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TIMO LEPPÄNEN

NOVEL METHODS FOR DIAGNOSTICS OF OBSTRUCTIVE SLEEP APNEA

- Effect of Weight Loss, Gender, and Sleeping Position on Severity of Apnea, Hypopnea and Desaturation Events

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ABSTRACT

The severity of obstructive sleep apnea (OSA) is currently estimated based on the apnea-hypopnea index (AHI) which is defined by the number of respiratory events per hour of sleep and classified into three categories: mild (5≤AHI<15), moderate (15≤AHI<30), and severe (30≤AHI). AHI does not take into account the severity of individual obstruction events (*i.e.* the durations of the apnea and hypopnea events or durations, depths and areas of desaturation events). However, longer respiratory events and prolonged and deeper desaturation events have been suggested to be more detrimental than shorter and shallower ones. We have previously devised novel diagnostic parameters incorporating the number and severity of individual obstruction events but these parameters have not been readily accessible for clinicians.

It has been shown that weight reduction alleviates the severity of OSA. In addition, AHI has been reported to be higher in males than in females and while sleeping in a supine compared to non-supine position. However, the effect of weight loss on the severity of individual obstruction events is unknown and differences in the severity of individual obstruction events between genders or sleeping positions have not been investigated thoroughly in the different OSA severity categories.

The aims of this thesis were to evaluate the effect of weight reduction on the severity of individual obstruction events and to determine whether the severity of individual obstruction events varies between genders and between sleeping positions. These aims were investigated by retrospective studies based on the ambulatory polygraphic recordings of patients (n=87-2057) with suspected OSA during the years 1992-2009 in the Department of Clinical Neurophysiology, Kuopio University Hospital and in the outpatient clinics of Otorhinolaryngology and Respiratory Medicine, Kuopio University Hospital. The polygraphic recordings were reanalysed and information on mortality and morbidities was collected. Finally, to enable the clinical application of our previously introduced novel pa-

rameters, a plug-in was designed which could be incorporated into widely used polysomnography software RemLogic (Embla, Thornton, MA, USA).

Over 5% weight loss during a two-year follow-up decreased the number of respiratory events by 58% ($p<0.001$) but the median durations of the apneas and hypopneas increased ($p<0.001$) by 62% and 20%, respectively. Sleeping in supine position prolonged the median length of apnea events in all OSA severity categories ($p<0.001$) and increased the median area of desaturation events in the moderate and severe categories ($p\leq0.001$). In male patients, the proportion of apneas was 496.4%, 329.0%, and 63.1% higher ($p\leq0.002$) compared to females in the mild, moderate, and severe OSA categories, respectively. Females had less severe individual desaturation and apnea events ($p\leq0.053$) in the moderate and severe OSA categories. In addition, the severity of individual obstruction events was linked to increased mortality and cardiovascular morbidities as the adjusted-AHI, incorporating the number and the severity of individual obstruction events, was found to be an independent risk factor for overall mortality and non-fatal cardiovascular events.

The effect of weight loss on severity of OSA is not as straightforward as would be indicated if one only utilizes the conventional AHI as the weight reduction decreased mainly the number of the shorter apnea and hypopnea events. The severity of individual obstruction events varies between genders and between sleeping positions and it is modulated by the severity of OSA. For these reasons, AHI might not be the optimal parameter for estimation of the overall severity of OSA. We suggest that these gender and sleeping position related differences as well as the severity of individual obstruction events should be taken into account when assessing the clinical severity of OSA. Therefore, the present plug-in, enabling the clinical application of these novel parameters, might improve the clinical estimation of the overall severity of OSA.

National Library of Medicine Classification: WB 286, QT 235, WA 900, WF 143

Medical Subject Headings: Sleep Apnea, Obstructive / diagnosis; Weight Loss; Sex Factors; Male; Female; Respiratory Rate; Hypoventilation; Anoxia; Posture; Supine Position; Mortality; Morbidity; Polysomnography; Follow-Up Studies

Yleinen suomalainen asiasanasto: unihäiriöt; apnea; uniapnea-oireyhtymä; diagnostiikka; painonhallinta; laihdutus; sukupuoli; sukupuolierot; miehet; naiset; asennot; kuolleisuus; sairastavuus; seurantatutkimus

to my family

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I owe my sincere gratitude to my co-authors: Hospital Physicist

Pekka Tiihonen, Ph.D., Anu Muraja-Murro, M.D., Ph.D., Salla Ylä-Herttuala, Scientific Director Brett Duce, B.Sc., Meri Julkunen, BLS, Taina Hukkanen, B.Sc., and Mikko Särkkä, B.Sc., for their contribution in the original publications. Furthermore, I would like to thank all my colleagues in the Department of Clinical Neurophysiology, the Department of Otorhinolaryngology, and in the Department of Respiratory Medicine who have been involved in the studies. In addition, I would like to give a special thanks to Hospital Physicist Pekka Tiihonen, Ph.D., for being my mentor and for teaching and guiding me through this journey, especially at the very beginning.

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Kuopio, November 2016

Timo Leppänen

ABBREVIATIONS

A-AHI	Adjusted apnea-hypopnea index (events/hour)
AASM	American Academy of Sleep Medicine
AHI	Apnea-hypopnea index (events/hour)
AI	Apnea index (events/hour)
APAP	Autotitrating positive airway pressure
ApDur	Individual apnea event duration (s)
BMI	Body mass index (kg/m^2)
CI	Confidence interval for differences
CPAP	Continuous positive airway pressure
CV	Cardiovascular
CVD	Cardiovascular disease
DesArea	Individual desaturation event area (s%)
DesDur	Individual desaturation event duration (s)
DesSev	Desaturation severity parameter (%)
ECG	Electrocardiogram
EEG	Electroencephalogram
EMG	Electromyogram
EOG	Electro-oculogram
ESS	Epworth sleepiness scale
GLM	General linear model
HI	Hypopnea index (events/hour)
HR	Heart rate (bpm)
HTML	Hyper text markup language
HypDur	Individual hypopnea event duration (s)
ICC	Intra-class correlation coefficient
MAD	Mandibular advancement device
MATLAB	Matrix laboratory -software
ObsSev	Obstruction severity parameter (s%)
ODI	Oxygen desaturation index (events/hour)
ODT	Oxygen desaturation threshold
OSA	Obstructive sleep apnea
PSG	Polysomnography
RDI	Respiratory disturbance index (events/hour)

RemLogic	Polysomnography software
RERA	Respiratory effort related arousal
RIP	Respiratory inductance plethysmography
SASI	Sleep apnea severity index
SD	Standard deviation
$SO2_j$	Value of oxygen saturation in j^{th} sampling point of the scored desaturation event
SpO_2	Saturation of peripheral oxygen
SPSS	Statistical Package for Social Sciences -software
UA	Upper airway
UPPP	Uvulopalatopharyngoplasty

Throughout the thesis, *obstruction events* denotes apnea, hypopnea and desaturation events and *respiratory events* refers to apnea and hypopnea events. *Obstruction event severity* designates the duration of individual apneas and hypopneas and area, depth and duration of individual desaturations.

SYMBOLS

hh:mm	hours:minutes
L	Number of the analysed events
n	Number of samples/patients
p	Probability to reject the correct null hypothesis
r	Correlation coefficient
S	Number of sampling points during a scored desaturation event
W	Sampling interval
Σ	Summation

LIST OF PUBLICATIONS

This thesis consists of a review of the author's work in the field of obstructive sleep apnea and the following selection of the author's publications:

I Kulkas A., Leppänen T., Sahlman J., Tiihonen P., Mervaala E., Kokkarinen J., Randell J., Seppä J., Tuomilehto H., & Töyräs J. "Novel parameters reflect changes in morphology of respiratory events during weight loss". *Physiological Measurement*. **34(9)**, 1013-1026 (2013).

II Leppänen T., Töyräs J., Muraja-Murro A., Kupari S., Tiihonen P., Mervaala E., & Kulkas A. "Length of individual apnea events is increased by supine position and modulated by severity of obstructive sleep apnea". *Sleep Disorders*. **2016**, ID 9645347.

III Leppänen T., Kulkas A., Duce B., Mervaala E., & Töyräs J. "Severity of individual obstruction events is gender dependent in sleep apnea". *Sleep and Breathing*. In press (2016), DOI: 10.1007/s11325-016-1430-0

IV Leppänen T., Särkkä M., Kulkas A., Muraja-Murro A., Kupari S., Anttonen M., Tiihonen P., Mervaala E., & Töyräs J. "RemLogic plug-in enables clinical application of apnea-hypopnea index adjusted for severity of individual obstruction events". *Journal of Medical Engineering & Technology*. **40(3)**, 119-126 (2016).

Throughout the thesis, these publications will be referred to by Roman numerals **I-IV**.

AUTHOR'S CONTRIBUTION

The publications included in this thesis were made in a collaboration between the Department of Clinical Neurophysiology, Diagnostic Imaging Center, Kuopio University Hospital; the Department of Clinical Neurophysiology, Seinäjoki Central Hospital; the Department of Respiratory & Sleep Medicine, Sleep Disorders Centre, Princess Alexandra Hospital; the outpatient clinics of Otorhinolaryngology and Respiratory Medicine, Kuopio University Hospital; and the Department of Applied Physics, University of Eastern Finland.

The author's contribution to studies **I-IV** was as follows:

I The author was responsible for the data analyses, interpreted the results in cooperation with the co-authors and contributed to writing of the manuscript.

II The author designed the study with the supervisors and participated in the study conception, was responsible for the data analyses, interpreted the results with the co-authors, and was the main writer of the manuscript.

III The author designed the study with the supervisors and participated in the study conception, was responsible for the data analyses, interpreted the results with the co-authors, and was the main writer of the manuscript.

IV The author was responsible for the data analyses, interpreted the results with the co-authors, and was the main writer of the manuscript.

In all manuscripts the collaboration with the co-authors has been significant.

Contents

1 Introduction

Obstructive sleep apnea (OSA) is a common nocturnal breathing disorder characterized by repeated partial narrowing of the upper airway (hypopnea) or complete cessations of breathing (apnea) [3]. The prevalence of OSA is estimated to be 5.6-49.7% in 30-85 year old individuals and the incidence is expected to increase in the future [52, 112, 169]. In numerous studies, OSA has been linked with cardiovascular disease (*e.g.* hypertension), deteriorations in the quality of life, and increased mortality rate [85, 93, 95, 140, 148, 167].

The current standard for diagnosis of OSA is in-laboratory polysomnography (PSG), although ambulatory polygraphic devices with a fewer number of recorded signals have been acknowledged to be sufficient for OSA diagnostics [29]. The most commonly used parameter in the diagnostics of OSA is apnea-hypopnea index (AHI) determined using PSG registration. It is defined as the number of breathing cessation events (apneas and hypopneas) per hour of sleep. Currently, OSA is diagnosed if AHI is at least five events per hour with associated symptoms (*e.g.* daytime sleepiness) or medical or psychiatric disorder (*e.g.* hypertension or mood disorder) [132]. Alternatively, AHI $\geq$ 15 events per hour is itself sufficient to diagnose OSA even without any symptoms or psychiatric disorders [132]. Based on their values of AHI, patients are classified as exhibiting mild ($5 \leq$AHI<15), moderate ($15 \leq$AHI<30), or severe ($30 \leq$AHI) OSA. However, AHI does not take into account the durations of the individual apneas and hypopneas nor incorporate the information on durations, depths, or areas of individual desaturation events even though it is evident that the severity of individual obstruction events is linked to increased mortality rate and cardiovascular morbidities [95].

Obesity is one of the most severe risk factors of OSA [171]. Weight loss has been shown to decrease AHI effectively and to reduce the symptoms of OSA [156]. Weight loss has also a posi-

tive effect on cardiovascular disease and it also plays an important role in treatment of metabolic syndrome [156]. However, the effect of weight loss on the severity of individual obstruction events (*i.e.* apneas, hypopneas or desaturations) has not been thoroughly investigated. AHI has been reported to be higher when the individual sleeps in a supine position compared to non-supine positions [89]. Furthermore, apneas are longer and desaturation events are deeper when supine compared to the lateral position in patients with severe OSA [106]. There is no corresponding comprehensive information on the severity of individual obstruction events in mild and moderate OSA. It is also well known that male patients have higher AHI and that their apnea events are longer, in general, than in female patients [78, 160]. However, whether the severity of individual obstruction events is different between genders has not been thoroughly explored in different OSA severity categories.

Previously, we have introduced novel parameters incorporating the number, duration, and morphology of individual obstruction events, but they have not been readily accessible for clinicians [75, 76, 94]. We have shown that the severity of individual obstruction events is connected to an increased mortality rate [95] and that the lengths of individual obstruction events can be different in patients with similar values of AHI [96]. In this thesis, differences in severity of individual obstruction events between genders and sleeping positions and the effect of weight loss on individual event severity were studied. In addition, one further aim of this thesis was to devise a tool suitable for clinical use incorporating the novel diagnostic parameters.

The hypotheses were that the effect of weight reduction on the severity of individual obstruction events would not be as linear as indicated by the change in AHI and that the characteristics of individual events would be different in different sleeping positions and between male and female patients. In this thesis, these hypotheses were tested by retrospective studies which evaluated ambulatory polygraphic recordings of patients (n=87-2057) conducted in Kuopio University Hospital during the years 1992-2009. Patients'

background information, treatments and cardiovascular morbidities were acquired from patient medical records collected in Kuopio University Hospital. Finally, the causes of death were obtained from Statistics Finland (Helsinki, Finland).

2 Obstructive sleep apnea

Obstructive sleep apnea (OSA) is a severe public health problem in which the patient has frequent breathing cessations during sleep. Complete breathing cessations are called apneas, and partial breathing cessations termed as hypopneas. An apnea is defined as a $\geq$ 10 seconds long episode in which the amplitude of airflow signal drops $\geq$ 90% from the reference level [61]. In 2007, the American Academy of Sleep Medicine (AASM) provided two alternative definitions (rules 4A and 4B) to score a hypopnea in which four criteria must be met. In rule 4A (recommended) the amplitude of airflow signal must drop $\geq$ 30% from the reference level for $\geq$ 10 seconds causing $\geq$ 4% drop in oxygen saturation signal [61]. In rule 4B (alternative) the amplitude of airflow signal must drop $\geq$ 50% from the reference level for $\geq$ 10 seconds causing either $\geq$ 3% drop in oxygen saturation signal or arousal detected by means of electroencephalography (EEG) [61]. Finally, in both of these hypopnea scoring rules (4A and 4B) $\geq$ 90% of the duration of the hypopnea event must fullfil the amplitude reduction criterion [61]. The AASM updated the hypopnea scoring requirements in 2012 such that a $\geq$ 30% amplitude decline in the airflow signal followed by either $\geq$ 3% desaturation or arousal would be sufficient to be recognized as hypopnea (table 2.2) [14]. Apnea-hypopnea index (AHI), which is the most commonly used parameter to estimate the severity of OSA, is defined by the total number of the scored apneas and hypopneas normalized by total sleep time [3, 61].

In adults, OSA is diagnosed if the patient has AHI $\geq$ 5 events per hour with related symptoms or a psychiatric or medical disorder [132]. Alternatively, AHI $\geq$ 15 events per hour is sufficient to diagnose OSA even without related symptoms or disorders [132]. Currently, the prevalence of OSA (AHI $\geq$ 15) has been estimated to be 13.0% and 5.6% among 30-70 years old males and females, respectively [112]. However, more recently, Heinzer et al. reported

that the prevalence of OSA could be even higher; 49.7% in males and 23.4% in females with age of 40-85 years [52]. In Finland, it has been estimated that around 150 000 adults have OSA [71]. In addition, health care costs in Australia (20.1 million residents in 2004) related to sleep disorders were assessed as 7494 million U.S. dollars in 2004 [55]. Although OSA has already severe public health and economic consequences, its prevalence is expected to increase in future [44,169].

2.1 PATHOPHYSIOLOGY AND PATHOGENESIS

Currently, the pathophysiology of OSA is partially unknown and the pathogenesis is not fully understood. The structure of the upper airways (UA) is very complex and it participates in multiple physiological functions, for example speaking, swallowing, and breathing [137]. In most cases, frequent collapses of the UA (*i.e.* apneas or hypopneas) result from pathological changes in the UA structure and reduced activity of the pharyngeal dilator muscle. In addition, variations in the UA muscular neural activation, impairments of the UA functions and an increased arousal threshold level all further predispose the individual to UA obstructions. UA can be divided into three different sections, the nasopharynx, the oropharynx, and the hypopharynx (figure 2.1) of which the oropharynx is the region where the UA blockage most often occurs [90,129,137].

UA consists of several muscles and soft tissue but without supportive bony structures, it is prone to clog during sleep. Furthermore, a narrow UA is more susceptible to collapse compared to a wider one. It has been shown that when awake, OSA patients have a smaller UA size compared to patients without OSA [20, 59, 77] and that the variation of upper airway resistance from inspiration to expiration differs significantly between patients with different degrees of OSA severity [146]. The narrowing of the UA in OSA patients might be due to the fact that their lateral pharyngeal wall is thicker in comparison to healthy subjects [137]. In addition, it is well known that the majority of OSA patients are obese [170,171].

It has been reported that there is an increased amount of adipose tissue around the upper airways in patients with OSA leading to compression of UA [58, 141]. Furthermore, the size of the lateral parapharyngeal fat pads is elevated in obese OSA patients [141], which may further predispose these subjects to UA obstructions. This is supported by the fact that the collapsibility of UA is reduced due to weight loss and the related anatomical factors and the neuromuscular control are enhanced in OSA patients during weight loss [138, 151].

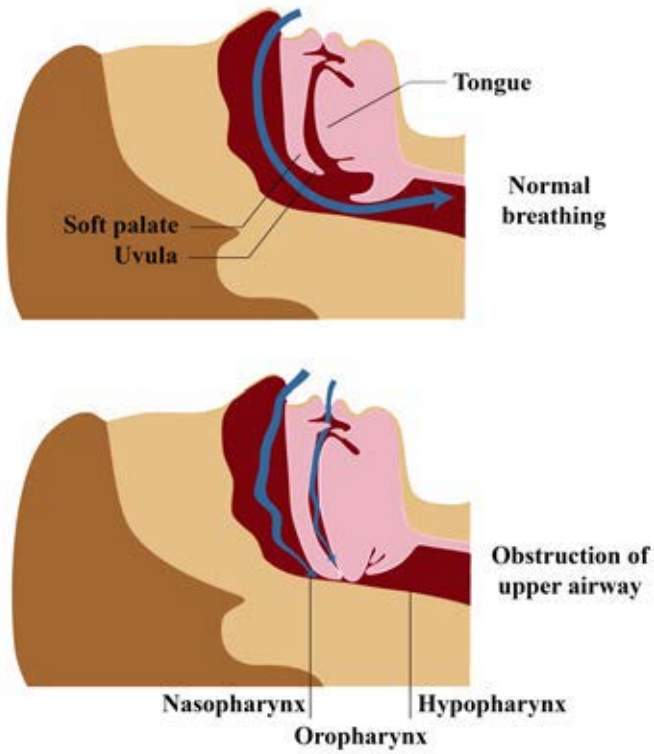

Figure 2.1: The upper airways (UA) can be divided into three different sections, the nasopharynx, the oropharynx, and the hypopharynx. In obstructive sleep apnea, the blockage of UA appears most often in the oropharynx. (Figure modified from [80]).

In patients with reduced pharyngeal size, increased negative airway pressure occurs in the UA during inhalation. This could stimulate pharyngeal muscle activity, leading to an expanded pharyngeal size maintaining airflow resistance at a sufficient level during wakefulness [90]. Therefore, it could be assumed that while awake, OSA patients would have higher UA muscle activity than patients without OSA. However, this muscle activity is diminished during sleep, leading to UA obstructions in patients with OSA [90]. Furthermore, the activity of UA muscles and structure of UA are different between males and females [136]. It has been shown that when awake females exhibit higher activity of genioglossal muscle (the most important pharyngeal dilator muscle in humans [23]) than males of similar age [120]. This is most probably due to fact that female sex hormones (possibly progesterone) may influence the activity of the genioglossus muscle [121]. In addition, the anatomy of the UA, especially the soft tissue structures, differs between genders [136]. Males seems to have a larger tongue, soft palate, and lateral pharyngeal wall in comparison to females [136]. Based on these facts, it would be expected that partial or complete collapses of the upper airways should be less common in females than in males during sleep.

While UA occlusions occur during sleep, a higher ventilatory effort is needed to keep open the upper airways. This increased ventilatory effort triggers a stress reaction resulting in arousal from sleep [19], which is an important mechanism ensuring that the pharynx will reopen [129]. Thus, it is assumed that increased ventilatory effort is the most important cause for the obstruction related arousals [45]. However, it has been shown that the arousal threshold level is increased by sleep apnea [15] which may indicate that stress reaction must be stronger in OSA patients than in patients without OSA in order that it triggers arousal and the subsequent reopening of the pharynx. Furthermore, individual obstruction event severity has been shown to increase with the severity of OSA [96] and longer apnea events increase the probability of the occurrence of long arousals (over 11 seconds) [103]. This could lead to a higher

degree of daytime sleepiness and cognitive impairment, especially in patients with moderate or severe OSA.

2.2 RISK FACTORS

Obesity (body mass index (BMI) ≥ 30 kg/m^2) is the most important independent risk factor for OSA and multiple studies have shown a strong relationship between overweight (BMI ≥ 25 kg/m^2) and OSA [32,158,169,171]. It has been estimated that $\geq 30\%$ of obese patients experience OSA and in the morbidly obese population (BMI ≥ 40 kg/m^2) the prevalence of OSA is very high (50-98%) [119,157]. In addition, it has been estimated that 60-90% of adults having OSA are overweight and the relative risk to develop OSA is over 10-fold in obese patients [119]. However, the connection between obesity and OSA is complex since the increased body weight can affect breathing in many ways. For example, the pharyngeal size can be reduced due to the increased amount of adipose tissue in the UA or its lateral walls [21, 135] and UA muscle force could be reduced or structure altered by increased adipose tissue deposited in the muscles [119]. Furthermore, the capacity of muscles to expand the pharynx may be reduced due to the altered shape of pharyngeal airway (towards a more oval shape) [79]. In contrast, Carrera et al. demonstrated that obesity did not influence either the structure or the function of the genioglossal muscle [23]. In addition, it has been proposed that waist circumference is a better estimator for OSA than BMI or neck circumference [49] while Stradling et al. examined over 1000 male patients; thay claimed that the severity of OSA, defined based on oxygen desaturation index (ODI), correlated best with neck circumference [149]. However, multiple studies have demonstrated the importance of fat accumulation in the abdomen, neck and especially in the pharyngeal area in contributing to the UA collapses due to the disturbed UA anatomy [119].

Men have between a two to four times higher prevalence of OSA compared to women [32, 150, 168]. Bixler et al. reported that 3.9% of men and 1.2% of women (age 20-100 years) exhibited AHI $\geq$

10 with daytime symptoms but they also found that menopause was an important risk factor of OSA in women [18]. The prevalence of OSA was only 0.6% in premenopausal women but more than quadrupled to 2.7% in postmenopausal women. However, hormone replacement therapy was found to reduce this risk *i.e.* OSA prevalence was 0.5% in postmenopausal women receiving hormone replacement therapy [18]. In addition to anatomical and functional differences in the upper airways between male and female patients (discussed in section 2.1), one possible explanation for increased prevalence of OSA among male patients might be due to the fact that females are less likely to report OSA related symptoms of snoring, gasping and apnea [127]. However, females do experience more often morning headaches, insomnia and depression than men [124]. As OSA is usually first recognized by a bed partner witnessing breathing cessations or possibly suspected by physician based on the patient's risk factors and symptoms [56], the majority of female patients might remain undiagnosed and untreated. In addition to different clinical expression of OSA between genders, family lifestyle and sociocultural factors are reasons why OSA may be more likely to remain underdiagnosed in women [124].

Sleeping position is known to have an effect on the severity of OSA. Supine predominant OSA is defined such that overall AHI must be at least 5 events per hour and supine AHI is at least twice as high as non-supine AHI [107]. In addition to these factors, if a patient has also non-supine AHI < 5, the patient is classified as having supine isolated OSA [82]. It has been estimated that in OSA patients, the prevalences of supine predominant OSA and supine isolated OSA are 50-60% and 25-30%, respectively [67]. In addition, Oksenberg et al. reported that during six years follow-up, patients with supine predominant OSA who converted to become non-positional patients displayed a significant increase in AHI (mean $\pm$ SD change: 33.1 $\pm$ 20.9 events/hour) [104]. On the contrary, the finding was opposite in the non-positional OSA patients who converted to supine predominant OSA (AHI decreased by (mean $\pm$ SD) 6.8 $\pm$ 24.8 events/hour) [104]. Moreover, supine isolated OSA

patients have been shown to have statistically significantly higher risk ratios of mortality and cardiovascular morbidity compared to non-supine OSA patients [74].

In addition to obesity, male gender and sleeping position, several other risk factors may affect OSA progression and development. Smoking increases sleep instability, which is further associated with sleep disordered breathing, and it has been shown that OSA is three times more common in smokers compared to non-smokers [162]. Even modest use of alcohol before sleeping has been shown to lead to a significant increase in AHI [134]. In addition, age is one of the risk factors of OSA *i.e.* younger patients have fewer apnea events than their older counterparts [160]. Furthermore, cardiovascular diseases are very common in patients having nocturnal breathing disorders [148] and therefore, heart failure, hypertension, stroke, atrial fibrillation, and type 2 diabetes are recognized risk factors for OSA [38, 40, 148].

2.3 EPIDEMIOLOGY AND SYMPTOMS

While it is unclear whether OSA is a progressive disease which develops over time, it has been shown that the severity of OSA increases with time [100,113,128,131,169], although conflicting results have also been reported [4, 39, 57]. In fact, the progression of OSA is more strongly related to changes in weight than with time from diagnosis or age [4, 13, 113]. Berger et al. reported that a weight increase exerted an almost seven times greater effect on AHI than time [13].

In its early stages, most of the patients are not aware of having OSA as the majority of the symptoms occur when thay are asleep. Therefore, OSA is usually first suspected by a bed partner. In addition, recognition of OSA might be troublesome as there is a huge variety in symptoms between individuals. Many of the symptoms (*e.g.* snoring and daytime sleepiness) are prevalent also in patients not having OSA.

2.3.1 Daytime symptoms

Excessive daytime sleepiness is the most common symptom of OSA and is due to sleep fragmentation [12]. However, the level of sleepiness experienced by a patient is highly subjective and varies significantly between individuals. Vgontzas et al. reported that only modest sleepiness may be experienced by patients with a high AHI while patients with a low AHI might complain of significant daytime sleepiness [159]. Instead of daytime sleepiness, patients may more often report vague symptoms like fatigue, tiredness, or lack of energy [28]. In the long term, individuals may become accustomed to sleepiness or tiredness which can lead to impairment in cognitive functions. This might partially explain why OSA has been linked to an increased risk of motor vehicle accidents, especially in patients with moderate to severe OSA [34, 60]. Furthermore, OSA patients have been reported to have significantly impaired quality of life and elevated prevalence of psychiatric morbidities (*e.g.* depression) which may be related to sleepiness or reduced mood and motivation [34]. In addition, the prevalence of morning headaches is estimated to be as high as 74% among patients with OSA and its occurrence is significantly correlated with the severity of OSA [2]. However, in OSA patients, headaches are more likely related to the cerebral hemodynamic effects of hypoxia or hypercapnia rather than to the sleep disturbances *per se* [30].

2.3.2 Nocturnal symptoms

Snoring is a common symptom in OSA patients as it has been reported that the vast majority (96%) of patients with a snoring problem have OSA [68]. However, snoring is not a reliable parameter to diagnose OSA because a lean patient with mild snoring is unlikely to suffer from moderate or severe OSA [97]. In addition, nocturia is common in OSA patients, especially in women. It has been shown that in OSA patients, 60.0% of females and 40.9% of males suffer from nocturia and that AHI is a significant predictor of nocturia (independently of BMI and co-morbidities) [53]. This is due to fact

that frequent UA blockages increase negative pressure in the thorax leading to atrial stretch causing a false signal of fluid overload in the heart. Subsequently, atrial natriuretic peptide is produced due to compensatory response of the heart, resulting in elevated urine production by the kidneys [27]. Furthermore, even though OSA patients may complain of excessive daytime sleepiness, 39% of OSA patients suffer from insomnia and the severity of insomnia increases with increasing severity of OSA [145]. The prevalence of a dry mouth upon awakening, which is not considered as a common symptom of OSA but is still prevalent in OSA patients (31.6%), has been shown to be doubled in patients with OSA compared to habitual snorers (16.4%) [105]. Furthermore, this prevalence increases with an increasing severity of OSA, being relatively high (40.7%) among the patients with severe OSA [105]. Some other nocturnal features are also related to OSA *e.g.* nocturnal gasping or choking [97], restless sleep (especially in children) [26], gastro-oesophageal reflux [33], and nocturnal sweating [5].

2.4 MORTALITY AND CO-MORBIDITIES

Patients with untreated severe OSA have a higher risk of cardiovascular mortality compared to untreated patients with mild or moderate OSA [85]. Similarly, several studies have confirmed the increased mortality among untreated OSA patients [87, 123, 163, 165]. In addition, the hazard ratio of overall mortality (hazard ratio 3.13) has been shown to be significantly higher in patients with moderate to severe OSA compared to patients without OSA (hazard ratio 1.0) even after adjustment for age, BMI, and smoking [93]. In all these studies, the severity of OSA was defined based on conventional AHI. However, Muraja-Murro et al. revealed that risk ratios of overall mortality and cardiovascular mortality are higher (3.08 and 3.29 versus 2.14 and 2.18, respectively) in patients with moderate or severe OSA when the severity of OSA had been determined based on a novel adjusted-AHI parameter (table 4.3), instead of the conventional AHI assessment [94].

2.4.1 Cardiovascular morbidities

Cardiovascular diseases (CVD) are independently associated with obstructive sleep apnea, especially in patients with moderate to severe OSA [9]. It has been shown that OSA is more common in individuals with CVD compared to the general population [168]. However, the mechanisms connecting OSA to CVD are not fully understood. This is not only due to the complexity of OSA but also to the presence of obesity, which is strongly linked to both OSA and cardiovascular health [9]. In OSA, there is elevated sympathetic activity due to upper airway blockage resulting in an increase in negative intrathoracic pressure. This, together with elevated left ventricular afterload, increases right ventricular return and, therefore, preload. In addition, pulmonary vasoconstriction caused by hypoxia leads to an elevated right ventricular afterload and distension resulting in a reduced left ventricular preload. This further decreases cardiac stroke volume [9]. These frequent changes in myocardial functions could weaken ventricular function in OSA [9] and subsequently contribute to the induction of cardiovascular comorbidities. Figure 2.2 illustrates the possible pathophysiological mechanisms which may be involved in the link between OSA and CVD.

The incidence of hypertension, independently of other cardiovascular diseases, is strongly associated to OSA [102]. It has been proposed that changes in blood pressure and increased sympathetic activity induced by apnea or hypopnea events could cause hypertension [114]. It has been reported that the risk of hypertension increases with increasing the severity of OSA and patients with moderate or severe OSA have a three times higher risk of suffering hypertension compared to patients without OSA [48,114]. In addition, OSA is rather common among stroke patients *i.e.* as many as 72% of stroke patients have been reported to have at least mild OSA [66] and that the risk of stroke is significantly elevated by OSA [165]. The elevated risk of stroke or death (hazard ratio 1.97) in patients with OSA was reported to be statistically significant after adjust-

ment for age, gender, race, smoking, alcohol consumption, BMI, and co-morbidities (*i.e.* diabetes, hyperlipidemia, atrial fibrillation, and hypertension) [165]. This indicates that OSA increases the risk of stroke and mortality independently of other risk factors such as hypertension [165].

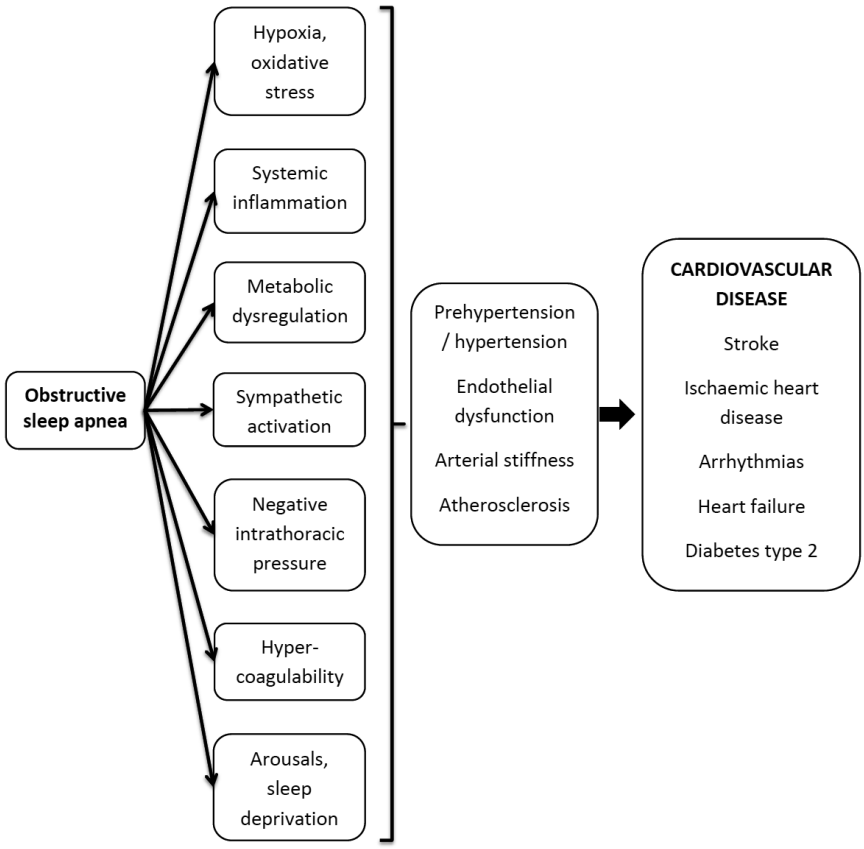

Figure 2.2: Possible pathophysiological mechanisms which may causally link obstructive sleep apnea to cardiovascular disease. (Figure modified from [9]).

Severe OSA has been reported to increase the risk of coronary heart disease by 68% in 40 to 70 year old males but not in females [47]. In contrast, Xie et al. reported that OSA was not significantly connected to ischemic heart disease in the general population [164] but in patients with ischemic heart disease OSA is a common finding [164,172]. Furthermore, 66% of the patients with acute coronary syndrome were reported to have AHI > 20 events per hour [9]. OSA is also an independent predictor for heart failure in males but not in females [47]. It has been shown that men with severe OSA display a higher (+58%) risk for heart failure compared to men without OSA [47]. However, the link between OSA and heart failure might be bidirectional as heart failure affects ventilatory control periodically decreasing pharyngeal dilator muscle function which may further lead to OSA [47]. In addition, it has been reported that patients with respiratory disturbance index (RDI) $\geq$ 30 have almost a four fold elevated risk of experiencing atrial fibrillation, a three fold risk of nonsustained ventricular tachycardia, and a two fold risk of ventricular ectopy compared to patients with RDI < 5 after adjustment for age, gender, BMI, and coronary artery disease [88].

Obstructive sleep apnea has been associated with insulin resistance and reduced glucose tolerance [62]. Hypoxia causes glucose intolerance [108] but elevated insulin resistance may also contribute to the development of glucose intolerance [126]. These are also risk factors of type 2 diabetes which is further connected to OSA. It has been reported that the prevalence of type 2 diabetes is increased in male patients with OSA [155] and similarly, that the prevalence of OSA may be increased in patients with type 2 diabetes [25]. However, despite the strong association between OSA and type 2 diabetes, the majority of the patients with type 2 diabetes may remain undiagnosed for OSA [25,40].

2.4.2 Non-cardiovascular morbidities

OSA has been shown to have connections to various non-cardiovascular morbidities. As OSA causes hypoxia and nocturnal hypoxia is connected with an elevated risk of cancer [22] this might explain

increased cancer mortality in OSA patients [22, 101]. Nieto et al. reported that the hazard ratio of cancer mortality was 1.1, 2.0, and 4.8 in patients having mild, moderate, and severe OSA, respectively after adjustment for age, gender, BMI, and smoking habits [101]. In addition, OSA patients commonly suffer from headaches, morning headaches, and cluster headache [42]. As snoring is a common symptom in patients with OSA, the link between OSA and headaches might be partially due to fact that morning headaches are very common in habitual snorers [42]. However, these findings are not supported by all studies *i.e.* Jensen et al. reported no relationship between sleep-disordered breathing and morning headaches [63] and Kristiansen et al. reported no relationship between OSA and migraine [70].

Epilepsy has been associated with OSA but this relationship may be bidirectional. It has been reported that 49% of patients with epilepsy have at least mild OSA [116]. In contrast, periodical hypoxia and changes in sympathetic activity are general problems in OSA patients which may further activate epileptogenic regions of the brain, and predispose to seizures [83]. Furthermore, the prevalence of depression (7-63%) and anxiety (11-70%) is high in patients with OSA [133]. Depression is more common among females than males and age may have an effect on occurrence of mood disorders as menopausal females have been shown to experience depressive symptoms more often than premenopausal females [133].

2.5 DIAGNOSTICS AND MEASUREMENTS

Currently, the diagnosis of OSA is recommended to be based on full overnight in-laboratory polysomnographic (PSG) recording [29] including registration of electroencephalography (EEG), electro-oculography (EOG), chin and leg electromyography (EMG), electrocardiography (ECG), oronasal airflow, oxygen saturation (SpO_2), breathing effort related movements, sleeping position, and snoring. In most modern sleep laboratories, full night video recording is recorded alongside PSG. However, conducting PSG recordings in

a sleep laboratory is expensive requiring trained staff and therefore, is not available for all patients. In addition, some patients sleep restlessly due to the unfamiliar sleeping environment [11]. For these reasons, more compact ambulatory monitoring devices have been developed and used since the late 1980s [110]. Compared to the standard PSG, ambulatory devices are beneficial due to their lower costs and better availability. Patients also sleep better during the recording as it can be conducted in their home. In contrast, ambulatory recordings may underestimate AHI due to lack of EEG since without EEG, total sleep time cannot be measured accurately and hypopneas followed by arousal cannot be detected. However, ambulatory polygraphic recording devices have been shown to be sufficiently accurate for the diagnosis of OSA and that they can be safely used as an alternative to PSG [29]. It has been suggested that combining clinical symptoms and risk factors with overnight registration of oxygen saturation would be sufficient for initial discrimination of the suspected OSA patients [11]. For the screening and estimation of OSA severity, methods based on a recording of breath sounds when awake have been introduced and tested with excellent results [81,91]. Furthermore, a snore sound based method for screening of OSA has been introduced and shown to be accurate in the detection of OSA [1,7]. Due to different recording devices incorporating different number of recorded signals, Task Force of the Standards of Practice Committee of the American Sleep Disorder Association defined specifications for four types of monitoring devices (table 2.1) [37].

Table 2.1: Classification and specifications of monitoring devices for the diagnostics of sleep apnea [37]. The signals which are required to be measured, but not limited to, with each device type are represented. (Table modified from [16, 92]).

	Type I	**Type II**	**Type III**	**Type IV**
Depiction	attended standard PSG, recorded in a sleep center	ambulatory unattended complete PSG	ambulatory recording only for sleep apnea diagnostics	ambulatory continuous single or dual channel recording, not recommended
Channels	$\geq$ 7 channels: EEG, EOG, EMG, ECG, airflow, respiratory effort, SpO_2	$\geq$ 7 channels: EEG, EOG, EMG, ECG or HR, respiratory effort, airflow, SpO_2	$\geq$ 4 channels: ECG or HR, respiratory effort, airflow, SpO_2	$\geq$ 1 channel: respiratory effort, airflow, or SpO_2
Body position	documented or measured objectively	optional	optional	no

PSG = polysomnography, EEG = electroencephalography, EOG = electro-oculography, EMG = electromyography, ECG = electrocardiography, SpO_2 = oxygen saturation, HR = heart rate

The American Academy of Sleep Medicine (AASM) stated in 2007 that portable recording devices could be used for the diagnosis of OSA and provided detailed recommendations for ambulatory polygraphic recordings and analyses (AASM 2007) [29]. AASM updated these recommendations in 2012 (AASM 2012) the most significant change being in the hypopnea scoring criteria. The AASM 2012 recommendations allow scoring hypopnea with related 3% oxygen desaturation instead of 4% desaturation limit applied earlier [14, 61]. However, different sleep centers have adopted these new recommendations in different timeframes and at the moment, the AASM 2012 recommendations are still more rarely used than those published in 2007. It has been shown that by applying the AASM 2012 recommendations, the value of AHI is increased significantly [98]. Therefore, the classification of patients into OSA severity categories can differ between hospitals and sleep centers using different scoring criteria and therefore, the diagnosed sever-

ity of OSA may not be comparable [98]. In addition, insurance companies have been dissatisfied with the updated scoring criteria due to increased insurance premiums [98]. The AASM recommendations are summarized in table 2.2.

Table 2.2: Diagnostic criteria for respiratory events defined by American Academy of Sleep Medicine in 2007 and 2012 [14, 61]. (Table modified from [92]).

Event	**Sensor**	**Amplitude drop**	**Duration**	**Related SpO_2 drop**	**Respiratory effort**	**EEG arousal**
apnea	oronasal thermistor	$\geq$ 90%	$\geq$ 10s			
obstructive central mixed					entire period none latter part of the event	
hypopnea	nasal pressure	$\geq$ 30%	$\geq$ 10s	$\geq$ 4%		
		$\geq$ 50%	$\geq$ 10s	$\geq$ 3%		
		$\geq$ 50%	$\geq$ 10s			yes
hypopnea*	nasal pressure	$\geq$ 30%	$\geq$ 10s	$\geq$ 3%		
		$\geq$ 30%	$\geq$ 10s			yes
RERA	nasal pressure	flattening	$\geq$ 10s			effort related
RERA	thoraco-abdominal RIP belt		$\geq$ 10s		increased	effort related

Hypopneas can be classified to be obstructive or central type. An obstructive hypopnea requires snoring during the event, increased respiratory flattening of the pressure signal or out of phase movement of thorax and abdomen. To score a central hypopnea, none of these criteria are met.
The recommendations updated in 2012 are marked with an asterisk.
SpO_2 = oxygen saturation, EEG = electroencephalography, RERA = respiratory effort related arousal, RIP = respiratory inductance plethysmography

The diagnosis of OSA is based on the number of apneas and hypopneas per hour of sleep (*i.e.* AHI) with related symptoms or disorders [3]. In adults, the diagnosis of OSA requires AHI $\geq$ 5 either with symptoms (*e.g.* excessive daytime sleepiness, fatigue, snoring or observed apneas) or medical or a psychiatric disorder (*e.g* hypertension, coronary artery disease, or mood disorder) [132]. In addition, AHI $\geq$ 15 is sufficient to diagnose OSA even without any associated symptoms or disorders [132]. Alternatively, the number of oxygen desaturations per hour of sleep (oxygen desaturation index, ODI) can be used as a diagnostic parameter [3]. In contrast to AHI and ODI, Herath et al. reported that snoring sounds differ between OSA patients having AHI < 15 or AHI $\geq$ 15 and that the distibutions of snore episode could be used to estimate the severity of OSA [54]. In addition to the frequency of abnormal respiratory events per hour of sleep, the severity of OSA is assessed also based on the severity of sleepiness [3]. It has been recommended that the severity classification of OSA should include both of these aspects and be based on the most severe component [3]. Table 2.3 summarizes the classification criteria.

Table 2.3: Criteria for severity classification of obstructive sleep apnea [3].

Severity	**Sleepiness**	**AHI**
Mild	during activities requiring little attention (*e.g.* watching TV/reading), minor impairment of social life, not a daily problem	5 $\leq$ AHI < 15
Moderate	during mild physical activities requiring moderate attention (*e.g.* concerts/movies), moderate impairment of social life, a daily problem	15 $\leq$ AHI < 30
Severe	during physical activities requiring moderate attention (*e.g.* driving/walking), marked impairment of social life, a daily problem	AHI $\geq$ 30

It has been suggested that the apnea index (AI) was first coined by Guilleminault et al. [50] in the 1970s and then adopted by other research groups in the early 1980s [139]. The apnea index was subsequently replaced by AHI and since 1983 it has been also known by another self-explanatory name, the respiratory disturbance index (RDI) [139]. Despite the worldwide usage of AHI to approximate the severity of OSA in clinical practice and research, it has several limitations. First, all definitions for obstruction events and thresholds of severity categories of OSA (*i.e.* mild-moderate-severe) are arbitrary [111]. Perhaps for these reasons, although AHI helps when estimating the severity of OSA, it has been claimed that researchers accepted AHI too quickly as a standardized measure and that it is not necessarily a perfectly optimized parameter for this purpose [139]. For instance, AHI counts all apneas and hypopneas as identical events but does not take any account of the event type or duration. However, one could claim that a 60 second long complete cessation of breathing would be much more detrimental than a 20 second period of shallow breathing. In addition, OSA is linked to daytime sleepiness but so is the amount of sleep. Therefore, AHI where the denominator is sleep duration, might not be an optimal parameter with which to estimate the relationship between OSA and daytime sleepiness [139]. Furthermore, AHI is dependent on several physiological and technical factors, for example, sleeping position [24, 89], sleep stage [115, 143], scoring rules [31, 98], and quality of recorded signals [152]. These factors also influence the severity of individual obstruction events [111].

Currently, it is not clear why the number of respiratory events per hour of sleep would be a better estimate for OSA severity than, for example, total number and type of respiratory events [139], the total duration of respiratory events [96], or some other proposed parameters (*e.g.* obstruction severity, adjusted-AHI, or sleep apnea severity index) [8, 76, 94]. Our research group has previously introduced novel parameters termed as obstruction severity and adjusted-AHI, which take into account the number and severity of individual obstruction events (table 4.3). We have shown that these

parameters can provide supplementary information useful in the diagnostics of OSA and thus enhancing the estimation of the severity of OSA. The obstruction severity parameter has been shown to be more strongly linked to increased cardiovascular morbidities and mortality rate in patients with OSA compared to the conventional AHI [95]. In addition, risk ratios of overall mortality and cardiovascular morbidity were higher in patients with moderate or severe OSA when the severity of OSA was judged based on adjusted-AHI instead of its conventional counterpart [94]. This indicates that adjusted-AHI might improve the recognition of OSA patients with an elevated risk for severe OSA related health consequences. Furthermore, adjusted-AHI (table 4.3) has been shown to be more stable parameter compared to conventional AHI when different oxygen desaturation threshold (ODT) levels are used in hypopnea scoring [98]. In addition to our novel parameters, sleep apnea severity index (SASI) was proposed by Piccirillo et al. and further evaluated by Balakrishnan et al. through a cross-sectional study [8,117]. SASI incorporates physical, functional, and polysomnographic severity indices, as illustrated in figure 2.3. Balakrishnan et al. reported that SASI was a statistically significantly better ($p < 0.001$) estimator for sleep apnea specific quality of life, vitality status and sleep quality compared to AHI even though AHI was more strongly correlated with 3% desaturation index and mean arterial pressure [8].

It has been stated that AHI is useful at its low and high values and that it is applicable to estimate the occurrence of OSA as a high AHI is an obvious sign of the disease [125]. However, it is not as useful in the middle zone (*i.e.* $5 < \text{AHI} < 30$) [125]. There is no doubt that a patient with an extremely high AHI has severe disease and the probability of OSA related severe health consequences is higher than in patients with low AHI. However, the estimation of severity of OSA should be made more accurate in those patients with mild to moderate OSA in order to prevent harmful consequences of the OSA and to target the limited treatment resources to those with the greatest need. It has been stated that AHI is "the best we can do" to diagnose OSA, to estimate the patients' long-term conse-

quences and effect of the treatments [125]. However, AHI assumes that all apneas and hypopneas have equal physiological effects and all hypopneas exceeding the desaturation threshold are considered as being biologically equivalent without considering the depth of the related desaturation [122]. Furthermore, AHI do not take into account the duration of the obstruction events and whether they occur in clusters or are evenly spaced across the night [122]. For these reasons, it has been claimed that AHI should be considered as only a crude and inaccurate metric of OSA [122].

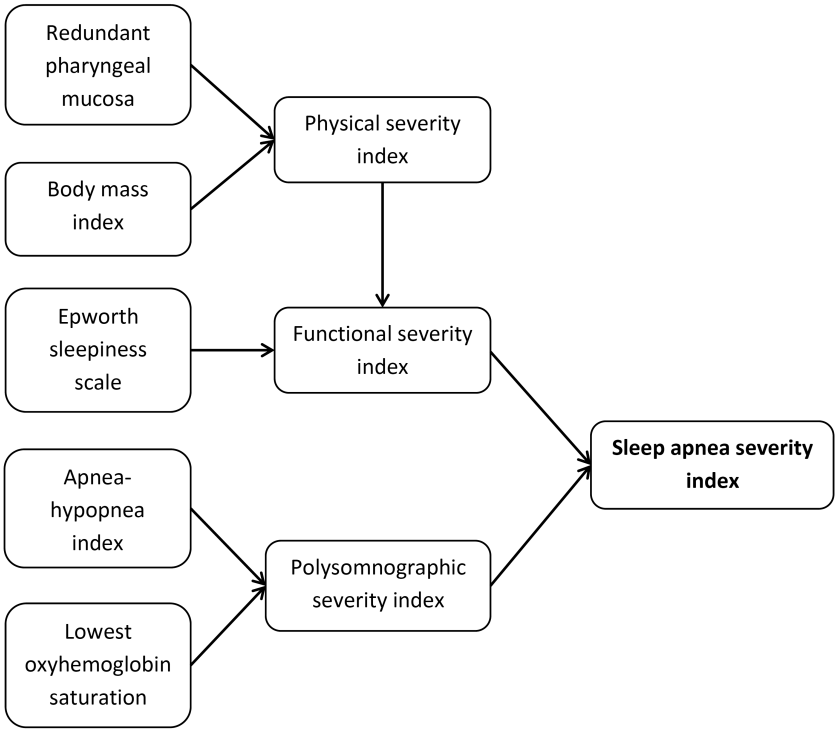

Figure 2.3: Schematic presentation of definition of the sleep apnea severity index (SASI). (Figure modified from [8]).

Although AHI has several limitations, it is not totally useless and previous studies that used AHI must not be ignored. However, researchers should be aware of the fact that AHI includes bias when it is used to assess the severity of OSA [139]. It can be compared to a situation where the amount of body fat is estimated based on BMI (elevated BMI does not always indicate that the subject is obese). Furthermore, as a clinically useful parameter may not be optimal for biomedical science [139], it should always be stated explicitly what is being measured with a derived variable. At the moment, this is far from clear with AHI. Therefore, AHI as a measure of severity of OSA should and needs to be challenged and questioned.

2.6 TREATMENT

Continuous positive airway pressure (CPAP) is the most commonly used treatment for OSA. However, it is only provided for the patients with moderate to severe OSA or patients with mild OSA with associated severe symptoms. In CPAP treatment, air is gently blown at low pressure to the upper airways by CPAP device through a mask inserted on the patient's face (figure 2.4). The flow of air prevents upper airway occlusions further reducing intrathoracic pressure and stabilizing heart functions [43, 92]. It has been reported that the risk of lethal cardiovascular events is lower in patients treated with CPAP compared to untreated patients [85]. In addition, CPAP has been shown to reduce blood pressure and decrease the risk of hypertension over the long term [10,84]. However, CPAP is not suitable for all patients. It has been reported that the adherence rate of CPAP treatment is only 30-60% [161]. This is its major limitation, decreasing the effectiveness of the CPAP treatment [130,161]. Despite the counseling of the patients and improvements made to these devices, the adherence of CPAP treatment has not improved during the most recent decades [130]. This might be partially due to the fact that some patients experience discomfort wearing the mask and find it hard to tolerate its presence [144]. The mask might leak and cause pressure ulcers or claustrophobia [144].

Figure 2.4: Examples of masks used in CPAP treatment. Air is driven into the upper airways with low pressure through the mask.

However, the adherence of the CPAP treatment appears to be a complex and multifactorial problem which still needs more research in order that it can be better understood.

As obesity is one of the most important risk factors of OSA, weight reduction is an effective treatment for OSA [156]. It has been reported that even a minor, 3-18%, weight reduction combined with a healthy diet and improved lifestyle can lead to 3-62% decrease in AHI [156]. In addition to the fact that weight reduction and increased physical activity mitigate OSA related symptoms, they are important factors in the treatment and prevention of the metabolic syndrome as well as being beneficial to improving general wellbeing [156]. Furthermore, weight loss has a positive effect on cardiovascular disease and type 2 diabetes, both of which are connected to OSA [154, 156]. Previously, it has been shown that a higher level of weight reduction leads to a greater reduction in AHI and decreases the severity of individual obstruction events more effectively than

a lower level weight loss [72]. However, the effect of weight loss on AHI differs according to the patient's sleeping position [73]. In the supine position, the weight loss decreases mainly the number of shorter apnea and hypopnea events while in the non-supine position, the effect is more focused on the most severe respiratory events [73].

Positional therapy, in which patient tries to avoid sleeping in the supine position, has been shown to be effective treatment for patients with positional OSA [35]. Although positional therapy has been claimed to decrease AHI by 15-53%, it is still less effective than CPAP treatment [51]. Devices used in positional therapy include, for example, alarm systems, pillows and tennis balls [35]. The so-called tennis ball therapy is the one of the oldest and simplest treatment methods in which a tennis ball is mounted onto the patient's back using a belt or a strap to prevent him/her sleeping in a supine position [17].

Several other methods and devices have been introduced to treat OSA, for example, autotitrating positive airway pressure (APAP), oral appliances, and different forms of surgery. The operating principle behind an APAP device is the same as utilized in CPAP except that air pressure is not constant with respect to the amount of air being forced into the upper airways [6]. The air pressure is automatically adjusted based on patient's needs; during an upper airway obstruction, the device increases air pressure and when no obstructions occur, the APAP device reduces its airflow. APAP has been shown to be as effective as CPAP, but it is much more expensive [6]. In patients who cannot be treated with CPAP, oral appliances may be used. The most commonly used oral appliances are mandibular advancement devices (MAD) which increase the upper airway size by relocating the pharyngeal fat pads laterally and tongue base muscle anteriorly [86]. However, the oral appliances are not as effective as CPAP in eliminating abnormal breathing events, even though the effect of MAD and CPAP on daytime cardiac autonomic function has been claimed to be similar [46]. Furthermore, MADs may cause pain in the teeth and jaws [86]. In patients with severe

obesity, bariatric surgery may be an option as it has been shown to achieve a significant decrease in AHI [156]. Furthermore, other surgical procedures (*e.g.* uvulopalatopharyngoplasty (UPPP) and repositioning of genioglossal muscle), which are focused on modifying dysfunctional pharyngeal anatomy, can be performed in order to prevent upper airway blockages. Regrettably, the effect of surgical methods diminishes with time, leading to poor long-term results [142].

3 Aims of the thesis

Currently, the diagnosis of OSA is based on medical and physical examination and overnight polygraphic registration. The most commonly used diagnostic parameter, AHI, does not include information on the severity of individual obstruction events. AHI decreases after the patient loses weight, is elevated if he/she sleeps in a supine position, and is higher in male than in female patients. In this thesis, the severity of OSA was investigated from a novel perspective taking into account not only the number but also the severity of individual obstruction events. The main aims of the present thesis are to demonstrate that the severity of OSA depends on several factors, not only on the number of the events, and to devise an upgraded clinical tool for enhanced diagnostics of OSA.

The specific aims of this thesis were:

1. To explore the effect of weight loss on the characteristics of individual apnea, hypopnea, and desaturation events.
2. To evaluate the effect of sleeping position on the duration and morphology of individual obstruction events in different OSA severity categories.
3. To study whether the severity of individual obstruction events is increased as the severity of OSA worsens.
4. To investigate the connection between gender and the severity of individual obstruction events in all OSA severity categories.
5. To examine the potential of utilizing the adjusted-AHI parameter to discriminate OSA patients with the highest risk for related mortality and cardiovascular morbidities.
6. To create a RemLogic plug-in which would make adoption of these novel parameters more convenient for clinicians.

4 Patients and methods

This thesis consists of four studies (**I-IV**). In all studies, custom-made MATLAB (Mathworks, Natick, MA, USA) functions were used to calculate the durations of individual apneas and hypopneas as well as the durations, depths, and areas of individual desaturation events in addition to the novel parameters introduced in section 4.3 (table 4.3). The effects of weight reduction (study **I**), sleeping position (study **II**), and gender (study **III**) on the characteristics of individual obstruction events were evaluated. In study **IV**, the adjusted-AHI parameter (table 4.3) was used to classify patients into the different OSA severity categories and then mortality and cardiovascular morbidities were compared between the OSA severity categories formed based on either conventional AHI or adjusted-AHI. Furthermore, to encourage the clinical use of the novel parameters, a plug-in was written so that it could be incorporated into widely used polysomnography software, RemLogic (Embla, Thornton, MA, USA).

4.1 PATIENTS AND STUDY POPULATIONS

All studies were performed using ambulatory polygraphic devices. In study **I**, subjects (n = 87) were recruited among patients studied (in 2004-2009) in outpatient clinics of Otorhinolaryngology or Respiratory Medicine at Kuopio University Hospital due to a clinical suspicion of OSA. Patients underwent polygraphic recordings at the baseline and after two years' follow-up. Anthropometric data were collected and patients filled in the Epworth Sleepiness Scale (ESS) questionnaire [65] at both time points. The patients were divided randomly into control and intervention groups at the baseline. The patients in the intervention group received one year of lifestyle guidance starting with a 12-week very low calorie diet. The patients in the control group received only general information on exercise and diet. The study participation was confirmed by patients who

signed the informed consent form. After the follow-up, the original groups were combined and patients were redivided into two new subcategories: control group (weight loss < 5% or weight gain) and weight loss group (weight loss > 5%). In studies **II, III,** and **IV** all ambulatory recordings (n = 2057 conducted in 1992-2003) were initially analyzed in the Department of Clinical Neurophysiology, Kuopio University Hospital and then reanalyzed during the years 2012-2015. The features of the patient populations are summarized in table 4.1. Basic background information (*e.g.* age, BMI, smoking), treatments, medications, and cardiovascular morbidities were acquired from patient medical records collected in Kuopio University Hospital. In addition, in study **IV**, the causes of death were obtained from Statistics Finland (Helsinki, Finland) in June 2014. The study protocols of these studies were given a favourable statements by the Research Ethics Committee of the Hospital District of Northern Savo, Kuopio, Finland (decision numbers 127/2004 and 24/2013).

In study **I**, inclusion criteria were 1) age $\geq$ 18 years, 2) BMI 26-45 kg/m^2, and 3) AHI $\geq$ 5 events/h. In total, 87 patients fulfilled these criteria and were included in the study. However, four patients were excluded at the baseline and five patients after two years' follow-up due to technically partially failed polygraphic recordings. In addition, eleven patients dropped out during the follow-up. In study **II**, from the original group of 2026 patients 526 patients were included into the study. Eleven patients had to be excluded due to the lack of the information on their sleeping position. In the further analysis, 60 minutes of recorded time in both supine and non-supine positions were required (552 patients excluded). Furthermore, 937 patients were excluded because they have not had apnea, hypopnea or desaturation events in both supine and non-supine positions. In study **III**, all patients of the original patient population (n = 2057) with AHI $\geq$ 5 events/h (n = 1090) were included into the study. In study **IV**, 1459 working-age (age 20-68 years) men were reanalyzed and 331 patients were excluded since they had been prescribed continuous positive airway pressure treatment. In addition, one hun-

dred polygraphic recordings were randomly chosen from among the 1459 recordings to test the accuracy of the plug-in. The accuracy of the plug-in was tested by calculating the values of adjusted-AHI for these hundred randomly chosen patients using MATLAB functions and the plug-in. Furthermore, the correlation and mean ($\pm$SD) difference of the values calculated with these two different methods were investigated.

Table 4.1: Patient demographics in studies **I-IV**.

Study	Original patient population (*n*)	Included patients (*n*)	Number of males / females	Age range (years)	BMI range (kg/m^2)
I	87	67	50/17	33-69	26.0-41.4
II	2026*	526	466/60	21-81	19.9-55.8
III	2057	1090	893/197	21-84	18.7-74.0
IV	1459*	1128	1128/0	20-68	17.5-74.0

*Subgroup of patients (n = 2057) used in study **III**

4.2 POLYGRAPHIC RECORDING DEVICES

In study **I**, polygraphic recordings were conducted using ambulatory Embletta (Embla, Broomfield, CO, USA) devices in the patients' own homes. Embletta records oronasal airflow, peripheral blood oxygen saturation, respiratory movements of thorax and abdomen, snoring, heart rate and sleeping position (prone, left, supine, right) (figure 4.1a and table 4.2). In studies **II-IV**, all polygraphic recordings were performed using an in-hospital made (designed by Hospital Physicist Pekka Tiihonen, Ph.D.) four-channel polygraphic device, *"Unisalkku"*, which incorporates recording of oronasal airflow, respiratory efforts, sleeping positions, and arterial oxygen saturation (figure 4.1b and table 4.2).

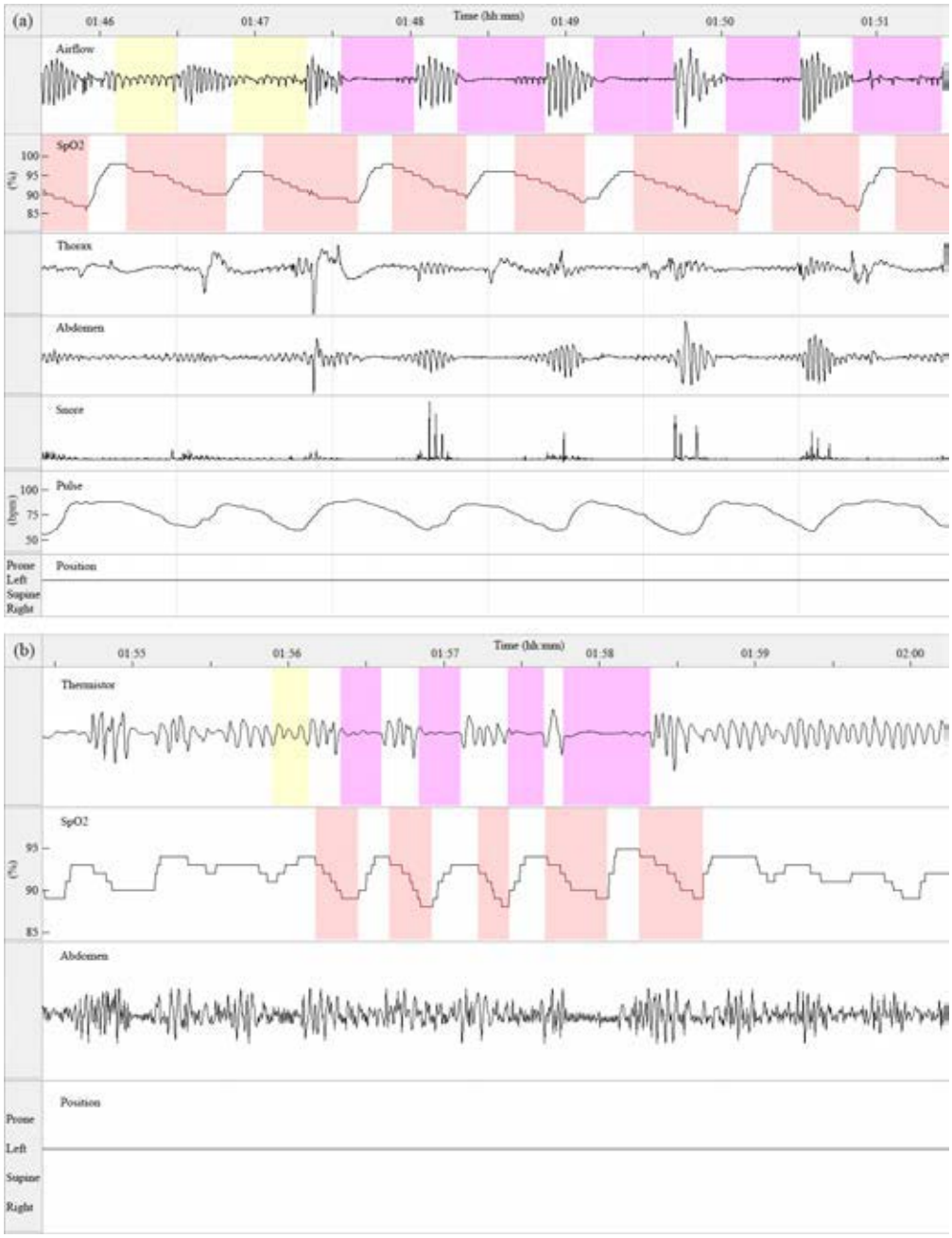

Figure 4.1: Example of signals recorded with Embletta (a) and Unisalkku (b) devices. After automatic analysis, the lengths of all detected obstruction events were visually inspected. Hypopnea, apnea, and desaturation event are scored with yellow, purple, and pink colors, respectively.

Table 4.2: Summary of the ambulatory recording devices used in this thesis. (Table modified from [153]).

	Unisalkku	**Embletta**
Airflow	Oronasal thermistor	Nasal pressure sensor + oronasal thermistor
Blood oxygen saturation (SpO_2)	Minolta Pulsox 7	Nonin XPOD 3012
Respiratory movements **Thorax** **Abdomen**	 - Piezoelectric sensor	 Piezoelectric belt Piezoelectric belt
Sleeping position	Gravitionally sensitive tilt switches	Internal accelerometer
Heart rate (HR)	-	Oximeter
Snoring	-	Nasal pressure sensor + snoring sensor
Signal sampling frequency	4 Hz for all	3 Hz for SpO_2 and HR, 20 Hz for pressure, and 10 Hz for rest
Number of channels	4	≥ 7
Used in studies	II-IV	I

4.3 SIGNAL ANALYSIS AND NOVEL PARAMETERS

All ambulatory polygraphic recordings were reanalyzed (in 2012-2015) by applying the standard respiratory rules defined by AASM in 2007 [61] and following the clinical practice of Kuopio University Hospital (table 2.2). At least a 10 seconds long $\geq$ 90% amplitude drop in the nasal pressure (study **I**) or in the thermistor signal (studies **II-IV**) was required to be scored as an apnea event. The scoring of hypopnea event demanded that the following criteria were met according to AASM rule 4A applied in this thesis: 1) at least a 30% drop in the nasal pressure (study **I**) or in the thermistor sig-

nal (studies **II-IV**), 2) at least 10 seconds duration, 3) at least a 4% drop in oxygen saturation signal, and 4) at least 90% of the hypopnea duration must fulfil criterion 1 [61]. In addition, custom-made MATLAB functions were used to calculate the novel parameters (table 4.3) and to determine durations and morphologies of individual obstruction events. When calculating the depth and area of individual desaturation events, the desaturation event was scored to start at the first baseline point before the onset of the drop and its end at the point where values of blood oxygen saturation began to rise again (figure 4.1). The interval between these two points was divided into bins, the widths of which were defined by the sampling interval (0.25 s). The height of the bins was defined as a difference between the baseline value of blood oxygen saturation signal and the value under the bin in question. The area of individual desaturation event (*DesArea*, table 4.3) was calculated as a sum of the areas of these bins. The depth of the desaturation was calculated as the difference between the baseline value of oxygen saturation and the lowest value of oxygen saturation during the desaturation event.

Table 4.3: Summary and definitions of the parameters used in this thesis.

Parameter	Abbreviation	Definition	
Apnea-hypopnea index (1/h)	AHI	$\frac{\sum \text{Apnea events} + \sum \text{Hypopnea events}}{\text{Index time}}$	(1)
Oxygen desaturation index (1/h)	ODI	$\frac{\sum \text{Desaturation events}}{\text{Index time}}$	(2)
Hypopnea index (1/h)	HI	$\frac{\sum \text{Hypopnea events}}{\text{Index time}}$	(3)
Apnea index (1/h)	AI	$\frac{\sum \text{Apnea events}}{\text{Index time}}$	(4)
Individual apnea event duration (s)	ApDur_l		(5)
Individual hypopnea event duration (s)	HypDur_l		(6)
Individual desaturation event duration (s)	DesDur_l		(7)
Individual desaturation event severity (s%)	DesArea_l	$\sum_{j=1}^{S-1} (\text{SO2}_1 - \text{SO2}_{j+1}) \times \text{W}$	(8)
Individual apnea event severity (s^2%)		$\text{ApDur}_l \times \text{DesArea}_l$	(9)
Individual hypopnea event severity (s^2%)		$\text{HypDur}_m \times \text{DesArea}_m$	(10)
Obstruction duration (%)		$\frac{\sum_{l=1}^{L} \text{ApDur}_l + \sum_{m=1}^{L} \text{HypDur}_m}{\text{Index time}} \times 100\%$	(11)
Desaturation duration (%)		$\frac{\sum_{l=1}^{L} \text{DesDur}_l}{\text{Index time}} \times 100\%$	(12)
Obstruction severity (s%)	ObsSev	$\frac{\sum_{l=1}^{L} (\text{ApDur}_l \times \text{DesArea}_l) + \sum_{m=1}^{L} (\text{HypDur}_m \times \text{DesArea}_m)}{\text{Index time}}$	(13)
Desaturation severity (%)	DesSev	$\frac{\sum_{l=1}^{L} \text{DesArea}_l}{\text{Index time}}$	(14)
Adjusted-AHI (1/h)	A-AHI	$5.328 \times \sqrt{\frac{\sum_{l=1}^{L} (\text{ApDur}_l \times \text{DesArea}_l) + \sum_{m=1}^{L} (\text{HypDur}_m \times \text{DesArea}_m)}{\text{Index time}}}$	(15)

L denotes the total number of scored events and *Index time* refers to the total analysed time (s). $SO2_j$ denotes the value of oxygen saturation signal in j^{th} sampling point of the scored desaturation event, W is the sampling interval and S denotes the number of sampling points during the desaturation event.

In study **IV**, Somnologica 3.3.2 (Flaga, Reykjavik, Iceland) Software Development Kit with C++ language was used for writing the RemLogic plug-in which was further compiled with Microsoft Visual C++ 6.0 (Microsoft, Redmond, WA, USA). The plug-in reads scored events and the oxygen saturation trace from RemLogic and calculates parameters (equations 11-15) defined in table 4.3. In study **IV**, when the novel parameters were calculated, a desaturation event was considered to be related to a respiratory event if the desaturation event started within 60 seconds after an apnea or hypopnea event. However, when using the plug-in in clinical practice or research, the different settings allow the user to modify the criteria affecting to determination of the novel parameters (figure 4.2). For instance, the minimum drop of desaturation can be modified to determine how deep desaturation events should be included into the analysis and in addition, the timespan between start of apnea or hypopnea event and start of desaturation event can be changed in order to connect a respiratory event with an associated desaturation. Furthermore, event classification allows determination of specific event types which are taken into account by the plug-in when calculating the novel parameters (*e.g.* if apneas are determined to be of the central type, then only central apneas with associated desaturations will be included to analysis). After the calculations, the plug-in prints values of the novel parameters in an HTML (Hyper Text Markup Language) file (figure 4.3).

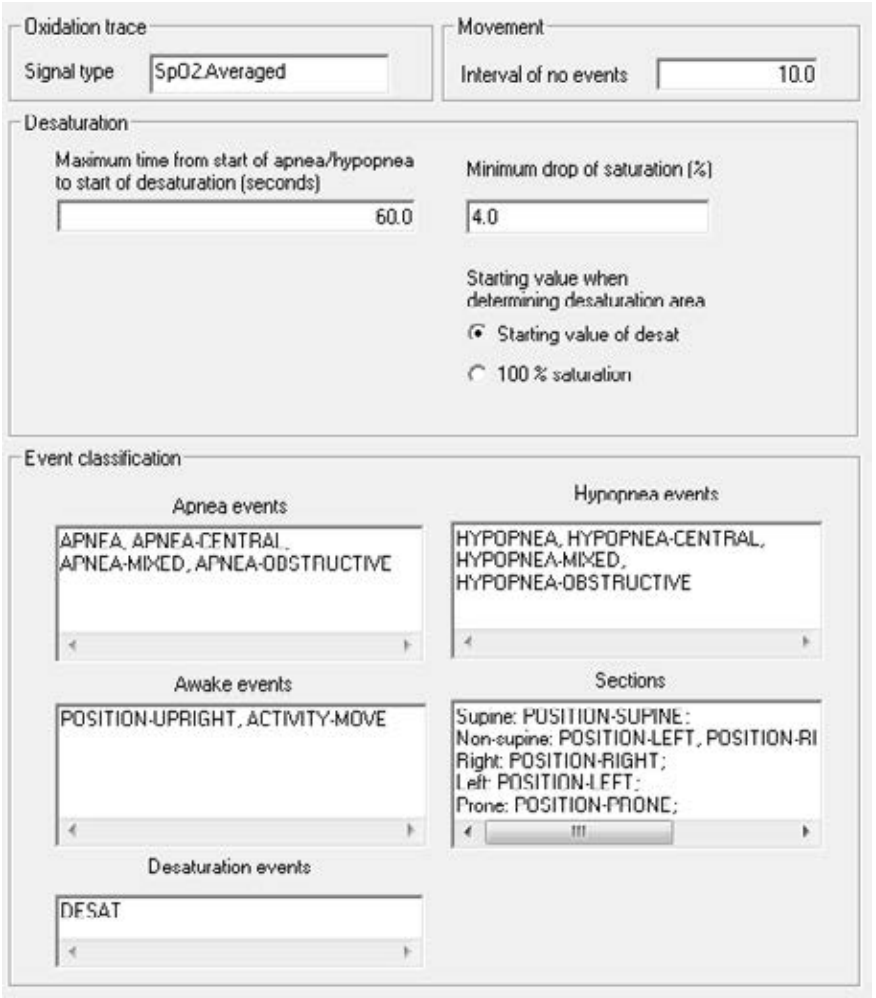

Figure 4.2: Setting menu of the RemLogic plug-in. User can specify the event types and set minimum saturation drop for desaturation events which are taken into account when calculating the novel parameters. Furthermore, maximum time from an apnea or hypopnea event to desaturation determines whether the respiratory event is associated with the desaturation.

A-AHI Report

Index time:	452.8 min
Summary:	
Obstruction duration:	3.4 %
Desaturation duration:	3.1 %
Desaturation severity:	0.10 %
Obstruction severity:	2.73 s%
Adjusted AHI:	8.81
Supine:	
Time:	94.1 min
Obstruction duration:	15.2 %
Desaturation duration:	13.5 %
Desaturation severity:	0.42 %
Obstruction severity:	11.84 s%
Adjusted AHI:	18.34
Non-supine:	
Time:	358.7 min
Obstruction duration:	0.3 %
Desaturation duration:	0.2 %
Desaturation severity:	0.01 %
Obstruction severity:	0.10 s%
Adjusted AHI:	1.70
Right:	
Time:	67.1 min
Obstruction duration:	0.3 %
Desaturation duration:	0.0 %
Desaturation severity:	0.00 %
Obstruction severity:	0.00 s%
Adjusted AHI:	0.00
Left:	
Time:	291.6 min
Obstruction duration:	0.4 %
Desaturation duration:	0.2 %
Desaturation severity:	0.01 %
Obstruction severity:	0.13 s%
Adjusted AHI:	1.88
Prone:	
Time:	0.0 min
Obstruction duration:	0.0 %
Desaturation duration:	0.0 %
Desaturation severity:	0.00 %
Obstruction severity:	0.00 s%
Adjusted AHI:	0.00

Figure 4.3: An HTML file produced by the plug-in. The file incorporates full night (summary) and sleeping position related values of the novel parameters. Non-supine position contains right, left, and prone positions. Definitions of the novel parameters are presented in table 4.3.

4.4 STATISTICAL ANALYSIS

All statistical analyses were done using SPSS (SPSS Inc., Chicago, IL, USA) software and throughout this thesis $p < 0.05$ was set as the limit of statistical significance (table 4.4). In study **I**, statistical significance of differences in the anthropometric and demographic data between the control and weight loss groups at the baseline was evaluated using Mann-Whitney U-test. Statistical significance of the changes in values of calculated parameters (equations 1, 2, 5-8 and 11-14 in table 4.3) within the weight loss and control groups between the baseline and two years' follow-up time points were investigated using Wilcoxon signed rank test. In addition, mixed model analysis was run to test statistical significance of differences in distributions of individual obstruction events within the groups between the baseline and two years' follow-up time points.

In study **II**, Wilcoxon signed rank test was utilized to test statistical significance of the differences in the median values of obstruction events between the supine and non-supine positions in the different OSA severity categories. Kruskal-Wallis test was used to evaluate the significance of differences between the OSA severity categories. Mixed model analysis was used to explore statistical significance of differences in distributions of individual event severities between the supine and non-supine positions.

In study **III**, Chi-square test was used for evaluation of statistical significance of differences in smoking, snoring, daytime sleepiness, and heart failure between male and female patients within the OSA severity categories. General linear model (GLM) univariate analysis and Mann-Whitney U-test were performed to assess the statistical significance of the differences in the median values of the calculated parameters (*i.e.* AHI, ODI, AI, HI, ObsSev) and the severity of individual obstruction events between male and female patients within the OSA severity categories. GLM univariate analysis was adjusted for age, BMI, smoking, daytime sleepiness, snoring, and heart failure. Kruskal-Wallis test was used to investigate the statistical significance of differences between the OSA severity categories.

Evaluation of the statistical significance of differences in the individual events distributions between genders was done using mixed model analysis.

In study **IV**, intra-class correlation coefficient (ICC) was used to test correlation between the values of parameters determined with the RemLogic plug-in and MATLAB. The significance of ICC was investigated by conducting F-test. Mann-Whitney U-test was conducted to evaluate the statistical significance of differences in patient demographics between the OSA severity categories formed based on conventional AHI and adjusted-AHI. Hazard ratios adjusted for age, BMI, and smoking were calculated in the different OSA severity categories using Cox regression.

Table 4.4: Summary of the statistical analyses used in this thesis.

Study	Statistical analyses	Software
I	Mann-Whitney U-test, Mixed model analysis, Wilcoxon signed rank test	SPSS version 20.0
II	Kruskal-Wallis test, Mixed model analysis, Wilcoxon signed rank test	SPSS version 19.0
III	Chi-square test, General linear model univariate analysis, Kruskal-Wallis test, Mann-Whitney U-test, Mixed model analysis	SPSS version 20.0
IV	Cox regression, F-test, Intra-class correlation coefficient, Mann-Whitney U-test	SPSS version 19.0

5 Results

In summary, weight loss decreased AHI but the reduction of the apnea and hypopnea events was mainly focused on the shorter events. Sleeping in a supine position elevated the number and severity of the individual apnea and desaturation events in all OSA severity categories. In the moderate and severe OSA categories, men experienced more severe apneas, hypopneas, and desaturations than females with similar conventional AHI values. Finally, in contrast to conventional AHI, the adjusted-AHI parameter explained independently both an increased overall mortality and the occurrence of non-fatal cardiovascular events. The introduced RemLogic plug-in was confirmed to be accurate and a convenient way to calculate novel parameters in a clinical environment.

5.1 EFFECT OF WEIGHT LOSS ON THE SEVERITY OF INDIVIDUAL OBSTRUCTION EVENTS

In contrast to the control group, the median values of AHI and ODI decreased statistically significantly ($p \leq 0.001$) in the weight loss group during the two year follow-up (study **I**, table 5.1). In addition, the number of apneas, hypopneas, and desaturations decreased considerably in the weight loss group while in the control group, the numbers of events remained almost unchanged (table 5.1). However, the median durations of apnea events increased during the follow-up in the weight loss group (median durations 13 vs. 21 seconds, $p < 0.001$). In the control group, this increase was not statistically significant (median durations 14 vs. 15 seconds, $p = 0.552$). The median duration of hypopnea events and the median area of desaturation events were found to increase statistically significantly ($p < 0.001$) during the follow-up in both groups (table 5.1). In the weight loss group, there was a clear decrease in the number of less severe individual apneas, hypopneas and desaturation events (figure 5.1). In contrast, in the control group, the

distributions of the durations of individual apnea and hypopnea events and desaturation areas remained almost unchanged, only a minor increase in the number of the most severe events was detected during the follow-up period (figure 5.1).

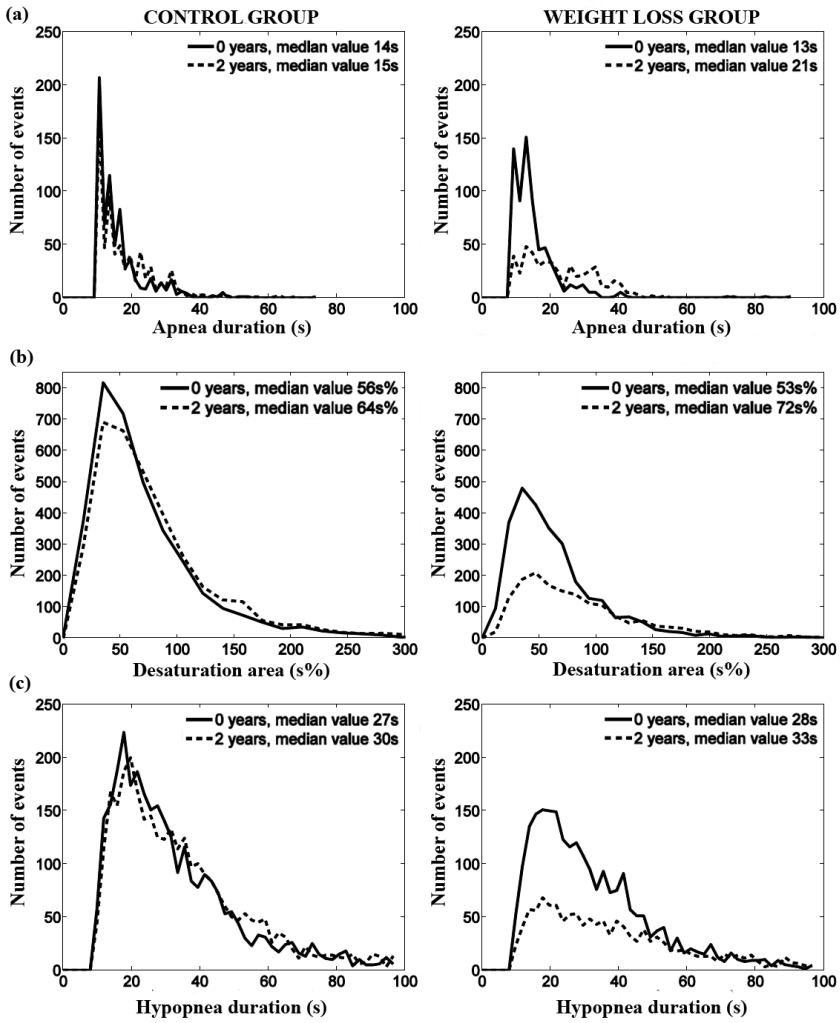

Figure 5.1: Distributions of individual apnea event durations (a), individual desaturation event areas (b), and individual hypopnea event durations (c) in control and weight loss groups at baseline and after the two years' follow-up. (Figure modified from original publication ***I****).*

*Table 5.1: The values (median (range)) of AHI, ODI and individual event data in control and weight loss groups at baseline and after 2 years' follow-up. (Table modified from original publication **I**).*

	Control group				Weight loss group (>5%)			
	0 years	2 years	Difference (%)	*p*-value	0 years	2 years	Difference (%)	*p*-value
AHI (1/h)	13.5 (5.7-21.2)	9.7 (0.6-45.2)	-28	0.316	12.2 (6.3-29.8)	5.1 (1.8-31.4)	-58	<0.001
ODI (1/h)	12.9 (4.6-20.3)	8.7 (0.7-44.6)	-32	0.402	12.0 (5.9-23.9)	5.1 (1.7-29.2)	-57	0.001
Apnea duration (s)	14 (10-75)	15 (10-67)	7	0.552	13 (10-92)	21 (10-74)	62	<0.001
Hypopnea duration (s)	27 (10-99)	30 (10-99)	11	<0.001	28 (10-99)	33 (10-99)	20	<0.001
Desaturation area (s%)	56 (4-874)	64 (10-843)	14	<0.001	53 (9-586)	72 (10-521)	36	<0.001
Number of apnea events (n)	710	669	-6		674	477	-29	
Number of hypopnea events (n)	3014	3029	0.5		2372	1233	-48	
Number of desaturation events (n)	3518	3504	0.5		2774	1632	-41	

5.2 EFFECT OF SLEEPING POSITION AND GENDER ON SEVERITY OF INDIVIDUAL OBSTRUCTION EVENTS

Apnea events were longer ($p \leq 0.015$) and the proportion of apneas higher ($p \leq 0.022$) in the supine position compared to the non-supine position and in males than in females in every OSA severity category (studies **II** and **III**, tables 5.2 and 5.3). In addition, the areas of individual desaturation events were larger ($p \leq 0.024$) in males and in supine position in moderate and severe OSA categories (tables 5.2 and 5.3). Individual hypopnea events were longer ($p = 0.001$) in females having mild OSA but shorter ($p = 0.024$) in females having severe OSA compared to their male counterparts with similar AHI values. The median durations of hypopnea events were statistically significantly ($p = 0.001$) different between supine and non-supine positions only in the moderate OSA category (tables 5.2 and 5.3). When patients were divided into OSA severity categories based on conventional AHI parameter, AHI was statistically significantly higher ($p < 0.001$) in the supine position compared to the non-supine position in every OSA severity category. However, AHI did not differ statistically significantly between genders within the OSA severity categories although females were proportionally more often diagnosed as exhibiting mild OSA.

Based on GLM univariate analysis (adjusted for age, BMI, smoking habits, daytime sleepiness, snoring, and heart failure), apneas were still statistically significantly ($p \leq 0.036$) longer in males compared to females in moderate and severe OSA categories (table 5.4). The proportion of apneas was also higher in males with mild, moderate, and severe OSA ($p < 0.001$, $p = 0.054$, $p = 0.013$, respectively) compared to female patients with similar AHI (table 5.4). Areas of desaturation events were statistically significantly larger in males with severe OSA ($p = 0.007$), while no statistically significant differences between genders were observed in the durations of hypopneas in moderate and severe OSA categories. In contrast, females had statistically significantly longer hypopneas ($p < 0.001$) and larger areas of desaturations ($p = 0.025$) in the mild OSA cate-

gory (table 5.4).

In the mixed model analysis, there were statistically significant ($p < 0.05$) differences detected in the durations of apnea events between supine and non-supine positions as well as between male and female patients in all OSA severity categories. Sleeping in a supine position elevated the number of the apnea events and furthermore, the durations of apnea events were distributed more towards longer events compared to the apnea events occurring when the individuals were in the non-supine position (figure 5.2). A higher number of more severe apnea events was observed in male patients compared to female patients (figure 5.3). Statistically significant ($p < 0.05$) differences in the distributions of areas of desaturations between supine and non-supine positions were evident in moderate and severe OSA categories and between male and female patients in severe OSA category (figures 5.2 and 5.3). Furthermore, differences between genders in the distributions of durations of hypopnea events reached statistical significance ($p < 0.05$) in the mild and severe OSA categories and between sleeping positions in mild, moderate and severe OSA categories (figures 5.2 and 5.3).

The median duration of apnea events increased in conjunction with increasing severity of OSA in both supine and non-supine positions but also in males and females (tables 5.2 and 5.3). In addition, the median area of desaturation events increased towards more severe OSA in both sleeping positions and in male patients but not in female patients. In contrast, the median duration of hypopnea events decreased with increasing AHI irrespective of the sleeping position or gender (tables 5.2 and 5.3).

*Table 5.2: The values (median (range)) of AHI and individual event data in different sleeping positions (study **II**) as a function of severity of OSA defined based on AHI. (Table modified from original publication **II**).*

	Mild			**Moderate**			**Severe**		
	Supine	Non-supine	*p*-value	Supine	Non-supine	*p*-value	Supine	Non-supine	*p*-value
Patients (*n*)	158			117			161		
AHI total (1/h)	9.4 (5.0-14.9)			21.3 (15.1-29.5)			50.2 (30.0-148.4)		
AHI (1/h)	16.6 (3.6–65.7)	3.9 (0.5–20.4)	<0.001	39.6 (2.7–77.9)	8.7 (0.4–30.8)	<0.001	63.9 (16.4–179.6)	42.2 (0.9–125.5)	<0.001
Apnea duration (s)	15.1 (10.1-55.6)	14.2 (10.0-51.0)	<0.001	18.0 (10.7-44.0)	16.0 (10.8-92.5)	<0.001	22.0 (10.5-52.2)	19.8 (11.0-64.3)	<0.001
Hypopnea duration (s)	27.0 (13.8-56.3)	27.4 (11.0-74.5)	0.257	26.5 (16.0-42.0)	27.3 (13.0-61.0)	0.001	25.0 (13.0-54.0)	25.0 (12.3-63.0)	0.221
Desaturation area (s%)	75.6 (29.5-240.0)	75.7 (24.5-187.1)	0.294	83.3 (39.4-345.5)	78.8 (24.0-184.8)	0.001	127.3 (35.3-795.3)	101.8 (22.9-807.5)	<0.001
Proportion of apneas (%)	31.2 (1.0-97.8)	25.0 (1.2-94.7)	0.022	43.5 (1.3-97.7)	23.1 (1.3-91.2)	<0.001	43.5 (0.8-99.5)	24.1 (0.4-99.0)	<0.001

Statistical significance of differences in values between supine and non-supine positions was evaluated using Wilcoxon signed rank test.

*Table 5.3: The values (median (range)) of AHI and individual event data of male and female patients (study **III**) as a function of severity of OSA defined based on AHI. (Table modified from original publication **III**).*

	Mild			**Moderate**			**Severe**		
	Male	Female	*p*-value	Male	Female	*p*-value	Male	Female	*p*-value
Patients (*n*)	409	121		236	46		248	30	
AHI (1/h)	8.7 (5.0-14.9)	8.6 (5.0-14.9)	0.957	20.6 (15.0-29.8)	20.2 (15.1-28.7)	0.851	48.1 (30.0-148.7)	45.2 (30.1-124.3)	0.169
Apnea duration (s)	17.0 (10.0-62.4)	13.5 (10.1-47.9)	<0.001	18.0 (10.0-39.9)	15.4 (10.5-42.0)	0.001	22.0 (11.0-50.1)	18.4 (10.9-38.5)	0.015
Hypopnea duration (s)	28.0 (13.0-74.0)	30.8 (16.4-75.3)	0.001	27.0 (12.0-53.0)	25.6 (15.0-40.0)	0.150	25.9 (12.3-54.5)	23.5 (15.1-39.0)	0.024
Desaturation area (s%)	79.9 (31.0-363.9)	85.0 (42.1-220.0)	0.114	87.6 (35.5-247.8)	75.9 (41.3-171.8)	0.005	120.0 (38.3-825.4)	97.0 (42.9-270.3)	0.024
Proportion of apneas (%)	16.7 (0.0-100.0)	2.8 (0.0-86.5)	<0.001	29.6 (0.0-97.5)	6.9 (0.0-98.9)	<0.001	36.2 (0.0-95.5)	22.2 (0.0-96.8)	0.002

Statistical significance of differences in values between male and female patients was evaluated using Mann-Whitney U-test.

*Table 5.4: Evaluation of differences in AHI, ODI, and individual event data between male and female patients using general linear model univariate analysis adjusted for age, BMI, smoking, daytime sleepiness, snoring, and heart failure. In the model, male gender was used as the reference category (i.e. females were compared to males). (Table modified from original publication **III**).*

	Mild			**Moderate**			**Severe**		
	B	*SD error*	*p*-value	*B*	*SD error*	*p*-value	*B*	*SD error*	*p*-value
AHI (1/h)	-0.244	0.320	0.446	-0.265	0.762	0.728	-8.860	3.831	0.022
ODI (1/h)	0.332	0.340	0.345	0.285	0.883	0.747	-8.906	3.897	0.023
Apnea duration (s)	-1.428	0.865	0.099	-2.595	1.232	0.036	-3.588	1.546	0.021
Hypopnea duration (s)	3.798	0.896	<0.001	-0.753	1.173	0.552	-2.455	1.394	0.079
Desaturation area (s%)	7.434	3.314	0.025	-10.738	5.529	0.053	-61.274	22.479	0.007
Proportion of apneas (%)	-12.889	2.733	<0.001	-9.185	4.746	0.054	-13.567	5.407	0.013

B denotes a partial regression coefficient and *SD error* denotes the variation of the partial regression coefficient.

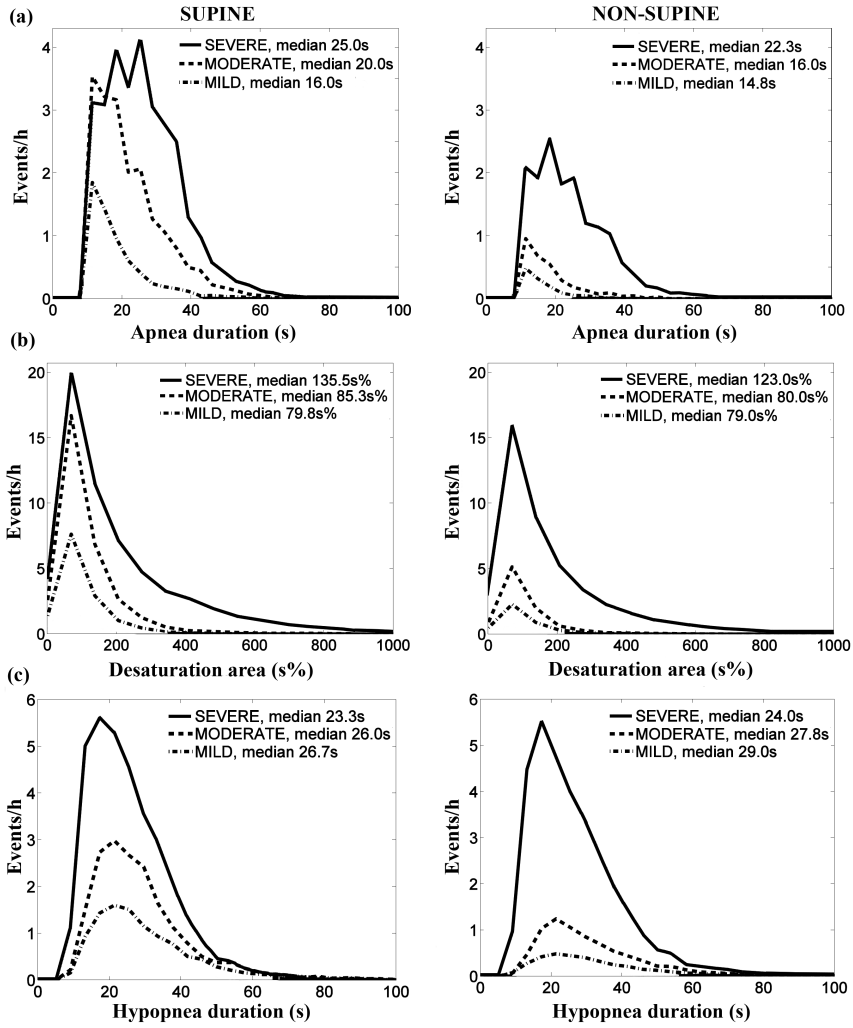

Figure 5.2: Distributions of individual apnea event durations (a), individual desaturation event areas (b), and individual hypopnea event durations (c) in supine and non-supine positions in different OSA severity categories normalized according to the positional sleeping time. (Figure modified from original publication ***II****).*

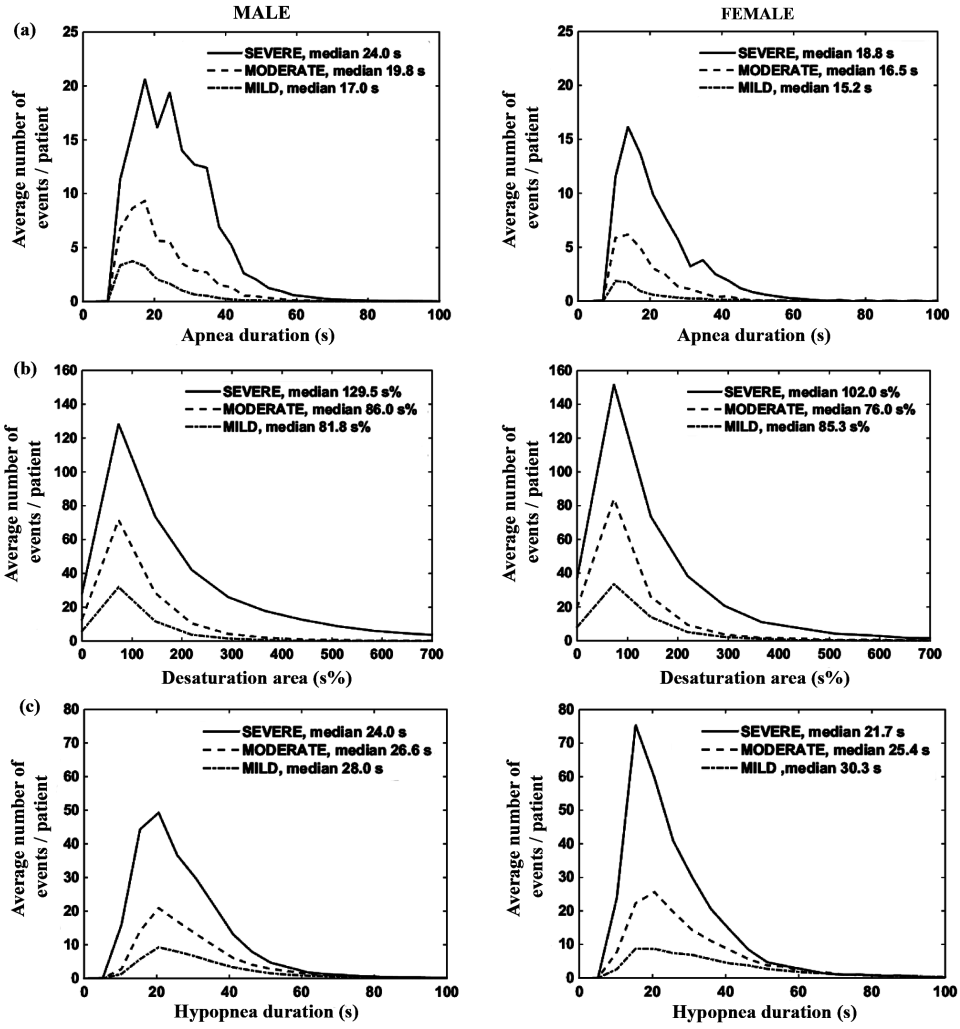

Figure 5.3: Distributions of individual apnea event durations (a), individual desaturation event areas (b), and individual hypopnea event durations (c) in male and female patients in different OSA severity categories normalized according to the number of patients. (Figure modified from original publication ***III****).*

5.3 CLINICAL APPLICATION OF THE NOVEL PARAMETERS

Based on the hundred polygraphic recordings investigated, the plug-in was confirmed to be as accurate as MATLAB functions for calculating the novel parameters (including adjusted-AHI). There was a perfect correlation between the values of adjusted-AHI parameter calculated with the RemLogic plug-in and MATLAB (r = 1.000, p < 0.001). The mean (±SD) difference between these values was 0.15% (±0.38%) (figure 5.4). As the plug-in allows calculation of novel parameters by utilizing commonly used RemLogic software, it makes possible the clinical application of the novel parameters.

When the adjusted-AHI parameter was used to define the severity of OSA, it was found that the hazard ratio of overall mortality was statistically significantly higher (p < 0.05) in the severe OSA category (hazard ratio 2.45) compared to patients without OSA (hazard ratio 1.0) (table 5.5). This hazard ratio of overall mortality in severe OSA was higher than estimated with conventional AHI (hazard ratio 1.43) which did not differ statistically significantly from that of patients without OSA (hazard ratio 1.0) (table 5.5). Furthermore, adjusted-AHI, in contrast to conventional AHI, was found to explain independently elevated mortality rate (p = 0.04) and incidence of non-fatal cardiovascular events (p = 0.04) (table 5.5).

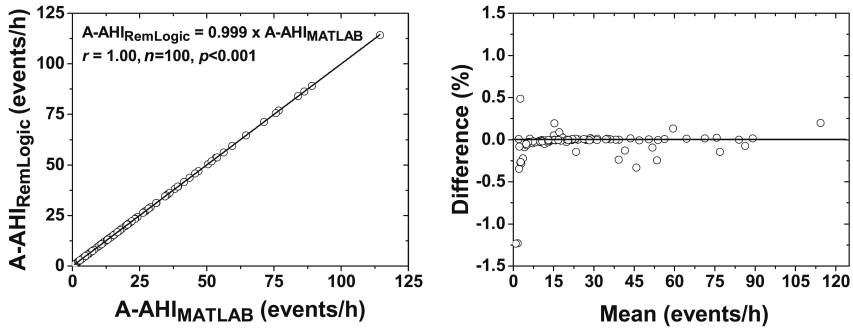

Figure 5.4: Intra-class correlation and Bland-Altman plot between values of adjusted-AHI (A-AHI) calculated with MATLAB and the plug-in. In the Bland-Altman plot, the differences are presented in percentages. (Figure modified from original publication ***IV****).*

*Table 5.5: Hazard ratios (CI 95%) of overall mortality and non-fatal cardiovascular (CV) events in OSA severity categories formed based on conventional AHI and adjusted-AHI (A-AHI). The hazard ratios for patients judged to have normal findings were set to be 1.0. (Table modified from original publication **IV**).*

	Mild		**Moderate**		**Severe**		**Test for trend**[1]	
	AHI	A-AHI	AHI	A-AHI	AHI	A-AHI	AHI	A-AHI
Overall mortality	1.10 (0.73-1.65)	1.43 (0.87-2.35)	1.83* (1.17-2.88)	1.79* (1.05-3.05)	1.43 (0.82-2.50)	2.45* (1.29-4.66)	0.052	0.040*
Non-fatal CV events	1.24 (0.85-1.83)	1.21 (0.75-1.96)	1.77* (1.12-2.79)	1.89* (1.14-3.14)	1.27 (0.71-2.26)	1.31 (0.64-2.70)	0.108	0.040*

[1]Test for trend is adjusted for age, BMI, and smoking.
Statistical significance of differences in hazard ratios compared to patients judged to have normal findings are indicated with an asterisk and evaluated using Cox regression.

6 Discussion

6.1 EFFECT OF WEIGHT LOSS ON THE SEVERITY OF INDIVIDUAL OBSTRUCTION EVENTS

In study **I**, the effects of weight reduction on severity of OSA as well as on the severity of individual apneas, hypopneas and desaturations were investigated by conducting a two-year follow-up study with 67 patients. The results were compared between the control group (n = 37) and the weight loss group (weight loss > 5%, n = 30). During the follow-up, AHI decreased in both control and weight loss groups but the decrease was statistically significant only in the weight loss group. This finding agrees with numerous studies where the impact of weight reduction on AHI has been investigated [41,64,99,154].

In a more detailed analysis, weight reduction decreased mainly the number of shorter apnea and hypopnea events and the number of desaturation events with the smallest areas. In fact, the number of the longer apnea events (duration 20-40s) increased in the weight loss group during the follow-up and furthermore, the weight loss exerted only minor effects on the number of longer hypopnea events and desaturation events with larger areas. This meant that there was a statistically significant increase in the median durations of apnea and hypopnea events and the median areas of desaturation events although AHI decreased significantly. On the contrary, the differences in the distributions of individual event severities in baseline and after two-year follow-up were minor in the control group even though the median values of durations of individual apnea and hypopnea events and areas of individual desaturation events were found to increase during the follow-up period. As AHI did not differ statistically significantly between the baseline and follow-up points in the control group, although OSA is a progressive disease especially if accompanied by weight gain [13], it could be speculated that OSA can progress in different ways *e.g.*

by increasing either the number or the severity of individual obstruction events or both of these phenomena can occur at the same time.

Even though AHI decreased significantly in response to the weight loss, the changes in the characteristics of the individual events suggest that the effect of weight reduction on severity of OSA is not as straightforward as would be appear to be indicated by the AHI value. It is important to notice that even though weight loss exerts a positive effect on the severity of OSA, the longer breathing cessations still remain. Furthermore, it could be argued that longer respiratory events and larger desaturation areas would be more detrimental than shorter and shallower ones as individual event severity is connected to increased mortality rate in patients with severe OSA [95]. Therefore, the severity aspect of individual apneas, hypopneas, and desaturations should be taken into account in the diagnosis of OSA, as well as when assessing the effect of weight reduction on the severity of OSA.

6.2 EFFECT OF SLEEPING POSITION AND GENDER ON SEVERITY OF INDIVIDUAL OBSTRUCTION EVENTS

In study **II**, the severity of individual obstruction events was compared between supine and non-supine positions in 526 suspected obstructive sleep apnea patients whose had undergone amblulatory polygraphic recordings. Previously, apnea events have been shown to be longer when patients with severe OSA are sleeping in a supine compared to a non-supine position [106]. We found that this applies also to patients having mild or moderate OSA. In addition, the proportion of apneas was higher in the supine position in all OSA severity categories, which is in line with a previous study in which the severity of OSA, based in AI, increased while the patients were sleeping in a supine position [89]. OSA patients have a smaller cross-sectional area in their upper airways compared to patients without OSA [137]. In addition, their pharynx is further narrowed when they are in a supine position [166] and the upper

airway resistance is also elevated in that position due to anatomical changes in the upper airways caused by gravity [107]. The combination of these factors might explain the greater proportion of apneas in supine position.

Desaturation events have been reported to be deeper when patients with severe OSA are lying in the supine position [106]. This is in line with our present finding that individual areas of desaturation events are statistically significantly larger when individuals classified to experience moderate or severe OSA are lying in the supine position. This might increase the overall severity of OSA as physiological stress is elevated by deeper desaturation events [147]. The only statistically significant difference in the median values of the durations of hypopnea events between supine and non-supine positions was seen in the moderate OSA category where hypopnea events were longer in the non-supine position. As the proportion of apnea events is elevated with increasing AHI, the differences (not statistically significant) in the durations of hypopnea events between sleeping positions in patients with severe OSA might be due to the fact that instead of lengthening hypopnea events, these will be converted into apnea events as OSA progresses.

Furthermore, the median durations of apneas and the median areas of desaturation events became elevated with increasing severity of OSA in both the supine and non-supine positions, with this increase being greater in the supine position. It has been reported that the severity of individual obstruction events is connected with an increased risk of mortality and cardiovascular morbidity [95] and that these risks are further elevated in supine isolated OSA patients [74]. Therefore, the severity of individual obstruction events and sleeping position should not be ignored when assessing the severity of OSA.

In study **III**, the difference in the severity of individual obstruction events was explored between male (n = 893) and female (n = 197) patients in different severity categories of OSA. Male patients experienced statistically significantly longer apnea events in all OSA severity categories except in mild OSA severity category (p

= 0.099) after the statistical model was adjusted for age, BMI, smoking habits, daytime sleepiness, snoring, and heart failure. This is in line with several previous studies where males have been reported to have longer apnea events in general [78, 160]. In study **II**, we demonstrated that sleeping in a supine position elevates the durations of individual apnea events. However, even though males had longer apnea events, they slept less in a supine position than their female counterparts. In addition, females had a significantly lower proportion of apnea events compared to men (except in moderate OSA category, when adjusted GLM was used (p = 0.054)). The elevated proportion of apneas in male might be due to the fact that combined estrogen and progesterone treatment has been shown to reduce the number of apnea and hypopnea events in females [118], most likely due to elevated respiratory drive [69]. Therefore, these female hormones apparently transform apneas into hypopnea events. In addition, the proportion of apnea events increased proportionally more in female patients compared to male patients with increasing severity of OSA, possibly indicating that the effect of estrogen and progesterone is reduced when OSA becomes more severe.

Females have been reported to have less severe desaturation events compared to men [160]. This agrees with our findings as we observed that the areas of desaturations were larger in males having moderate or severe OSA. In contrast, males with mild OSA had smaller areas of desaturations and significantly shorter hypopneas. It has been shown that applying an oxygen desaturation threshold (ODT) level of 3%, instead of 4% (AASM 2007, rule 4A [61]) leads to a statistically significant increase in AHI [98]. In study **III**, the ODT level of 4% was used for scoring hypopneas. As respiratory events are mainly hypopneas in female patients and desaturation events are less severe compared to the situation in men, it may be assumed that using a more stringent ODT level would lead to a relatively higher increase in AHI in females.

Finally, the median durations of apnea events increased with AHI in male and female patients but the median areas of desat-

uration events only in male patients. On the contrary, the median durations of hypopnea events decreased as patients of both genders progressed towards more severe OSA. The increase in the severity of individual apneas and desaturations might be due to the OSA progression. However, when OSA progresses it may also decrease the durations of individual hypopnea events by converting them into apneas which is supported by the fact that the proportion of apneas tended to increase in patients with more severe OSA. Because the characteristics of OSA are different between males and females with similar degrees of AHI, it could be argued that these gender based variations should be included into any estimation of OSA severity.

In summary, it appears that the increase in severity of OSA is expressed by the increased number and the duration of individual apnea events together with the larger areas of desaturations and in parallel with decreased number and duration of hypopnea events. These phenomena were seen in both genders and in supine and non-supine positions but they were more clearly observable in men and in the supine position. However, these findings should be corroborated with a larger pool of female patients and using polysomnographic recordings including EEG registration.

6.3 CLINICAL APPLICATION OF THE NOVEL PARAMETERS

In study **IV**, we created a RemLogic plug-in enabling clinical use of the novel parameters. Its accuracy was tested using ambulatory polygraphic recordings of one hundred patients by comparing the values of the adjusted-AHI parameter (table 4.3) calculated with the RemLogic plug-in and MATLAB. Furthermore, the potential of adjusted-AHI to distinguish the patients with elevated risks of OSA related severe health consequences was studied by retrospective follow-up (mean $\pm$ SD follow-up time: 194.1 $\pm$ 54.0 months) using polygraphic recordings of 1128 working-age male patients.

The differences between the values of adjusted-AHI parameter calculated with the RemLogic plug-in and MATLAB were minimal

and therefore, the present plug-in can be feasibly used by clinicians. The minimal difference between the values calculated using the two methods is due to a difference in rounding of the durations of scored events. In RemLogic, the data is interpolated which makes it possible to place the start and end points of the scored event between the original sampling points. While exporting data from RemLogic, the start and end points are rounded to the nearest sample point. Therefore, as MATLAB calculates values of the novel parameters based on exported files and the plug-in does not round up the durations of events, a small difference between individual event durations occurs. Hence, as the plug-in does not allow rounding up, the values of parameters can be assumed to be slightly more accurate when calculated with the plug-in.

Patients with severe OSA suffer a higher cardiovascular mortality compared to patients without OSA [123, 167]. In study **IV**, the hazard ratios of overall mortality and nonfatal cardiovascular events were higher in the severe OSA category which had been formed based on adjusted-AHI compared to that based on conventional AHI. The hazard ratio of overall mortality was increased towards more severe OSA when the adjusted-AHI was used in OSA severity estimation, while the hazard ratio of nonfatal cardiovascular events was highest in the moderate OSA category. This might indicate that the cardiovascular events in patients with severe OSA are more often fatal than non-fatal. In addition, adjusted-AHI, in contrast to conventional AHI, was found to be an independent explaining factor for overall mortality and non-fatal cardiovascular events. Therefore, the adjusted-AHI parameter might be a better estimator for severity of OSA and provide important supplementary information than can be obtained with conventional AHI.

6.4 LIMITATIONS AND FUTURE ASPECTS

In 2007, AASM provided two alternative definitions for scoring hypopneas [61]. In rule 4A (recommended) at least a 10 seconds long, $\geq$ 30% drop in nasal airflow signal must be followed by $\geq$ 4% desat-

uration and in rule 4B (alternative) at least a 10 seconds long, $\geq$ 50% drop in nasal airflow signal must be followed by either $\geq$ 3% desaturation or arousal [61]. All studies in this thesis were conducted using ambulatory polygraphic recordings without EEG registration. Therefore, hypopneas followed by arousals could not be detected and therefore rule 4B could not be applied. In addition, since total sleep time could not be defined due to lack of EEG recording data, index time was used instead in all studies (**I-IV**). Index time was defined as time between the start and end points of the analyzed period (*i.e.* approximated time when patients felt asleep and woke up, respectively) subtracting upright time and time during movements (+ interval of no events). Start and end points were estimated based on the recorded signals. This may have affected the results as all conventional and novel parameters were normalized by index time. Despite these limitations, ambulatory recording devices without EEG have been certified to be sufficient for diagnosis of OSA and they can be used as an alternative to in-laboratory polysomnographic registrations [29]. In addition, a triple-head thermistor was used to record airflow in studies **II-IV**. In comparison to thermistors, variations in breathing flow can be measured more sensitively using nasal prongs although detection of apneas is more reliable with thermistors [36].

The patient population used in study **I** did not contain patients with severe OSA at baseline and therefore, the results of study **I** may not be generalized to all patients having OSA. It is acknowledged that these promising results need to be further confirmed in patients with more severe OSA. In addition, as all polygraphic recordings used in studies **I-IV** were conducted using ambulatory devices without EEG, the potential of novel parameters to enhance diagnosis of OSA must be further confirmed by using PSG recordings including EEG registration. In addition, as a hypopnea followed by an arousal can be scored from polysomnographic recordings which include EEG and nasal prongs would be more sensitive at detecting fluctuations in breathing flow compared to thermistors, in future studies, nasal prongs should be used alongside a ther-

mistor to measure airflow. Because the limited number of female patients in studies **I** and **II**, data was not analyzed separately by gender and therefore, broad generalizations of these results cannot be extended to both genders. It is also acknowledged that the relatively small number of female patients (n=197) is a limitation of the study **III**. In addition, in study **III**, information of menopausal status of females was not collected and for this reason, it could not be included into the analysis. However, as the differences in severity of individual obstruction events were clearly observable and most of the female patients could be considered as being postmenopausal (average age 53.0 years), we believe that these limitations do not jeopardize the validity of the results of study **III**.

In the future, we aim to investigate the potential of novel parameters to enhance assessment of severity of OSA using in-laboratory PSG recordings including EEG registration. This makes it possible to evaluate the differences in severity of individual obstruction events between sleep stages and investigate whether the frequency and durations of arousals are modulated by severity of individual obstruction events in different OSA severity categories. Currently, the novel parameters do not take into account hypopnea events followed by arousal. By using polysomnographic recordings including EEG, it would be possible to develop novel parameters to take into account also these kinds of hypopnea events. In addition, it can be claimed that the pathophysiological effects of complete and partial collapses of the UA (*i.e.* apneas and hypopneas, respectively) are not equivalent [122]. As clinical evidence for this is limited, we will investigate whether apneas are more hazardous than hypopneas and therefore should apnea events be given greater weight than hypopnea events when estimating the overall severity of OSA. Furthermore, it would be useful to evaluate whether apnea events not followed by desaturation should also be taken into account when calculating the novel parameters. Finally, we also intend to study the relationship between severity of individual obstruction events and subjective OSA symptoms, changes in heart rate, pulse transit time, and heart rate variability.

7 Conclusions

This thesis demonstrates that weight reduction affects the severity of individual obstruction events, not only the frequency of the events. In addition, the duration and morphology of individual obstruction events were found to vary depending on gender, sleeping position and severity of OSA. The main conclusions can be summarized regarding to the aims of the thesis as follows:

1. The effect of weight loss in patients with mild or moderate OSA is reflected mainly by a reduction of the shorter respiratory events without a significant change in the longer ones.

2. Adopting a supine position was associated with an increase in the number of breathing cessation events and proportion of apneas in all OSA severity categories. In addition, sleeping in the supine position increased the duration of apnea events in all OSA severity categories and there was also an increase in the areas of desaturation events in moderate and severe OSA.

3. In general, an increase in the severity of OSA is associated with an increase in the duration of apneas and areas of desaturations and with a decrease in the durations of hypopnea events. These associations are unrelated to sleeping position and almost unrelated to gender.

4. Males have longer apneas and a higher proportion of apneas compared to females in all OSA severity categories. In addition, the areas of desaturations are larger in males with moderate or severe OSA.

5. Adjusted-AHI, in contrast to the conventional AHI, was found to be an independent risk factor for overall mortality and non-fatal cardiovascular events highlighting the higher sensitivity of this novel parameter for assessing the severity of OSA.

6. The RemLogic plug–in introduced in this thesis, makes possible an accurate calculation not only of full night values of the novel parameters (including A-AHI), but also in each sleeping position, thus enhancing the assessment of the OSA severity.

To conclude, in this thesis, the severity of individual obstruction events was found to depend on multiple factors. As the severity of obstruction events has been linked to an increased mortality rate and an elevated risk of suffering cardiovascular morbidities, AHI might not be a truly optimal parameter for the estimation of the severity of OSA. Therefore, the plug-in application, which makes possible to calculate the novel parameters in a clinical environment, can help clinicians to improve the accuracy of their OSA diagnosis.

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TIMO LEPPÄNEN

Obstructive sleep apnea (OSA) is a common nocturnal breathing disorder characterized by frequent cessations of breathing. Currently, it is diagnosed based on only the number of obstruction events. The present thesis demonstrates that the severities of OSA and obstruction events are affected also by weight change, sleeping position, and gender. Thus, the severity of OSA is not only influenced by the number of the events. Furthermore, a clinical tool for enhanced diagnostics of OSA is introduced.

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