depressive symptoms at the baseline, and higher baseline BMI influencing weight gain, remained constant among the CPAP users. More depressive symptoms at the beginning can be associated with the fact, that these patients could have had a habit of alleviating their psychological stress with eating, and that habit remained, even when the SDB was treated. Moreover, patients with more depressive symptoms could have had a clinical depression revealed behind the depressive symptoms that related to SDB, and during the three-year follow-up, the antidepressant medication was initiated, often associated with weight gain.

The increase in the use of antidepressant medication has been suggested as being one contributor to the rising number of people with obesity. However, in our study population we could only evaluate the amount of medications used for severe psychiatric disorders, which excluded milder depression, and therefore we could not evaluate this aspect sufficiently enough (Gafoor et al. 2018). Baseline BMI being higher at the beginning can simply imply that these patients ate more or ate more unhealthy food to begin with, making it more difficult for them to lose weight, as no lifestyle intervention, such as weight loss support, was included in this study. In previous studies it has been shown, that CPAP alone does not lead to positive lifestyle changes (Bamberga et al. 2015; Chirinos et al. 2014). Of note, craving less sweets at the three-year follow-up was associated with weight gain when using CPAP. This association could be due to methodological factors, as in the regression analysis the association between the craving less sweets and weight gain disappeared.

Contrary to our expectations, weight gain was not associated with craving more sweets or high-carbohydrate foods. Unfortunately, our questionnaires were introduced to patients right after having a full meal, which could explain the absence of any cravings, and the unexpected association of their craving fewer sweets. In addition, the severity of SDB was not associated with weight gain. This finding is in line with the previous studies (Myllylä et al. 2016). Moreover, weight gain in the CPAP group was not associated with exercise habits or their duration, the craving for distinct food categories, or any food quantity. As mentioned earlier, lifestyle changes in SDB patients leading to weight loss are rare if additional support is not provided.

Even though we used an extensive array of questionnaires along with cardiorespiratory polygraphy, we were unable to determine the factors or establish any markers, that predicted the weight changes in SDB patients using CPAP therapy. However, our study still reinforces the association between the CPAP therapy and weight gain if no additional support is provided.

6.2 Mood

Our study showed that in patients with SDB, depressive symptoms and anxiety were alleviated, as expected (Gupta & Simpson 2015) during CPAP therapy.

SDB and depressive disorder have a strong association, and the symptoms also overlap (Hobzova et al. 2017). It has been suggested that 35 % of patients with OSA have depressive symptoms (Garbarino et al. 2018a) and that women with OSAS have more depressive symptoms than men (Pillar & Lavie, 1998). Our Study I, which investigated the association of CPAP and mood, was gender balanced as it had 46 % women. Depressive symptoms overlapping with SDB can lead to a situation when treating SDB with CPAP can reveal underlying clinical depression. In our study, part of the depressive symptoms at the baseline could have been secondary to the untreated SDB, whereas the residual depressive symptoms could have been a sign of "true" depression.

Previous studies have offered diverse results on the effect of CPAP therapy on depressive symptoms, especially during long-term therapy (Hobzova et al. 2017). There are studies that suggest that CPAP therapy alleviates depressive symptoms (Sánchez et al. 2001) while others have had no effect (Muñoz et al. 2000). In our study population, 56.6 % of CPAP users had over 9 points in DEPS questionnaire before CPAP initiation, suggesting clinical depression. Among the non-users, 34.2 % had clinical depression according to DEPS. In the follow-up, 22.4 % of CPAP users and 35.6 % of non-users had over 9 points, indicating a reduction of depressive symptoms if CPAP was used. However, there was no significant correlation between the hours of use and DEPS score. It is unlikely that the reduction of depressive symptoms observed in our study was due to a placebo-response, as has been the case in some other studies (Yu et al. 1999), because our follow-up time was three years and the use of CPAP was controlled and was of sufficient length.

Anxiety is a common symptom in OSAS, and its prevalence is reported to be as high as 53.9 % (Rezaeitalab et al. 2014). The knowledge of the effect of CPAP therapy on anxiety remained scarce until recently, but the interest has risen as SDB has become more common and anxiety now recognized as a common symptom, especially among women. However, the results are controversial. Our results are in line with an earlier study, in which CPAP therapy alleviated anxiety particularly in women (Campos-Rodriguez et al. 2016). Yet recently, a systematic meta-analysis of 20 randomised trials estimated that CPAP had no effect on anxiety (Zheng et al. 2019). In our study, the level of anxiety was similar at the baseline among the CPAP users and the controls, but after the three-year follow-up, the scores on the anxiety questionnaire had decreased for CPAP users and increased for non-users.

The median scores in both groups did not reach the level of clinical anxiety; therefore, these scores illustrate a trend in symptoms rather than noting anxiety as a disease. Since the sleep studies were not repeated, we were not able to assess if there

were changes in SDB during the three years, and whether the worsening of symptoms was associated with SDB. Moreover, in patients with more anxiety symptoms at follow-up**,** their anxiety symptoms might initially not have been related to SDB but rather could contribute to the discontinuation of CPAP therapy. The questionnaire used to assess the effect of CPAP therapy on anxiety is a standardised tool, used to screen the corresponding disease. The STAI questionnaire has two parts, and the STAI-S questionnaire used is validated for screening especially the state anxiety, which illustrates a tendency to react to uncomfortable situation with anxiety, also the case in the anxiety associated with CPAP therapy. In studies assessing anxiety and SDB, other questionnaires have also been used, such as Hospital Anxiety and Depression Scale (HADS), which has seven questions for assessing anxiety. The STAI-S questionnaire was chosen as a more precise questionnaire, focusing only on anxiety.

6.3 Lifestyle

The most detrimental symptoms of SDB, namely, sleepiness and poor sleep quality, improved among CPAP users in our study, a result in line with previous studies. In one meta-analysis, CPAP therapy alleviated sleepiness in patients with OSA in a diverse range of populations (Patel et al. 2003). Most of the previous studies have included mainly men, but in our study, the gender differences did not stand out. It has been previously shown that women report EDS as a SDB symptom more frequently than men do (Rezaeitalab et al. 2014), and in one study, 12 weeks of CPAP therapy reduced self-reported sleepiness in women (Campos-Rodriguez et al. 2016). Our study is in line with these previous findings.

Exercise habits, exercise duration, or cravings for different food categories did not differ at baseline between the groups, nor did these behaviours change during the follow-up. These findings are in line with previous results indicating that CPAP therapy alone does not result in a more active lifestyle or a more sensible diet. No changes in consumption of total calories, protein, carbohydrate, or fat were found in a study that followed patients with CPAP therapy for four months. There was a modest increase in recreational activity in women, but otherwise there were no changes in the activity patterns (Batool-Anwar et al. 2014). Physical activity was asked with two simple questions in our study. This is not, however, objective evaluation, but a subjective assessment, and there is always a chance that patients over- or underestimate their physical activity levels or do not notice the change in it. Actigraphy would have measured objectively the activity levels in different times of day and revealed day-to-day variation and would have given us a more precise picture of patients' activity levels. However, in previous studies, the results are in line with ours, suggesting that activity levels do not increase with CPAP therapy, even measured with actigraphy (West et al. 2009).

6.4 Leptin and IGF-1

In Study II, our finding was contrary to most of the previous studies that have suggested that leptin concentrations decrease, or remain unchanged, when OSAS patients are treated with CPAP (Shechter 2016). However, most of these studies had a shorter follow-up period and they also mostly consisted of men; hence the evidence in concentrations in long-term use remains low (Zhang et al. 2014). The only two randomised placebo-controlled trials reported no change, nor any differences in leptin concentrations between the CPAP-treated and the placebo groups during 2-3 months of therapy (Hoyos et al. 2012; Kritikou et al. 2014). The proportion of female patients in previous studies are low making our current study essential for implying the gender-specific difference in leptin levels during long-term CPAP therapy.

The major finding was that in female patients with OSAS, three years of CPAP therapy were associated with increased leptin concentrations compared to both non-users and men. Leptin concentrations increased autonomously for age or BMI. There was also a correlation between leptin increase and gender, as leptin increased in all females, but significantly more in female CPAP users. Alternatively, in men, leptin concentrations decreased regardless of CPAP use. Moreover, in men using CPAP, the leptin concentrations did not decrease as much as they did in the controls.

Women are known to have higher leptin concentrations than men have (Thomas et al. 2000). However, in our study population, the leptin concentrations at baseline did not differ between the genders. In one previous study, OSAS severity was related to higher leptin concentrations in women, but not in men (Akilli et al. 2014), and in addition, OSA patients were shown to have increased leptin concentrations when compared to age and BMI matched controls (Phillips et al. 2000). Moreover, obese patients usually develop leptin resistance that results in increased venous leptin concentrations (Zhang & Scarpace 2006), and the majority of our patients were obese. These factors could, at least in part, explain the lack of gender differences in leptin concentrations at our study baseline.

Previously, it has been suggested that CPAP therapy decreases leptin concentrations (Pan & Kastin 2014), but overall these results are controversial (Zhang et al. 2014). One study concluded that leptin concentrations decrease only if the CPAP treatment is effective, and poor adherence was associated with increased leptin concentrations (Sanner et al. 2004). Our study population did, indeed, use CPAP therapy efficiently. The hours of use were controlled once every year with built-in clocks, and the median usage was a sufficient six hours per night. However, we neither controlled for the residual AHI, nor repeated the polygraphy, in order to control the effectiveness of the therapy. Thus, the possibility of ineffective therapy pressure cannot be comprehensively ruled out. Nevertheless, the symptoms of SDB were alleviated during treatment, suggesting that the therapy was, in fact, effective. Short sleep duration is linked with decreased leptin concentrations (Taheri et al.

2004), and when SDB is treated, sleep duration and leptin concentrations may increase. However, in our study population, self-reported sleep duration did not change during follow-up. In addition, leptin has a circadian rhythm, and sleep timing might change due to CPAP treatment, thus affecting leptin's diurnal zenith and nadir times (Schoeller et al. 1997). Yet, the sleep timing did not change among our patients, based on their self-reported sleep timings.

The best explanation for elevated leptin concentration is the leptin resistance that develops with obesity. Perhaps the reduction in energy expenditure, due to toning down the nocturnal sympathetic overdrive, results in decreased energy consumption, accumulation of adipose tissue, and finally elevated leptin concentrations. Women have more adipose tissue, which could explain the differences between the genders after treatment, one that perhaps approaches the normal variation between the genders.

Leptin is known to have a correlation with visceral fat. Therefore, it has been discussed whether BMI is the right measurement for weight changes when specifically, visceral adipose tissue is controlled. In our study, we had only few patients with measurements of waist and hip circumference, therefore definite conclusions could not be drawn. Our results suggest, that when WHR is increased, the leptin concentrations decrease. However, we have a strong presentation of females in our study population, and in sub analysis 64 % were females, and they tend to have their adipose tissue distributed more in the hip area. Therefore, if our study population females tended to have lost more adipose tissue from the hips than from the waist, WHR was elevated and thus, inaccurately suggesting gain of adipose tissue if only WHR is included.

In our study population, IGF-1 concentrations did not change in either group during the three-year follow-up. The effect of CPAP therapy on IGF-1 concentrations in patients with OSAS remains controversial (Chen et al. 2015). In one study, it was reported that IGF-1 concentrations are increased in males ages 40-60 only (Münzer et al. 2010). In females and older men (over 60), the IGF-1 concentrations did not increase during the eight months of CPAP treatment. In our study, the median age was 54 years, and it included more females than most studies have, a factor that could help explain why the IGF-1 concentrations remained unchanged.

6.5 Medication use in comorbidities

Current knowledge on the effect of CPAP therapy on medicine use is controversial. Previously, the use of medication has been mainly studied as all-cause expenses, not as the actual use of medicines, let alone according to specific subcategories or diseases, or the effects of SDB type. Morbidity and mortality have been more

thoroughly studied, and it is thought that patients with OSAS have higher direct and indirect health costs than the controls. This aspect was shown in one study, where the effect was visible several years before the diagnosis and surprisingly, the effect extended even to their spouses (Jennum et al. 2014). CPAP therapy seems to decrease mortality in middle-age and old males, but it appears to have no effect on women (Jennum et al. 2015).

In our study III, female CPAP users had more illnesses than controls three years before CPAP initiation, which is in line with the previous data (Bonsignore et al. 2019a). The higher comorbidity noted already at baseline could explain why in our cohort, the total use of medication was higher in the CPAP therapy group at both time points, three years before and three years after CPAP introduction, when compared to the control group. Currently, only one registry study has evaluated the expenses of medication before and after CPAP treatment. The conclusion was that during an eight-year follow-up, the medication costs did not change in patients on CPAP therapy, but did increase in untreated group (Jennum & Kjellberg 2011). In our study, the increase in medication use was similar in both groups, regardless of CPAP use. Similar results were found in a Danish study, in which medication use was increased in patients with OSAS and correspondingly in the controls (Jennum et al. 2014).

In our female cohort, when different medication groups were analysed separately, the increase in medication use for obstructive respiratory diseases and severe mental illnesses was higher in the CPAP group when compared to the controls. These results went against our hypothesis that stated that CPAP therapy could be linked to reduced medication use. Moreover, in our study, the type of SDB did not have any influence on medication use, as the use was similar in patients with OSA and UAO. To our knowledge, the effect of the type of SDB on medicine use has not been studied previously. This aspect emphasises our earlier results and indicates that comorbidities are linked equally to both conditions, and accentuates that UAO is not a mild form of SDB (Anttalainen et al. 2010b).

To determine the validity of our control group; the data were compared to the entire Finnish female population. The medication use in all subcategories increased from year 1993 to 2001 in Finnish females. However, there was a trend of a slight decrease in medication when the first two years of follow-up were excluded, the years from 1995 to 2001 and in the same categories as found in the controls. Therefore, it can be stated here that our control group does represent the Finnish female population sufficiently, apart from severe mental illnesses, where for some reason, medication decreased among our controls.

6.5.1 Cardiovascular medication

Hypertension has had the most attention paid to it as a cardiovascular comorbidity of SDB (Bonsignore et al. 2019a). However, it has also been suggested that the effect of CPAP on blood pressure values is not as dramatic as previously thought. In one meta-analysis, the effect was small but significant, and in addition, the reduction was dependent on the OSAS severity, compliance, and blood pressure values before CPAP therapy was initiated (Haentjens et al. 2007). Since the effect of CPAP appears to be modest, currently it is advised to continue sufficient medication for blood pressure even if CPAP therapy is commenced. In our study, patients with SDB received more medications for hypertension than did controls. That disparity remained throughout the entire follow-up period. Therefore, our study reinforces the previous findings, that the medication use did not reduce with CPAP therapy.

In our clinical cohort of women, medicine use for arteriosclerosis and cardiac arrhythmias decreased in both the controls and the patients using CPAP therapy. The same phenomenon was observed in the entire Finnish female population. In previous studies the risk of cardiovascular disease events was suspected to be reduced with CPAP therapy (Myllylä et al. 2019), but the results were inconsistent. In one study, the adherence to CPAP > 4 h/night had to be achieved for any protective value (McEvoy et al. 2016). In our cohort, the decrease in use of these medications could be a result of changes in the Finnish guidelines for treatment of cardiovascular diseases.

The most common arrhythmia needing medical treatment is arterial fibrillation. When a patient is diagnosed with AF, anticoagulation therapy is initiated, and usually it must be continued for the rest of that patient's life. Currently, CPAP therapy is thought to have a protective effect on recurrent AF (Deng et al. 2018), but there are no studies that suggest a discontinuation of anticoagulant even if CPAP therapy is commenced. Therefore, the medication use does not change. The medication use for symptoms, e.g., beta blockers for tachycardia, could decrease due to AF treatment, or SDB treatment, resulting in a decrease in medication use.

6.5.2 Metabolic medication

The effect of CPAP therapy on blood glucose has had laborious investigation. SDB has been associated as being an independent factor for disturbed glucose metabolism in multiple studies (Anothaisintawee et al. 2016; Kent et al. 2013), and hence it is thought to be a risk factor for type 2 diabetes. However, currently it seems that glycemic control does not improve with CPAP therapy (Labarca et al. 2018; Zhu et al. 2018), although there are indications that sufficient CPAP adherence (over four hours per night) may have a protective impact on patients who have both cardiovascular complications and diabetes (McEvoy et al. 2016). Our study is in line

with these findings, as the medicine use for diabetes increased similarly in both groups, and CPAP did not have a protective effect. Therefore, we concur with the previous studies that it is essential to continue diabetes medication appropriately in OSAS patients, regardless of CPAP therapy initiation.

6.5.3 Respiratory medication

The use of medicines for asthma and/or COPD was increased in our CPAP group during the follow-up, unlike for the controls. In one previous study, a European cohort of SDB patients had a higher prevalence of asthma in females with obesity (Bonsignore et al. 2018), which was correspondingly reflected in our study population. Asthma and OSAS are thought to have a causative link (Kong et al. 2017) and there are studies both in favour (Julien et al. 2009) and against (Tveit et al. 2018) the relationship with asthma and the severity of OSAS. Referral policies for asthma patients to sleep studies can vary, and have thought to be linked with different results for various studies (Bonsignore et al., 2019a). This could also be the case in our study. Asthma patients have nocturnal symptoms similar to SDB; therefore, asthmatics can be overrepresented in the CPAP population, resulting in increased medication use. Moreover, the sleep study was conducted in a pulmonary clinic, where respiratory physicians tend to commence more vigorous treatment of respiratory diseases and that could result in higher medication consumption.

Our study supports the previous knowledge about asthma and COPD prevalence among females with obesity and OSAS. COPD is long known to coincide with OSAS (Flenley 1985), and CPAP therapy appears to reduce the risk of death and hospitalisation of patients with both COPD and SDB (Marin et al. 2010).To our knowledge, there are no previous studies on SDB and COPD overlap, and the effects of CPAP on medication. Our finding suggests that medication use for COPD is not decreased with CPAP therapy. One reason could be that COPD is a progressive disease with no curative medication, leading to increased use of medications even when the OSAS is treated sufficiently.

6.5.4 Psychiatric medication

In our female study cohort, there was a significant difference in the psychiatric medicines used between the study groups. The medication group of psychiatric medicines consisted of merely those medications used for severe mental illnesses, excluding e.g., mild depression and anxiety. In the CPAP user group, as well as in the Finnish female population, the use of these medications increased slightly during the follow-up time, whereas in our control group that use decreased. This finding could indicate that the controls who had similar symptoms suggesting SDB at the

beginning, possibly had another underlying condition, that manifested with similar symptoms. These conditions could have been diagnosed and probably treated during the follow-up, thereby resulting in decrease in medication use.

Symptoms of SDB come in broad variations and can bear a resemblance to those for mental disorders. SDB is estimated to be present in 15-48% of patients with schizophrenia (Kalucy et al. 2013), 21-47.5 % of patients with bipolar disorder (Kelly et al. 2013) and 11-18 % of patients with recurrent depressive disorder (Ohayon 2003). Moreover, some medications used for severe mental disorders can aggravate the symptoms of SDB, mainly via weight gain (Szaulińska et al. 2015). However, in one review, the prevalence of OSAS was not elevated in those patients with schizophrenia, bipolar disorder, or severe depression (Gupta & Simpson 2015).

6.6 The effect of sleep study

In Studies I and II, the sleep study was conducted with PG, which is a standard method for SDB diagnosis in Nordic countries. As mentioned before, PG focuses on respiratory events and cardiac reactions, and sleep stages are not visible, as EEG and EOG electrodes are not utilised. However, in the basic diagnostics of OSA or UAO, PG is sufficient. Therefore, our sleep studies undertaken in pulmonary wards were reliable and the diagnosis of SDB well assured. If the diagnosis was made with PSG, the REM-related OSA could have been detected with more certainty, since in PG, AHI dilutes when the wake time is included in the analysis, and the diagnosis can thus more possibly be left undiscovered. PG has been criticised for underestimating SDB, and being insufficient to rule out OSA when the respiratory events are mainly associated with arousals (Nerfeldt et al. 2014). Therefore, it is now suggested that PG scoring should have its own diagnostic guidelines (Escourrou et al. 2015).

A static-charge-sensitive bed was widely used in our clinical practise in the last decades of 20th century but has now been replaced with PG. After the time our study was performed, there has been discussion about the right categorisation of SCSB breathing patterns. However, in our study, the classification of obstructive breathing included the categories P2 and P3, which are considered as obstructive also today. SCSB has its advantages. For example, there are no electrodes or probes disturbing the sleep, making it ideal to evaluate sleep in infants or small children. Moreover, the traditional measurements of AHI with PG are unable to identify prolonged upper airway resistance from pure OSA as reliably as when examined with SCSB. Recent studies have also shown that AHI poorly correlates with cardiovascular comorbidity, suggesting that other parameters beyond AHI are needed to identify patients who will adhere and benefit from CPAP treatment (Saaresranta et al 2016; Zinchuk et al. 2019).

6.7 Strengths and limitations

In Study I and II, we had a medium sized and gender-balanced study population, and in Study III, we had only women. Previous studies have been undertaken mainly on men, and the effects of CPAP therapy cannot, therefore, be evaluated with certainty in women. Recent studies point toward the realisation that SDB in men and women are different, and the comorbidities and risks do vary between the genders. Our study provides more information on this gap, thereby making treatment of female SDB more efficient.

Weight change was evaluated with the help of BMI. It is an international and standardised method for weight assessment, but it has its limitations. Currently we know that waist hip ratio is more accurate in evaluating obesity, as BMI does not take e.g. muscles into account and can overestimate obesity, especially in men. Moreover, the health consequences of visceral adipose tissue are well known, and if the patient is not obese by BMI, but has visceral obesity, the risk for comorbidities is higher.

In Study I, we had substantial number of questionnaires to evaluate different aspects of patients' lives. We introduced the questionnaires in the evening, right after a full meal. This impacts on mood and cravings and the results might be different if the questionnaires were completed in the morning. Additionally, we did not use food diaries, which could have provided a deeper insight in the issues related to weight gain. Questionnaires administered at a single point at the baseline and follow-up could just reflect the feelings at the moment of filling out the questionnaire, even if the instructions referred to a longer time period. The questionnaires used were standardised and in wide clinical use, making our results reliable. Finally, a large set of data has its disadvantages. Methodologically, there can be associations based on the large number of variables that cannot be reproduced in different settings, and multiple statistical analyses can create incorrect associations. However, our results were critically administered, and the justification for all the variables and results were fully considered.

In Study II, there were only single measurements of leptin concentrations in two time points, although leptin is known to have a circadian rhythm. However, leptin concentrations were measured approximately at the same time of the day, both at baseline and at follow-up. In addition, we did not measure leptin concentrations shortly after the CPAP therapy was commenced. Therefore, we cannot know with certainty whether the leptin concentrations had increased already in the initiation phase of CPAP therapy, or if the concentrations increased later during the treatment. However, this does not compromise our finding that leptin concentrations undeniably increase among females after three years of CPAP use.

In Study III, our results can only be applied to women. Our study population was moderate in size, so therefore we must be cautious in drawing conclusions from the

study results regarding the subgroups of medication. Our study data are older in origin, but the basic guidelines for the treatments of illnesses that we evaluated have remained similar. The actual drugs can be different or have evolved, but the effect of CPAP therapy upon use can be evaluated from the data gathered even though that data are older. We compared the same patients, and we had a control group; therefore, the effects can be considered reliable. In addition, we controlled for the CPAP use.

6.8 Clinical implications and future considerations

In the future, the treatment of SDB is going to change and we need more information on the long-term effects of CPAP therapy, in order to provide the most tailored and cost-effective treatment. In our study, we have shown, that regardless of the efficient treatment of SDB and its symptoms, we have not been able to influence weight or lifestyle, both of which are the essence of our crusade to cure SDB permanently. Therefore, we suggest that in addition to CPAP therapy, lifestyle counselling should be provided to patients with SDB, a choice that rarely is the case currently. However, we have also proved that CPAP alleviates SDB symptoms efficiently, and in the treatment of resistant depression or anxiety, SDB should be considered and sleep study duly allocated whenever there are any suspicions of underlying SDB.

Leptin is of particular interest currently, as it is a promising candidate for the medical treatment of SDB. In mice, intranasal leptin has been proven to alleviate or even cure OSA (Berger et al. 2019), but the effects in humans are still unknown. However, our finding of gender-related reactions to CPAP therapy induced leptin concentrations could play a useful role in future treatments and should be considered in the development of the new drug.

The cost-effectiveness of CPAP therapy is something we also need to consider in the future. The rising number of patients can lead to rising costs for CPAP use, but if the treatment has a reductive effect on overall costs, CPAP therapy should be commenced earlier and SDB thereby treated more efficiently. The morbidity in our study was higher in SDB patients three years before CPAP initiation, and this finding is in line with earlier studies. In addition, patients with UAO had the same risk profile and morbidity as patients with OSA, indicating that perhaps these patients should also be treated more efficiently and much earlier than we currently do. Medication use remained the same despite the CPAP therapy, but it did not increase more than what was delivered to the controls, thus indicating that the increase in medication use might also be reduced.

More research is needed into all these aspects, as multiple and different variables must be taken into account in these exciting years, as the treatment protocol of SDB moves through further change.

7 CONCLUSIONS

The main results, according to the aims of the study were as follows:

1. Long-term CPAP therapy does not lead to weight reduction, more active lifestyle, or more healthy choices of food. However, it does alleviate efficiently sleepiness, depressive symptoms, and anxiety and improves sleep quality.
2. Leptin concentrations increase in females within time, but the increase is higher if a patient is using long-term CPAP therapy for OSA. In men, leptin concentrations decrease, but the reduction is lesser when using long-term CPAP therapy. Long-term CPAP therapy does not influence on IGF-1 concentrations. No reduction in weight was detected with long-term CPAP treatment.
3. Medication use for comorbidities does not decrease in women using long-term CPAP therapy for SDB. However, the increase in medication use might be reduced to the same level as in controls. The type of SDB, OSA or UAO, does not influence on medication use.

ACKNOWLEDGEMENTS

The work in this thesis was conducted in the Department of Pulmonary Diseases and Clinical Allergology, Turku University Hospital, and Sleep Centre in Turku University, during 2011–2020. This time frame is also the period I have worked in Turku University Hospital with an excellent team of respiratory physicians.
I would like to express my sincere gratitude to the following persons:

Most importantly my supervisors, Acting Professor Tarja Saaresranta MD, PhD, and Adjunct Professor Ulla Anttalainen MD, PhD, who have taught me patiently academic and research skills from the basics. Tarja, you have exceptional passion for research, and it is contagious. I value all the lessons you have taught me, not only in research, but also in life. Thank you for your patience and without your gentle pushing, I would never have completed my thesis. I consider myself lucky to have such an amazing and highly intelligent supervisor, who also has a heart of gold. Ulla, I could not be more grateful for all your guidance, patience, and understanding the rough parts in life. Your valuable comments and ability to make hard things suddenly easier, have been very important to me. Your heart-warming laughter and colourful personality have made my path very enjoyable. I am very grateful for having such an intelligent supervisor.

Adjunct professor Maritta Kilpeläinen MD, PhD, Head of the Department of Pulmonary Diseases and Allergology at the Turku University Hospital, for providing facilities and time to conduct this research. I would also like to thank other supervisors including Olli-Pekka Seppälä MD, PhD for providing occasional leave from clinical duties when possible.

The official reviewers of my thesis, Adjunct Professor Leena Tuomisto MD, PhD and Professor Brendon Yee MBChB, PhD, for their valuable comments and feedback which markedly improved the final form of this thesis. I appreciate your time and effort given for my manuscript. I had a lovely conversation with Leena discussing various aspects of my thesis and I truly appreciate that you have donated your time to my project. Thesis follow-up committee members Professor Pirkko Brander MD, PhD and Nea Kalleinen MD, PhD for the support and comments you have given me during this project. The biostatisticians Samu Kurki PhD and Tero Vahlberg MSc for your work in applying statistical methods in these studies. Thank

you for your patience with my basic questions and thank you for opening the world of statistics to me. In addition, I would like to thank the other co-writers in these studies, Olli Polo, MD, PhD and Kerttu Irjala, MD, PhD for your contribution and valuable comments, and I wish to express my sincere acknowledgement to both of them, as well as to Professor Sari-Leena Himanen for agreeing to be my opponent. In addition, I would like to thank the nurses and sleep technicians at the Department of Pulmonary Diseases in Turku University Hospital and Sleep Research Unit for the acquisition of the data.

Not directly linked to my scientific work, but providing the needed support otherwise, I would like to thank the following:

Minna Myllylä, MD, PhD, thank you for your support and our long talks. Thank you for walking this path with me and listening to my ventilation and anxiety. I have learned a lot from you over the years, and I value our friendship which will for sure continue even if our careers would not. The international conference in Tampere with you was one of the highlights of this path to dissertation!

My fantastic co-workers and supervisors in the Department of Pulmonary Diseases in Turku University Hospital, especially the "young ones", even though most of us are not so young anymore. Eeva-Liisa Junnila MD, Jaana Kaunisto MD, Päivi Oksman MD, Ilona Anttila MD and Aino Lammintausta MD, PhD, I thank you for the thousands of laughs both at work and at spare time. Thank you for sharing your lives with me and your friendship, which has evolved far beyond just colleagues. Maria Silvoniemi MD, PhD, I want to thank you for your support during the final months of writing this thesis. Someone who has gone through this and survived, is the best kind of peer support. All the physicians in Department of Pulmonary Diseases in Turku University Hospital will always have a special place in my heart. You are my tribe, my people, when work is considered.

My dear friends from Medical school, Ursus-tyttäret, Erika Storm, Jenni Anttila, Milla Ylijoki, Kristiina Pälve, Eeva Elamo, Elisa Kortela, Salla Fagerudd, Pia Ettala, Roosa Lankinen. We have shared the ups and downs for almost twenty years, and I treasure you forever. We have grown together into this profession, as well as shared the most valuable moments in our lives and our children's lives. Erika, thank you for all the support you have given me, not only by helping me through dissertation, but also in life. Jenni, you are my rock and the kindest person I know. You have the superpower of saying exactly the right words at the right time. My oldest friends from elementary school, Heli Heikkola, Pia Aulio, Satu Kivivuori, Jenni Tuorila, Reija Ahokoski and Tiina Vaitilo. We have known each other from the start and there are things that only those, who have grown up with you, can understand. Even if there is a distance in time or space between us, we always pick up where we left, and I can always count on your support.

My family, especially my parents, Seppo and Rea Isotalo for giving me your support and love throughout my life. Thank you for making this project even possible by taking care of our children while I had to work, and by saving us many times from difficult situations with a promise to pick up the children or taking care of them during sickness. Thank you for always being there for us, no matter what. I want to express my gratitude to my big brother Miika Isotalo and his wife Sanna and their lovely children Pinja and Aleksi, to my father-in-law Jouko Aro and his wife Nina, my sister-in-law Heli and brother-in-law Ville. I also value the memory of Leena, who helped us during the first years of making this thesis.

Finally, and most importantly, I would like to thank my husband Antti Aro. Thank you for your patience in those long hours when I had to write. Thank you for sharing my frustrations and celebrating my joys. Without you, there would not be this thesis. You are my everything and I love you until my very last breath. Thank you, my precious children Lukas, Elias, and Matias, for understanding that behind the closed bedroom door, mom was writing, and you had to wait for your hugs. I will compensate them all when this is finished!

This thesis was financially supported by the Clinical Research Fund of the Turku University Hospital, The Research Foundation of the Pulmonary Diseases, The Finnish Anti-Tuberculosis Foundation, Väinö and Laina Kivi Foundation, the Tampere Tuberculosis Foundation, and the Turku University Foundation.

Turku, September 2020
Miia Aro

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APPENDICES

Appendix 1.

EPWORTH SLEEPINESS SCALE (ESS)

The following questionnaire will help you measure your general level of daytime sleepiness. You are to rate the chance that you would *doze off or fall asleep* during different routine daytime situations. Answers to the questions are rated on a reliable scale called the Epworth Sleepiness Scale (ESS). Each item is rated from 0 to 3, with 0 meaning you would never *doze or fall asleep* in a given situation, and 3 meaning there is a very high chance that you would *doze or fall asleep* in that situation.

How likely are you to *doze off or fall asleep* in the following situations, in contrast to just feeling tired? Even if you haven't done some of the activities recently, think about how they would have affected you.

Use this scale to choose the most appropriate number for each situation:

0 = would never doze

1 = slight chance of dozing

2 = moderate chance of dozing

3 = high chance of dozing

It is important that you circle a number (0 to 3) for EACH situation.

SITUATION	**CHANCE OF DOZING**			
Sitting and reading	0	1	2	3
Watching television	0	1	2	3
Sitting inactive in a public place (theater/meeting)	0	1	2	3
As a passenger in a car for an hour without a break	0	1	2	3
Lying down to rest in the afternoon	0	1	2	3
Sitting and talking to someone	0	1	2	3
Sitting quietly after lunch (with no alcohol)	0	1	2	3
In a car, while stopped in traffic	0	1	2	3

Appendix 2.

DEPS.

Below there are some statements and questions, which we hope that you will answer by circling the alternative which best corresponds with your condition during the last month.

During the last month	Never	To some extent	Relatively much	Very much
I suffered from insomnia	0	1	2	3
I felt sorrowful	0	1	2	3
It felt that everything required exertion	0	1	2	3
I felt listless	0	1	2	3
I felt lonely	0	1	2	3
The future felt hopeless	0	1	2	3
I did not enjoy my life	0	1	2	3
I felt worthless	0	1	2	3
I felt that all joy had left life	0	1	2	3
I felt that my depression did not even ease with the help of family or friends	0	1	2	3

Appendix 3.

PITTSBURGH SLEEP QUALITY INDEX (PSQI)

INSTRUCTIONS: The following questions relate to your usual sleep habits during the past month only. Your answers should indicate the most accurate reply for the majority of days and nights in the past month. Please answer all questions.

1. During the past month, when have you usually gone to bed at night?

   USUAL BED TIME _____

2. During the past month, how long (in minutes) has it usually take you to fall asleep each night?

   NUMBER OF MINUTES _____

3. During the past month, when have you usually gotten up in the morning?

   USUAL GETTING UP TIME _____

4. During the past month, how many hours of actual sleep did you get at night? (This may be different than the number of hours you spend in bed.)

   HOURS OF SLEEP PER NIGHT _____

INSTRUCTIONS: For each of the remaining questions, check the one best response. Please answer all questions.

5. During the past month, how often have you had trouble sleeping because you...

	Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
(a) ...cannot get to sleep within 30 minutes	☐	☐	☐	☐
(b) ...wake up in the middle of the night or early morning	☐	☐	☐	☐
(c) ...have to get up to use the bathroom	☐	☐	☐	☐
(d ...cannot breathe comfortably	☐	☐	☐	☐
(e) ...cough or snore loudly	☐	☐	☐	☐
(f) ...feel too cold	☐	☐	☐	☐
(g) ...feel too hot	☐	☐	☐	☐
(h) ...had bad dreams	☐	☐	☐	☐
(i) ...have pain	☐	☐	☐	☐

(j) Other reason(s), please describe

_____

_____

How often during the past month have you had trouble sleeping because of this?	☐	☐	☐	☐

	Very good	Fairly good	Fairly bad	very bad
6. During the past month, how would you rate your sleep quality overall?	☐	☐	☐	☐

	Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
7. During the past month, how often have you taken medicine (prescribed or "over the counter") to help you sleep?	☐	☐	☐	☐
8. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?	☐	☐	☐	☐

	No problem at all	Only a very slight problem	Somewhat of a problem	A very big problem
9. During the past month, how much of a problem has it been for you to keep up enough enthusiasm to get things done?	☐	☐	☐	☐

	No bed partner or roommate	Partner/ roommate in other room	Partner in same room, but not same bed	Partner in same bed
10. During the past month, how much of a problem has it been for you to keep up enough enthusiasm to get things done?	☐	☐	☐	☐

If you have a roommate or bed partner, ask him/her how often in the past month you have had...

	Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
(a) ...loud snoring	☐	☐	☐	☐
(b) ...long pauses between breaths while asleep	☐	☐	☐	☐
(c) ...legs twitching or jerking while you sleep	☐	☐	☐	☐
(d) ...episodes of disorientation or confusion during sleep	☐	☐	☐	☐
(e) Other restlessness while you sleep; please describe	☐	☐	☐	☐

_____

_____

PSQI Page 2

Appendix 4.

State Trait Anxiety Inventory

Read each statement and select the appropriate response to indicate how you feel right now, that is, at this very moment. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe your present feelings best.

	1 Not at all	2 A little	3 Somewhat	4 Very much so
1. I feel calm	1	2	3	4
2. I feel secure	1	2	3	4
3. I feel tense	1	2	3	4
4. I feel strained	1	2	3	4
5. I feel at ease	1	2	3	4
6. I feel upset	1	2	3	4
7. I am presently worrying over possible misfortunes	1	2	3	4
8. I feel satisfied	1	2	3	4
9. I feel frightened	1	2	3	4
10. I feel uncomfortable	1	2	3	4
11. I feel self-confident	1	2	3	4
12. I feel nervous	1	2	3	4
13. I feel jittery	1	2	3	4
14. I feel indecisive	1	2	3	4
15. I am relaxed	1	2	3	4
16 I feel content	1	2	3	4
17. I am worried	1	2	3	4
18. I feel confused	1	2	3	4
19. I feel steady	1	2	3	4
20. I feel pleasant	1	2	3	4

Appendix 5.

SCALE FOR APPETITE

Please, answer the following questions according to how you feel RIGHT NOW. Please, answer how you actually feel, REGARDLESS OF CALORIES, FAT, OR, "HEALTHY FOOD". How much would you ENJOY eating the following 7 different categories of food?

SWEET FOOD such as cakes, sweets, cookies, ice cream, sweet pies
Not at all _____ **Very much**

SALTY FOOD such as chips, salty nuts, salty cucumber
Not at all _____ **Very much**

FOOD WITH STARCH such as bread, pasta, cereals, potatoes
Not at all _____ **Very much**

FRUIT AND JUICE
Not at all _____ **Very much**

VEGETABLES
Not at all _____ **Very much**

MEAT, CHICKEN, FISH, EGGS
Not at all _____ **Very much**

DAIRY PRODUCTS such as milk, cheese, or yoghurt
Not at all _____ **Very much**

SCALE FOR HUNGER

How hungry do you feel right now?
Not at all hungry _____ **Very Hungry**

How thirsty do you feel right now?
Not at all thirsty _____ **Very Thirsty**

How full do you feel your stomach is right now?
Not at all full _____ **Very full**

How strong desire do you have to eat right now?
No desire to eat at all _____ **Very strong desire**

How much do you think you could eat right now?
Not at all much _____ **Very much**

Appendix 6.

1. How often do you exercise? (choose one option)

1. not at all
2. less than once a week
3. once a week
4. 2 times a week
5. 3 times a week
6. 4 times a week
7. 5 times a week

2. What is the duration of your one exersice? (choose one option)

1. 0 - 20 minutes
2. 20 - 40 minutes
3. 40 - 60 minutes
4. yli 60 minutes

1. Have you ever smoked? (at least for 6 months straight)

1. yes
2. no

2. Alcohol use for the last six months:

1. Not at all
2. 0-6 bottles of beer per week or corresponding amount of any other alcohol
3. 7-14 bottles of beer, 1-2 bottles of wine, ½-1 bottles spirits or corresponding amount of any other alcohol in a week
4. 15-24 bottles of beer, 2-4 bottles of wine, or 1-2 bottles of spirits in a week.

Do you have any medication? Please write ALL the medications you use.

UNIVERSITY OF TURKU

Painosalama Oy, Turku, Finland 2020

ISBN 978-951-29-8198-4 (PRINT)
ISBN 978-951-29-8199-1 (PDF)
ISSN 0355-9483 (Print)
ISSN 2343-3213 (Online)