Obstructive sleep apnea

General characteristics in hypertensive patients,

position sensitivity,

and upper airway sensory neuropathy

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This thesis is based on the following papers, referred to in the text by their roman numerals:


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ABBREVIATIONS

AASM  American academy of sleep medicine
ACEI  Angiotensin converting enzyme inhibitor
AHI   Apnea hypopnea index
ARB   Angiotensin receptor blocker
B-blocker  Beta-blocker
BMI   Body mass index
BSAQ  Berlin sleep apnea questionnaire
CDT   Cold detection threshold
CI    Confidence interval
CPAP  Continuous positive airway pressure
DM    Diabetes mellitus
EDS   Excessive daytime sleepiness
EEG   Electroencephalogram
EMG   Electromyogram
EOG   Electrooculogram
ESS   Epworth sleepiness scale
HAD   Hospital anxiety and depression scale
HRT   Hormone replacement therapy
ICSD  International classification of sleep disorders
IHD   Ischemic heart disease
KSS   Karolinska sleepiness scale
MAD   Mandibular advancement device
MISS  Minimal Insomnia Symptoms Scale
MLE   Method of levels
MLI   Method of limits
MMA   Maxillo-mandibular advancement
MRI   Magnetic resonance imaging
MSLT  Multiple sleep latency test
MWT   Maintenance of wakefulness test
ODI   Oxygen desaturation index
OSA   Obstructive sleep apnea
OSAS  Obstructive sleep apnea syndrome
PG    Polygraphy
POSA  Position dependent obstructive sleep apnea
PSG   Polysomnography
QST   Quantitative sensory testing
r     Repeatability coefficient
RDI   Respiratory distress index
RERAS Respiratory related arousals
SaO2 M  Mean blood oxygen saturation
SaO2 N  Nadir blood oxygen saturation
SDB   Sleep-disordered breathing
SSS   Stanford sleepiness scale
TIA/Stroke Transient ischemic attack/stroke
UARS  Upper airway resistance syndrome
UPPP  Uvulopalatopharyngoplasty
INTRODUCTION

Everybody snores sometimes, or at least: most people are likely to snore sometime during their lifetime. “Everybody” does not only include humans, since also animals and cartoon heroes snore. In the worlds of literature and cinema, an audible sleep is often used as a metaphor for a good sleep. However, as all practitioners of sleep medicine know, snoring and a good sleep are sometimes the opposites of each other. Snoring definitely becomes menacing when combined with impaired quality of sleep and/or difficulties of breathing during sleep, such as in obstructive sleep apnea (OSA). OSA is characterized by repetitive episodes of upper airway obstruction that occur despite continuous or increased respiratory effort. The term apnea is used when obstruction is total and the term hypopnea when obstruction is partial. If the individual with OSA has accompanying symptoms (most often excessive daytime sleepiness, fatigue or tiredness), the term obstructive sleep apnea syndrome (OSAS) is used. “Obstructive sleep-related breathing disorders” is an all embracing term for these disorders (Figure 1).

Figure 1. Obstructive sleep-related breathing, from normal breathing to OSAS

In the literature the term sleep-disordered breathing (SDB) is sometimes used interchangeably with obstructive sleep-related breathing disorders. Strictly speaking, this term also includes other sleep-related breathing disorders than obstructive ones. The most important of those are central sleep apnea syndromes, characterized by disturbances in respiratory effort. Sleep-related breathing disorders that are not obstructive in nature will not be further discussed in this thesis.

OSA is highly prevalent in the adult population (Young et al., 1993; Dúran et al., 2001; Hrubos–Strøm et al., 2011) and even more prevalent in populations with overweight (Young et al., 2002a) and with cardiovascular disease (Bradley and Floras 2009). Today the most used diagnostic measure is the apnea-hypopnea index (AHI), which is the average number of apneas and hypopneas per hour of sleep. OSA is considered to be at hand when AHI ≥ 5. OSA with or without symptoms is associated with an increased likelihood of hypertension, cardiovascular disease, stroke, daytime sleepiness, and motor vehicle accidents (Young et al., 2002a).
Even though OSA has gained an increased interest both among medical practitioners and the general population in the last decades, the majority of subjects with sleep apnea remain undiagnosed (Bradley and Floras, 2009). This is, at least, partly explained by the fact that OSA in many cases is asymptomatic. With the associated morbidities and potential public-health implications in mind, it seems important to identify and treat subjects with OSA. This could be particularly important in populations with cardiovascular disease where the most beneficiary treatment effects could be expected. Therefore studies aimed to facilitate the identification of OSA subjects in such populations are warranted.

In order to find patients that would benefit from treatment, cost-efficient and accurate diagnostic measures must be used. One of the weaknesses using the AHI is that approximately half of the subjects evaluated for sleep apnea have more than twice the amount of apneas and hypopneas when sleeping on their backs compared to other sleeping positions (Oksenberg et al., 1997). Since most individuals change their sleeping positions several times during a night the proportion between supine and non-supine sleep may vary. This could have implications for OSA diagnosis based on the AHI. In order to increase the accuracy in OSA diagnosis, studies evaluating the potential impact of sleeping position on the AHI are needed.

The severity (Berger et al., 2009) and prevalence (Hrubos–Strøm et al., 2011) of OSA increase with time and age. Even though many factors associated with OSA incidence and progression has been described, there are still some pieces missing. Many patients describe that years of snoring have preceded witnessed breathing interruptions during sleep. From studies in the field of occupational medicine we know that long-standing vibrations may have deleterious effects on nerves and tissues (Virokannas, 1995; Strömberg et al., 1996). What is snoring if not vibrations? We also know that the negative pressure during inspiration tends to draw the soft tissues of pharyngeal airway together (since it lacks rigid supporting structures), predisposing airway collapse. Negative pressure initiates a complicated pattern of neural and muscular activity, so that collapse is counteracted (Horner, 1996). One possible mechanism in OSA pathogenesis is that snoring-induced vibrations impair these reflex circuits, which in fact have been indicated in several studies (Svanborg, 2005). To further evaluate these aspects of OSA pathogenesis, studies using validated methods encompassing both healthy subjects, snorers without apneas and snorers with apneas need to be performed.
A BRIEF HISTORY OF SNORING AND SLEEP APNEA

Snoring and sleep apnea are not new phenomena in human history. Already the writers of antiquity described snoring in both humans and gods. For example, Hermes was once reproached by the ferryman Charon for lying on the deck snoring instead of helping him row across the river (Pirsig, 2002). The writers of antiquity also mentioned today well described risk-factors for snoring such as alcohol, excessive food intake, high age and supine sleep (Pirsig, 2002).

From the age of renaissance, Shakespeare described an affliction similar to sleep apnea. In the play Henry IV, the character Falstaff in one scene is described to be fast asleep, snorting like a horse and then having to fetch his breath (Furman et al., 1997). Another contemporary writer, Cervantes, used snoring as a characteristic of a good sleep in his work Don Quixote. Here, Sancho Panza is described as fat, a good sleeper and a habitual heavy snorer in contrast to the insomniac Don Quixote (Iranzo et al., 2004). Some centuries later Charles Dickens (1837), in the Posthumous Papers of the Pickwick Club, gave a very detailed description of the loudly snoring fat boy Joe who suffered from somnolence, very much like many of today’s patients referred for evaluation of OSA.

From a modern medical perspective the first known descriptions of OSA date from the second half of the 19th century. In his review from 1984, Lavie tells that the first description of what probably was mixed sleep apnea was published by Broadbent in 1877, that Caton in 1889 presented A case of narcolepsy which most likely was a case of SDB, and that another case, similar to Catons, was described by Morison later the same year. Then, in 1889 the term Pickwickian was coined by Heath (the term borrowed from Charles Dickens) to describe the overweight patient suffering from breathing difficulties during sleep presented by Caton earlier the same year (Lavie, 1984).

After that, obstructive SDB seems to have been more or less forgotten during the first half of the 20th century. In 1965 Gastaut et al. (1965) devised the first polysomnographic recording to objectively showed the occurrence of repeated apneas during sleep in so-called Pickwickian patients. In 1967, Schwartz and Escande were able to show by cineradiography that the site where the apneas occurred was located in the upper airway. Fortunately for today’s patients, the last 30 years have seen a tremendously increasing interest in SDB and today the search terms “sleep disordered breathing” yields more than 20000 hits on the PubMed website.
Snoring
Snoring is a sound created by respiratory-related vibrations of upper airway soft tissues during sleep. Vibration results when the negative inspiratory pressure created in the thorax sucks the elastic soft tissues of the pharynx together thus creating a turbulent airflow.

Snoring can emanate from any of the soft structures in the pharynx such as the soft palate (including the uvula), the pharyngeal walls, the tonsils, the tongue base and the epiglottis, or any combination (Quinn et al., 1995). Snoring encompasses a wide range of frequencies and can be of nuisance to the snorer, family members, and other cohabiters. Decibel levels >100dB have been anecdotally reported in the lay press (and professor Svanborg has once recorded a level of 110 dB), but commonly snoring is in the range of 50-60 dB (Pevernagie et al., 2010). But even levels of 50-60 dB are enough to wake a person from sleep and this sound pressure level is well above the WHO 40 dB recommendations for environmental sound pressure levels at night (WHO, 2009). In the report Night noise guidelines for Europe the WHO concludes that sounds >40 dB may cause adverse health effects such as sleep disturbances, environmental insomnia and increased use of somnifacient drugs. At levels >55dB cardiovascular health becomes a concern (WHO, 2009).

Chronic exposure to snoring may even predispose hearing loss in partners to chronic snorers (Sardesai et al., 2003). These potential negative consequences of the audible part of snoring are often put aside in clinical practice in favor of the (so-considered) more negative somatic consequences of OSA. There is no doubt, however, that snoring in itself can be a great problem for many snorers and their partners.

The upper airway resistance syndrome
The term upper airway resistance syndrome (UARS) can be used when negative inspiratory pressure causes an increase in upper airway resistance and increased respiratory effort. This increase in respiratory effort can result in arousals affecting sleep quality. In UARS there are no distinct breathing interruptions (apneas and hypopneas) and no significant blood oxygen desaturations. Symptoms described in UARS are snoring, sleepiness and insomnia (Pépin et al., 2012).

Obstructive sleep apnea
OSA is characterized by repetitive apneas or hypopneas during sleep despite continuous respiratory effort. The site of obstruction is located in the pharynx and the structures involved are the same as those responsible for snoring.

The definitions of both OSA and OSAS have changed over the years. In 1999 the American Academy of Sleep Medicine (AASM) published recommendations for both the definition and severity classification of OSAS (AASM, 1999). These recommendations were, at least as suggested by the name of the article Sleep-related breathing disorders in adults: recommendation for syndrome definition and measurement techniques in clinical research, intended for
clinical research. For the determination of severity of the disease the AASM recommended that both subjective sleepiness and the result of overnight monitoring should be assessed and a severity level for both components should be specified. The severity of the syndrome should then be based on the most severe component (Table 1).

Table 1. Diagnostic criteria- and severity classification for Obstructive sleep apnea-hypopnea syndrome according to the American Academy of Sleep Medicine 1999 (AASM, 1999).

<table>
<thead>
<tr>
<th>Diagnostic criteria. The individual must fulfill criterion A or B, plus C</th>
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<tbody>
<tr>
<td><strong>A</strong></td>
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<td><strong>B</strong></td>
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<td></td>
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<tr>
<td><strong>C</strong></td>
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</tbody>
</table>

**Severity classification**

<table>
<thead>
<tr>
<th>Sleepiness</th>
<th>Mild: Unwanted sleepiness or involuntarily sleep episodes occur during activities that require little attention.</th>
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<tbody>
<tr>
<td></td>
<td>Symptoms produce only minor impairment of social or occupational function.</td>
</tr>
<tr>
<td>Moderate: Unwanted sleepiness or involuntarily sleep episodes occur during activities that require some attention.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Symptoms produce moderate impairment of social or occupational function.</td>
</tr>
<tr>
<td>Severe: Unwanted sleepiness or involuntary sleep episodes occur during activities that require more active attention.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Symptoms produce marked impairment in social or occupational function.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sleep related obstructive events</th>
<th>Mild: 5 to 15 events per hour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate: 15 to 30 events per hour</td>
<td></td>
</tr>
<tr>
<td>Severe: greater than 30 events per hour</td>
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</tbody>
</table>

Notably, these are definitions and criteria for OSAS only (OSA not included). A lower cut-off for number of obstructive events required was set at five.

Two years later the AASM (2001) published a new set of criteria in The International Classification of Sleep Disorders diagnostic and coding manual (ICSD). One difference is the absence of clearly defined criteria for the number of apneas and hypopneas needed for a diagnosis of OSAS (Table 2).
Table 2. International Classification of Sleep Disorders; main elements of diagnostic and severity criteria for Obstructive sleep apnea syndrome 2001 (AASM, 2001).

<table>
<thead>
<tr>
<th>Diagnostic criteria. Minimal criteria; A plus B plus C</th>
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<tbody>
<tr>
<td>A. The patient has a complaint of excessive sleepiness or insomnia.</td>
</tr>
<tr>
<td>B. Frequent episodes of obstructed breathing occur during sleep.</td>
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<tr>
<td>C. Associated features include: Loud snoring Morning headaches A dry mouth upon awakening</td>
</tr>
<tr>
<td>D. Polysomnographic monitoring demonstrates: 1. &gt; 5 obstructive apneas, &gt; 10 seconds in duration/ hour of sleep and one or more of the following: a. Frequent arousals from sleep associated with the apneas b. Bradytachycardia c. Arterial oxygen desaturation in association with the apneic episodes 2. MSLT may or may not demonstrate a mean sleep latency of less than 10 minutes.</td>
</tr>
</tbody>
</table>

Severity classification

Mild:
Associated with mild sleepiness or mild insomnia.
Most of the habitual sleep period is free of respiratory disturbance.
The apneic episodes are associated with mild oxygen desaturation or benign cardiac arrhythmias.

Moderate:
Associated with moderate sleepiness or mild insomnia.
The apneic episodes can be associated with moderate oxygen desaturation or mild cardiac arrhythmias

Severe:
Associated with severe sleepiness.
Most of the habitual sleep period is associated with respiratory disturbance, with severe oxygen desaturation or moderate to severe cardiac arrhythmias.
There can be evidence of associated cardiac or pulmonary failure.

Although a minimal criteria for diagnosis did not include any defined number of apneas and hypopneas a non-obligatory apnea-index (apneas/hour of sleep) >5 is mentioned in criteria D (note: hypopneas not mentioned).

Four years later, in 2005, a new edition of the ICSD was published by the AASM with a new version of diagnostic criteria for OSA (AASM, 2005) (Table 3).
Table 3. International Classification of Sleep Disorders. Diagnostic criteria for Obstructive Sleep Apnea 2005 (AASM 2005).

<table>
<thead>
<tr>
<th>Diagnostic criteria; A, B, and D or C and D satisfy the criteria</th>
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<tr>
<td><strong>A</strong> At least one of the following applies:</td>
</tr>
<tr>
<td>i. The patient complains of unintentional sleep episodes during wakefulness, daytime sleepiness, unrefreshing sleep, fatigue, or insomnia</td>
</tr>
<tr>
<td>ii. The patient wakes with breath holding, gasping, or choking</td>
</tr>
<tr>
<td>iii. The bed partner reports loud snoring, breathing interruptions, or both during the patient’s sleep</td>
</tr>
<tr>
<td><strong>B</strong> Polysomnographic recording shows the following:</td>
</tr>
<tr>
<td>i. Five or more scoreable events (i.e., apneas, hypopneas, or RERAs*) per hour of sleep</td>
</tr>
<tr>
<td>ii. Evidence of respiratory effort during all or a portion of each respiratory event</td>
</tr>
<tr>
<td><em>(In the case of a RERA, this is best seen with the use of esophageal manometry)</em></td>
</tr>
<tr>
<td>or <strong>C</strong> Polysomnographic recording shows the following:</td>
</tr>
<tr>
<td>i. Fifteen or more scoreable events (i.e., apneas, hypopneas, or RERAs) per hour of sleep</td>
</tr>
<tr>
<td>ii. Evidence of respiratory effort during all or a portion of each respiratory event</td>
</tr>
<tr>
<td><em>(In the case of a RERA, this is best seen with the use of esophageal manometry)</em></td>
</tr>
<tr>
<td>and <strong>D</strong> The disorder is not better explained by another current sleep disorder, medical or neurological disorder, medication use, or substance use disorder.</td>
</tr>
</tbody>
</table>

*RERAs: respiratory related arousals

The most important difference is that the term *Obstructive sleep apnea* is used instead of the previously used *Obstructive sleep apnea syndrome*. Now, OSA is defined as either 5 obstructive events/hour of sleep with symptoms (somewhat similar to what in the previous definitions was called OSAS) or 15 obstructive events without symptoms.

These criteria are mirrored in the 2009 AASM publication *Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults* (Epstein et al., 2009). The reason to include $\geq 15$ obstructive events without symptoms as an alternative definition was due to an increased cardiovascular disease risk associated with $\text{AHI} \geq 15$ (Epstein et al., 2009). The 2005 ICSD version did not include a severity classification for OSA, but in the AASM clinical guidelines of 2009 OSA severity is defined as mild when the respiratory distress index (RDI, the number of obstructive respiratory events/hour of sleep) is $\geq 5$ and $<15$, moderate when RDI is $\geq 15$ and $<30$, and severe when RDI $\geq 30$. This classification does not take account of symptom severity.
CLINICAL ASPECTS

Signs and symptoms
There is a great variety of signs and symptoms related to OSA. Most interestingly, the relationship between the number of pathologic respiratory events and symptoms is far from straightforward. Patients with low numbers of apneas and hypopneas can present with significant sleepiness and patients with high numbers of apneas and hypopneas can present without sleepiness (Vgontzas, 2008). Several studies on OSA and OSAS prevalence have shown that OSA without symptoms is more prevalent than OSA with symptoms (Young et al., 1993; Bixler et al., 2001; Dúran et al., 2001). This means that most individuals with OSA can be expected to have few and possibly mild if any symptoms at all.

In patients referred to sleep clinics for OSA evaluation, symptoms are often evident and marked. The patient or their partner/cohabitant often describes nocturnal snoring, choking, gasping sounds and breathing interruptions. Daytime sleepiness is a common complaint but it must be acknowledged that the patient instead of sleepiness can describe fatigue, lack of energy, tiredness or sleeping spells during the day (Chervin, 2000). Other common complaints include a sense of unrefreshing sleep, restless sleep, insomnia with or without frequent awakenings, nocturnal sweating, morning headaches, nocturia and dry mouth in the morning. Some patients describe forgetfulness, impaired concentration, decreased libido, personality changes or attention deficits (Hoffstein and Szalai, 1993; Chervin, 2000; Cao et al., 2011).

What causes the symptoms?
It does not seem far-fetched to believe of an association between apneas, hypopneas and other measurable physiological features of OSA and degree of symptoms. Many of the physiologic characteristics of OSA (including number of apneas and hypopneas, hypoxemia, snoring, increased respiratory effort, arousals from sleep, and impaired quality of sleep) have been evaluated in relation to symptoms but with divergent results. Most often variables have been evaluated against sleepiness, since sleepiness for decades has been regarded as the cardinal symptom of obstructive SDB.

Svensson et al. (2008) showed that self reported habitual snoring (but not elevated AHI) was independently related to excessive daytime sleepiness (EDS) as measured by the Epworth Sleepiness scale (ESS), falling asleep involuntarily during the daytime, waking up unrefreshed and daytime fatigue after adjusting for AHI, age and body-mass index (BMI) in a cohort of 400 Swedish women. In a recently published article no association between daytime sleepiness and mild-, moderate or severe degrees of sleep apnea was found (Franklin et al., 2012). Similar findings were reported from Dúran et al. (2001) who investigated a sample drawn from the Spanish general population. In this study daytime hypersomnia was found in 31% of men and 26% of women with an AHI≥5. It was also reported in 12% of men and 28% of women with AHI<5 however, and a significant association between daytime hypersomnia and OSA could not be found.
This in contrast to reports from the Sleep Heart Health Study where significant associations between daytime sleepiness and both self-reported snoring (Gottlieb et al., 2000) and RDI (Gottlieb et al., 1999) have been found. In another article from the same database, the prevalence of sleepiness was found to increase with severity of SDB and sleepy subjects were found to have a higher AHI and hypoxemic burden (Kapur et al., 2005). In the latter study sleep-stage distribution, sleep time, sleep efficiency, and arousal index were not associated with sleepiness.

Goncalves et al. (2004) reported that EDS (as measured by ESS) was significantly correlated with arousal index, AHI and negatively correlated with lowest SaO2 during the night. Similarly, Mediano et al. (2007) reported that nocturnal hypoxemia might be a major determinant of EDS in OSA patients but these findings could not be reproduced in a larger follow-up study by the same research group (Roure et al., 2008). In this study OSA patients with EDS were shown to sleep longer and more efficiently with only mildly increased AHI, arousals and decreased nocturnal SaO2 nadir (but not mean oxygen saturation) compared with OSA patients without EDS. In fact, the positive associations between SaO2 parameters and arousals with EDS were so weak that the authors concluded that the clinical relevance of these findings was marginal (Roure et al., 2008).

In 1991 two studies were published with somewhat contradictory results on the association between nocturnal hypoxemia and sleepiness; Colt et al. (1991) found that experimentally induced intermittent hypoxemia after elimination of apneas and hypopneas by continuous positive airway pressure (CPAP) did not diminish objective improvement in daytime somnolence and therefore the authors attributed sleep fragmentation as the cause. However, Bédard et al. (1991) found that severity of nocturnal hypoxemia in OSA was associated to daytime vigilance. Both studies used the Multiple Sleep Latency Test - (MSLT) as a measure of EDS. Intermittent hypoxemia has also been shown to increase circulating levels of tumor necrosis factor-α, a cytokine found to be independently associated with EDS in OSAS patients (Ryan et al., 2006).

Guilleminault et al. (1993) showed that increased respiratory effort in the absence of apneas and hypopneas could cause EDS by causing arousals from sleep leading to sleep fragmentation. Similar findings have been reported by Pelin et al. (2003) who found that inspiratory effort was correlated to subjective sleepiness in both OSAS and UARS patients.

Berg et al. (1997) found no difference in total amount of sleep or the total number of arousals between non-apneic sleepy snorers (AHI<10) and non-sleepy snorers (even though the sleepy snorers were found to have more respiratory events and more respiratory related arousals). Severe snoring, higher sleep efficiency and an increased amount of arousals were found to predict EDS in a group of OSA patients studied by Senerivatne and Puvanendran (2004).
DIAGNOSTIC MEASURES AND METHODS

**Apneas, hypopneas and the AHI**
The definitions of apneas and hypopneas (as well as the equipment that should be used to detect them) have been discussed and challenged since they were first introduced. In 1975 Guilleminault et al. defined an apnea as a cessation of airflow over the nose and mouth lasting at least 10 seconds. Later it was recognized that also events with partial obstruction, called hypo-apneas, could have the same negative impact as apneas (Kurtz et al., 1976). In 1979 Block et al. used the term hypopneas to describe respiratory events when the airflow over the nose and mouth was only decreased in comparison to completely suspended as in apneas. These authors also used an additional criteria of a ≥4% oxygen desaturation with continued respiratory effort in the definition of an obstructive hypopnea. Nearly two decades later, data from The Sleep Heart Health Study showed that hypopneas associated with an oxygen desaturation of 4% were associated with increased prevalence of cardiovascular disease independent of confounding covariates in contrast to hypopneas with less severe desaturations (Punjabi et al., 2008). In 1988 Gould et al. defined hypopneas as events with a reduction in oro-nasal airflow of 50% lasting for at least 10 seconds.

Historically many different definitions of apneas and hypopneas have been in use, but as Hirshkowitz and Kryger (2011) put it; having two definitions for a single term is ill advised because it creates ambiguity, confusion, and miscommunication. In 2007 the AASM published The AASM Manual for the Scoring of Sleep and Associated Events (Iber et al., 2007) with recommendations for the scoring of both apneas and hypopneas. According to these guidelines an apnea shall meet the following criteria; a decrease of airflow (≥90% of baseline amplitude) over the nose and mouth for at least 10 seconds with ≥90% of the event’s duration meeting the amplitude reduction criteria together with continued respiratory effort throughout the entire period of absent airflow. A hypopnea shall meet the following criteria: a drop by ≥30% of baseline in the nasal pressure signal excursions for at least 10 seconds with ≥90% of the event’s duration meeting the amplitude reduction criteria and finally, the event should be associated with a ≥4% oxygen desaturation from pre-event baseline.

**The diagnostic process**
At least from a clinical perspective the diagnostic procedure of OSA can be divided in two parts, the measurement of obstructive respiratory events and the evaluation of symptoms. The two factors most focused on are AHI and excessive daytime sleepiness. Therefore, some of the challenges in the assessment of these factors will be discussed in the following sections.

**Evaluation of apneas and hypopneas**
Polysomnography (PSG) is the golden standard for measuring the AHI and should include electroencephalogram (EEG), electrooculogram (EOG), chin electromyogram (EMG), airflow over the nose and mouth, oxygen saturation and heart rate under the attendance of trained personnel (Epstein et al., 2009). A full PSG records both sleep and breathing parameters. A fully attended in-lab PSG recording is highly resource-demanding and in most countries scarcely available. PSG can also be performed unattended in-lab or
at home. Due to the large number of patients referred for OSA evaluation, simpler diagnostic equipments have been developed. Most used in Sweden are polygraphic recordings (PG) also called sleep apnea recordings/nightly respiratory recordings/type III portable monitors or cardiopulmonary studies. There are even more simple recording devices not yet in routine use in Sweden.

The main difference between attended or unattended PSG and PG is that the latter does not record EEG. This means that actual sleep is not recorded, and since the AHI ideally should be calculated from total sleep time, the AHI assessed by PG devices has to be calculated from total recording time or an estimation of sleep time. In clinical practice the recording time is often preset to cover the whole sleep period, meaning that total recording time in most PG recordings will be longer than actual sleep time. Thus, if used as a surrogate for actual sleep, total recording time is at risk to give a diluted (lower) AHI.

The most recent guidelines on portable monitors (e.g. PG as described above) from the AASM (Collop et al., 2007) lays down that portable monitors to diagnose OSA should (as minimum) record air-flow, respiratory effort, and blood oxygenation. The specific sensors for each type of recording should be the same as recommended for PSG (i.e., oro-nasal thermal sensors for detection of apneas, nasal air-pressure transducers for detection of hypopneas, and inductance plethysmography for detection of respiratory effort). The devices used must allow review of raw data, and the data should be manually scored according to AASM criteria by trained personnel (Collop et al., 2007; Iber et al., 2007). Portable monitors should always be used in conjunction with a comprehensive evaluation of patients by a physician trained in the field of sleep medicine.

If the outlined circumstances are fulfilled the AASM states that PG monitoring may be performed unattended in the home in patients with high probability for OSA based on a clinical investigation and without evidence of other significant co-morbidities (other sleep-disorders, pulmonary disease, neuromuscular disease, or congestive heart failure) (Collop et al., 2007). The reasons for these recommendations are that comparative studies on PG and PSG have mostly been done in OSA high-risk populations and therefore, until further evidence is gathered, the use should be limited to these groups. However, the authors of these guidelines state that that future studies will probably expand the populations considered as appropriate for PG studies (Collop et al., 2007).

In a systematic literature review on OSAS published in 2007 by the Scandinavian agencies for Health Technology Assessment, the conclusion was that manually scored portable devices measuring airflow, respiratory effort and blood oxygen saturation have a high sensitivity and specificity to identify different cut-off values of pathologic AHI (from 5 to 15) (SBU, 2007).

Since 2007 several studies has been published strengthening the role of PG as a diagnostic tool for OSA. Santos-Silva et al. (2009) found strong correlations and strong agreement (using Bland-Altman analyses) between AHI values obtained at 3 different occasions with PG and PSG. In this study the participants were asked to record when going to sleep, wake-up time, and wake periods of >15 minutes during the night for a better estimation of sleep time in the PG recordings.
Ng et al. (2010) reported high correlations between AHI obtained by hospital based PSG and PG (performed simultaneously) in patients with suspected OSAS. Good agreements were also shown by Bland-Altman analysis. The mean AHI in this study was 21.6 for PSG and 20.8 for PG. AASM criteria for scoring apneas and hypopneas were not used and different criteria for apneas and hypopneas were used for PSG and PG scoring. Total recording time was used for AHI calculation for the PG data without any attempt to subtract wake time from total recording time such as subjective sleep onset and wake up time. However respiratory events that occurred concurrently with moving artifacts were not scored in the PG recordings.

In a study by Driver et al. (2011) PG was found to accurately identify patients without OSA and to have a high sensitivity to identify moderate to severe OSA in patients referred to a sleep laboratory. In this study PG and PSG recordings were performed simultaneously and PG showed a tendency of under-reporting the AHI compared to PSG. Respiratory events that were clearly associated with movement were not scored in the PG data. There was no attempt to extract subjective wake time from recording time, and different definitions for hypopneas but not for apneas were used for scoring the PSG and PM recordings.

In a study of 47 women with clinically suspected OSA (Gjevre et al., 2011), PG was shown to be highly sensitive compared to PSG to determine presence of OSA when AHI ≥5 was used as cut-off. The PG recording was performed one week before or after the PSG recording, but in this study the participants were asked to approximate time of sleep onset and awakenings to allow an estimation of sleep time in the PG recordings. The authors did not use the same criteria for scoring apneas and hypopneas in the PG and PSG recordings.

As shown in some of the above mentioned studies there are ways to minimize the main disadvantage of PG compared to PSG, for the lack of sleep data. When using PG, recording time can be decided beforehand in the clinic when the staff prepares the equipment. Alternately it can be started and stopped by the patient at bedtime and wake-up time. As an alternative or as complement the subject can be asked to record bed-time, wake-up time and wake periods during the night, which can be used to estimate sleep time. The estimation of sleep time can also be sharpened through a visual analysis of breathing patterns, i.e. stabilization of breathing patterns when the subject is asleep and irregular patterns when awake. In addition, many PG devices record other variables that can help in estimating sleep time such as activity-, movement- and position markers.

Franklin and Svanborg (2000) have in fact shown that subjective sleep time correlates fairly well with PSG recorded sleep time (with a mean difference between estimated- and PSG recorded sleep time of 4 minutes). In this study 70% of the subjects had a difference <1h, and 36% had a difference of <30 min. That respiratory pattern and body movements can be helpful in estimating sleep time has been shown by Svanborg et al. (1990) who reported that sleep time could be fairly well estimated from respiratory and movement patterns measured by a static charge sensitive bed. In this study sleep time estimated from respiratory- and movement patterns showed a mean difference of only 16 minutes compared to PSG measured sleep time. In a study by Lysdahl (2002) the mean
difference between PSG recorded sleep time and sleep time estimated from body movements and respiratory patterns recorded by a movement sensitive mattress was -6 minutes and +22 minutes respectively for two different researchers.

Another potential disadvantage of PG is that sleep stages cannot be assessed. REM sleep related OSA is a variant of OSA where apneas and hypopneas occur mainly during REM-sleep. During REM-sleep both the pharyngeal muscle activity and the respiratory effort in response to upper airway occlusion are reduced (in OSA patients) compared to non-REM sleep and thus increase the risk for upper airway collapse (Krieger et al., 1997 a; Mokleshi and Punjabi, 2012). To diagnose REM-related OSA PSG must be used, but the clinical significance of REM-related OSA remains to be established (Mokleshi and Punjabi, 2012).

In conclusion: an AHI obtained with a PG can be expected to correlate fairly well with an AHI obtained by PSG.

**Night to night variability**

Does the AHI differ between nights and is one night enough for a correct diagnosis? In clinical practice and most research settings one night is used. In a review published by the Scandinavian Agencies for Health Technology Assessment based on the available data in 2007 the authors concluded that the AHI shows good agreement between two nights of PSG recordings (SBU, 2007). However, this can be questioned and there are several publications that indicate otherwise.

Le Bon et al. (2000) made a retrospective study of two nights of PSG in 169 subjects evaluated for sleep apnea and reported significant differences in both the AHI and ODI (oxygen desaturation index) between the nights which was unassociated with differences in sleep position pattern. A substantial number of subjects had false- negative results on the first night. Another study used four consecutive nights of PSG to evaluate the variability of the AHI (n=20) and although there was no significant difference in mean AHI between nights, a Bland-Altman plot analysis showed a substantial individual variability. In fact, 50% of the participants changed the classification of OSA severity from the first to the subsequent nights (Bittencourt et al., 2001). Another study comparing four nights of PSG (mean interval of 3.3 weeks between studies) showed that although no differences were found in the average AHI values of the four recordings there was a considerable intra-individual variability in the AHI (Aarab et al., 2009).

In a study by Levendowski et al. (2009) 20 patients underwent two PSG recordings with at least one night between: the correlation of the overall AHI was found to be poor, a mean increase of 7 events per hour on night two was found, 25% of the patients had an increase of >20 events on night two and only 45% of patients had a night-to-night difference of ≤5 events/hour. From a retrospective study of 193 sleep clinic patients with regard to night to night variability of the AHI, Ahmadi et al. (2009) report that 21% of the patients had an AHI variability between nights of >5 and 28% of the patients had an AHI <5 on one night and >5 on the other night while the AHI means of the two nights were similar. Gouveris et al. (2010) performed a retrospective study of 130 patients who had undergone PSG recordings on two consecutive nights and reported a significant night to night variability in 15% of the patients.
**Sleeping position**

AHI is the most important variable used for deciding both diagnosis and severity of OSA. However, traditional OSA classification based on total AHI does not take into consideration that many OSA subjects have higher AHI in the supine position compared to non-supine positions, i.e., position dependent OSA (POSA) (Cartwright, 1984; Oksenberg et al., 1997). If a subject has a higher AHI in the supine position than in other positions, a combination of the difference between supine- and non-supine AHI values and the amount of supine sleep time will decide the AHI. Thus, with the assumption that most individuals vary the proportions of supine- and non-supine sleep between nights, supine- and non-supine AHI discrepancy in POSA subjects might cause variations in AHI between nights.

**Evaluation of daytime sleepiness**

As described earlier in this thesis, daytime sleepiness is regarded as the cardinal symptom of OSA(S) and it is a common complaint in patients referred for OSA evaluation. The challenge in evaluating sleepiness has at least two dimensions; what is sleepiness and how should it be measured? Sleepiness means different things to different people and the word sleepiness can be used to describe subjective feelings of drowsiness, physiological changes that occur during the sleep-onset process or the propensity to fall asleep under a given set of circumstances (Johns, 2000). In a clinical setting the patient and the doctor might have different opinions of what sleepiness is, use different words to describe it and have different ideas of when and to which extent sleepiness is normal (or rather to be expected according to the circumstances). Another aspect is that fatigue, tiredness and lack of energy seem to be as important complaints as sleepiness in OSAS patients, at least in those referred to a sleep laboratory (Chervin, 2000). Furthermore, and again, OSA is not necessarily symptomatic and most symptoms, not least sleepiness, connected with OSA can have other causes, a fact reflected in the 1999 AASM diagnostic criteria for OSA: *Excessive daytime sleepiness that is not better explained by other factors* (AASM, 1999).

When evaluating sleepiness in a subject with suspected or verified OSA a thorough evaluation of clinical history is essential to rule out other factors that can cause sleepiness. Major factors that have to be evaluated are other somatic and psychiatric disorders, shift work, poor sleep hygiene, medication causing sleepiness etc. In most settings, the clinical evaluation of sleepiness is complemented by questionnaires, and several questionnaires have been developed through the years. The ESS is a self-administered questionnaire focusing on the subjective report of the likelihood to fall asleep or doze in eight different common daily life situations (rated on a four point scale) (Johns, 1991). The ESS combines a retrospective and futuristic approach since the subject should give their ratings of the likeliness that they will fall asleep based on how it has been in recent times. Normative data has been established for the ESS. The Stanford Sleepiness Scale (SSS) (Hoddes et al., 1972) and the Karolinska Sleepiness Scale (KSS) (Åkerstedt and Gillberg, 1990) are two other self-administered questionnaires, similar in structure, where subjects should rate their degree of sleepiness at the particular moment when they are answering the questions. The SSS uses a 7-point scale and the KSS a 9-point scale. From a clinical OSA perspective the major differences between the ESS, the SSS and the KSS are that ESS seeks to make a generalization of sleepiness over a period of time while the SSS and the KSS seeks to reflect the degree of sleepiness that the subject experiences the moment the questionnaire is filled in.
EDS can also be evaluated through objective testing. These tests are time consuming and demands sleep laboratory facilities, making them unsuitable for routine clinical practice. They will be shortly discussed as they might be used in research and other special settings. The MSLT measures the tendency or ability to fall asleep while the maintenance of wakefulness (MWT) tests the ability to stay awake. In the MSLT the subject is instructed not to fight sleep while in the MWT the subject is instructed to stay awake. The procedures for the MSLT and MWT are similar, both tests consists of scheduled naps of either 20- (MSLT) or 40 minutes (MWT) each (4-5 naps, with 2 hours interval) during the day. The subject is monitored regarding sleep and sleep stages recumbent in a dark room with a comfortable bed (MSLT) or sitting in a dimly lit room (MWT). The tests record the latency to sleep, and in the MSLT the latency to stage REM sleep.

The OSLER test (Bennett et al., 1997) was developed as an alternative to the MWT without the need for EEG monitoring. The structure of the test resembles the MWT with four trials (40 minutes each) during a day with the tested subject lying semi-recumbent in a dark room. The subject is supposed to press a button in response to a regularly signaling light and the determination of the time when failure to maintain wakefulness occurs is based on response lapsing. A similar test is the psychomotor vigilance test consisting of one trial of approximately 10 minutes where the response latencies to a visual target stimuli is recorded (Kribbs et al., 1993).

In the AASM Practice parameters for clinical use of the multiple sleep latency test and the maintenance of wakefulness test (Littner et al., 2005), MSLT is considered as a validated objective measure of the ability or tendency to fall asleep and the MWT is a validated objective measure of the ability to stay awake. Nevertheless the author’s conclusion is that there is no indication for MSLT in the initial evaluation of patients with suspected OSA and the only OSA-related indication for MWT is for individual employed in occupations concerning public or personal safety.

There are disadvantages with all methods for evaluating EDS. Questionnaires are thought to be sensitive to motivation, recall bias, education level, and fatigue (Arand et al., 2005). Other factors such as personality traits might also influence how a subject responds to questionnaires. On the other hand, objective test methods are complicated, scarcely available and expensive (money- and time wise). The correlation between test results acquired from “artificial“tests and performance in real life situations can also be questioned. The relationship between subjective and objective testing is not straightforward. The ESS, MSLT and MWT are poorly correlated to each other (Sullivan and Kushida, 2008), and the results of both the SSS and ESS have been found to have low- or moderate correlations with the results of the MSLT (Arand et al., 2005).

Despite its limitations ESS is without doubt the most used tool (besides clinical history) in both clinical practice and research to evaluate OSA related daytime sleepiness.
PATHOPHYSIOLOGY AND RISK FACTORS

Any mechanism or factor that negatively affects the lumen or the patency of the pharyngeal airway increases the risk for airway collapse during sleep. During sleep, the muscular tone naturally decreases and the horizontal position is adopted (meaning that gravity works in right angle to the airway), increasing the propensity for pharyngeal collapse. Other specific factors associated with an increased risk for OSA include higher age, male sex, menopause in women, obesity, a family history of OSA, craniofacial abnormalities, cigarette smoking and alcohol use (Punjabi, 2008).

**Age**
OSA prevalence increases with age (Young et al., 2002a). Several potentially age-dependent factors may be in play: deteriorative changes in the structure of muscles and soft tissues, decreases in muscular tone during sleep (as proposed by Worsnop et al., 2000), or decreases in respiratory effort during obstructive events (as proposed by Krieger et al., 1997a). Furthermore, and as reviewed by Punjabi (2008), other factors that may be involved include increased deposition of fat in the parapharyngeal area, lengthening of the soft palate and changes in body structures surrounding the pharynx. In a study of 48 otherwise healthy men and women using PSG, magnetic resonance imaging (MRI), as well as methods to evaluate physiological aspects of the upper airway (EMG, airway resistance and collapsibility) Malhotra et al. (2006) showed an age-dependent decrease in the response to negative pressure, increased deposition of parapharyngeal fat, a lengthening of the soft palate, and a change in the bony shape surrounding the pharynx, all factors predisposing pharyngeal collapse.

**Upper airway anatomy**
All features of soft- and hard tissue anatomy that impairs the size of the upper airway may increase its propensity to collapse during sleep. In childhood enlarged pharyngeal tonsils and epipharyngeal adenoid is strongly associated with OSA (Marcus, 2001), but in adults enlarged tonsils and adenoids are rare.

Schellenberg et al. (2000) studied 420 patients referred to a sleep clinic with regard to anatomic abnormalities of the oropharynx. Even though a narrowing of the lateral pharyngeal wall, enlargements of the tonsils, the uvula, and the tongue were associated with OSA, only lateral narrowing and enlarged tonsils remained significant after adjusting for BMI and neck circumference. In this study, neither low-lying soft palate, retrognathia or overjet were found to be associated with OSA. In another study (case-control, using MRI) both the volume of the tongue and the lateral walls were shown to increase the risk of sleep apnea (Schwab et al., 2003).

Svensson et al. (2006) investigated anatomical and functional features as predictors of sleep apnea in women and found that in non-obese women a low soft palate, retrognathia, and a uvula touching the posterior pharyngeal wall in the supine position were significant predictors for OSA. In another study on men and women referred for evaluation of sleep apnea, large tonsils, a high tongue, and wide uvula in men and large tonsils and mandibular retrognathia in women were found to be independent factors
associated with an AHI>15 (Dahlqvist et al., 2007). Even though individuals with syndromes causing craniofacial abnormalities are at increased risk for OSA due to decreases in airway size, a meta-analysis of studies on the association between craniofacial structures in otherwise normal subjects and OSA showed that only a shorter mandibular length had a clinically significant association with OSA (Miles et al., 1996).

Male gender and female menopause
In general, men seem to be more vulnerable than women to develop OSA. Epidemiologic studies show higher prevalence rates in men than in women with a ratio of 2 to 3:1 (Punjabi, 2008). Differences in upper airway shape, craniofacial morphology, pattern of fat deposition, and occupational and environmental exposures have been proposed as explanations (Young et al., 2002 a).

The potential role of sex hormones was shown in an epidemiological study where pre-menopausal and post-menopausal women on hormone replacement therapy (HRT) were found to have a lower prevalence of OSA, as compared to post-menopausal women without HRT (Bixler et al., 2001). Also Shahar et al. (2003) has reported that HRT in post-menopausal women is associated with a lower prevalence of OSA.

Overweight
Overweight is considered as one of the major risk factors for OSA (Young et al., 2004). The prevalence of OSA in obese clinical patients has been reported to be as high as 50-80% and 60% to 90% of OSA patients may be overweight (Olson and Courcoulas, 2011). An association between overweight and OSA in the general population has also been shown in large epidemiological studies such as the Wisconsin Sleep Cohort Study (Young et al., 1993). In this study obesity was found to be a significant risk factor for an AHI of ≥5, and a single SD increase in BMI was associated with a 4-fold increase in OSA prevalence. Furthermore, longitudinal studies has showed that weight gain can contribute to increased severity of sleep apnea (Peppard et al., 2000; Berger et al., 2009).

As discussed by Olson and Courcoulas (2011), obesity may compress and/or alter the properties of the upper airway by the deposition of fat tissue. Another mechanism may be a central obesity-induced reduction in lung volume impairing a caudally directed pharyngeal stabilizing traction force directed via the trachea (the so called tracheal-tug).

Heredity
Several studies indicate a hereditary component in OSA pathology. Redline et al. (1992) reports of a significant familial aggregation of SDB symptoms after adjusting for bodyweight, age and gender. Pillar and Lavie (1995) reported that off-spring of OSAS patients have a high prevalence of both OSAS (47%) and snoring (22%). Lundkvist et al. (2012) studied Swedish hospital registers focusing on pediatric SDB and found a familial clustering. The specific traits of OSA disease that are genetically based remains to be determined but most dynamic and structural risk factors for OSA are potential candidates.

Smoking and alcohol
Smoking is correlated to an increased risk of obstructive SDB (Stradling and Crosby, 1991; SBU, 2007). One proposed mechanism is that smoking-induced upper airway
inflammation and damage alter the properties of the upper airway, rendering it more susceptible to collapse (Punjabi, 2008).

Alcohol has a depressive effect on muscular tone and alcohol intake has been shown to increase the AHI and worsen hypoxemia in otherwise normal men (Taasan et al., 1981; Izumi et al., 2005).

**Supine sleep**

Already in 1984, Cartwright reported that sleep in the supine position worsened the degree of OSA. In this study of patients referred for evaluation of OSA 24 of 30 had twice the AHI in the supine position compared to side positions, i.e., they exhibited POSA.

In a sample of 574 subjects with an RDI>10, age>20 years, and BMI >20, initially referred to a sleep clinic for evaluation of OSA, Oksenberg et al. (1997) showed that 56% of these patients had POSA (defined as a supine AHI twice the non-supine AHI). They also reported that a thin, young patient with mild-to moderate OSA was more likely to have POSA than an older, obese patient with severe OSA.

The most plausible reason for this discrepancy in severity of OSA between supine- and non-supine sleep is the effect of gravity in the supine position. Gravity predisposes the soft tissues in the upper airway (especially the tongue and mandible) to fall backwards thus narrowing the airway.

**Snore-induced mechanical damage**

Another potential pathogenic mechanism in OSA is mechanically induced damage to nerves, connective tissue and muscles in the upper airway. As described earlier the site of obstruction in OSA is located in the pharynx that lack rigid supporting structures (i.e. bone and cartilage). Even in normal subjects there are both naturally occurring neurological and soft tissue related factors that predispose to airway collapse during sleep: a decreased muscular tone (most pronounced during REM sleep), the effect of gravity in the horizontal position and the negative pressure created by the lungs during inspiration that tend to draw the soft tissues of the upper airway together (the Bernoulli effect).

In order to keep the airway open at all times (and especially during sleep), counter-acting neuromuscular forces has to sustain the patency of the airway. Several muscles and nerves are involved in maintaining the patency of the upper airway during inspiration and the major activating stimuli for pharyngeal dilator muscles is mediated by mechanoreceptors responding to inspiratory negative pressure (Horner, 1996). Thus, any factor that impairs either the function of the involved reflex circuits, its constituting components or their ability to function are risk factors for OSA.

As discussed by Schwab et al. (2011), apnea induced trauma can cause edema to the soft tissues structures surrounding the upper airway. In fact, edema in upper airway tissues in OSA patients has been suggested by both MRI and histological studies and it has also been shown that CPAP treatment reduces the edema (Schwab et al., 2011). Edema decreases the lumen of the upper airway and potentially it might also impair the function of upper airway dilating reflexes.
Trauma induced by apneas and snoring might also cause damage to both pharyngeal musculature and motor sensor neurons. Lindman and Ståhl (2002) reported increased amounts of connective tissue in palatopharyngeal muscles from patients with SDB and as reviewed by Svanborg (2005) there are several studies reporting signs of upper airway motor nervous lesions in subjects with SDB. There are also several studies reporting impaired upper airway sensory function in OSA patients (Larsson et al., 1992; Kimoff et al., 2001; Guilleminault et al., 2002; Nguyen et al., 2005; Hagander et al., 2009).

One proposed hypothesis on the pathogenesis of obstructive SDB is that the inability of the dilating upper airway muscles to maintain airway patency during sleep is the effect of peripheral nerve lesions, causing partial paresis and/or impaired dilating reflexes at inspiration, worsening over time (Svanborg, 2005). The mechanism for these lesions would be longstanding chronic vibrations (i.e. from snoring), possibly together with apnea-related stretch and tearing of pharyngeal soft tissues. It is known from occupational medicine that long-standing vibrations may cause nervous lesions in tissues, with an exposure–effect relationship between vibration and neuronal damage (Virokannas, 1995; Strömberg et al., 1996). That obstructive SDB gets worse over time (after prolonged exposure) is reflected in the observation that many patients report years of snoring before witnessed apneas and symptoms occur (Lugaresi and Plazzi, 1997) and also by several studies reporting OSA to be a progressive disease (see next chapter).
**EPIDEMIOLOGY**

**Prevalence**
Several studies have shown that OSA is more common in men than in women and that the prevalence increase with age (Table 4).

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Age (years)</th>
<th>Number</th>
<th>AHI≥5</th>
<th>AHI≥10</th>
<th>AHI≥15</th>
<th>OSAS*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young et al. 1993</td>
<td>USA</td>
<td>Men</td>
<td>352</td>
<td>24%</td>
<td>15%</td>
<td>9%</td>
<td>4%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Women</td>
<td>250</td>
<td>15%</td>
<td>5%</td>
<td>4%</td>
<td>2%</td>
</tr>
<tr>
<td>Bixler et al. 2001</td>
<td>USA</td>
<td>Men</td>
<td>741</td>
<td>26%</td>
<td>28%</td>
<td>26%</td>
<td>4%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Women</td>
<td>1000</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Durán et al. 2001</td>
<td>Spain</td>
<td>Men</td>
<td>1050</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Women</td>
<td>1098</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Young et al. 2002 (b)</td>
<td>USA</td>
<td>Men</td>
<td>2648</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Women</td>
<td>2967</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hrubos - Strøm et al. 2011</td>
<td>Norway</td>
<td>Men</td>
<td>284</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Women</td>
<td>234</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Franklin et al. 2012</td>
<td>Sweden</td>
<td>Women</td>
<td>399</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Notes:**
All studies used polysomnography to evaluate the AHI.

Definition of apneas:
Young et al. (1993), Bixler et al. (2001), Durán et al. (2001): complete cessation of airflow ≥ 10 s.
Young et al. (2002 b): 25% reduction in airflow for >10s accompanied by a 4% drop in SaO2
Hrubos-Strøm et al. (2011): 90% reduction in airflow >10 s.
Franklin et al. (2012): cessation of airflow for ≥10s.

Definition of hypopneas:
Young et al. (1993): reduction in airflow + decrease ≥ 4% in SaO2
Bixler et al. (2001): reduction in airflow = 50% associated with a 4% reduction in SaO2
Durán et al. (2001): 50% reduction in airflow accompanied by a 4% reduction in SaO2 or EEG arousal
Young et al. (2002 b) and Hrubos-Strøm et al. (2011): 30% reduction in airflow for > 10 s. with a ≥ 4% reduction in SaO2
Franklin et al. (2012): 50% reduction in airflow for ≥10s in combination with an arousal or 3% reduction in SaO2

*Definition of OSAS:
Young et al. (1993): OSAS = AHI ≥ 5 + daytime hypersomnia = (≥ 2 days per week) of feeling excessively sleepy during the daytime, of waking up unrefreshed regardless of sleep length, and of uncontrollable daytime sleepiness interfering with daily activities.
Bixler et al. (2001): OSAS = AHI ≥ 10 + daytime sleepiness, hypertension or other cardiovascular complication.
(a definition of daytime sleepiness was not described in the study)
Durán et al. (2001): OSAS = AHI≥10+ sleepiness ≥3 days/week during the past 3 months in one or more: after awakening, during free time, at work or driving, or during daytime in general.
Franklin et al. (2012): AHI≥5 + ESS score≥10
When comparing the studies above it is worth noticing that different definitions for apneas, hypopneas and OSAS have been used. Notably, there is a large difference in prevalence rates between OSA and OSAS with OSA being more prevalent than OSAS (i.e. asymptomatic OSA is more common than symptomatic OSA). In clinical samples (with subjects referred for evaluation of OSA) the picture is different and EDS is a common complaint (Vgontzas, 2008; Cao et al., 2011). The prevalence of OSA in both men and women seem to increase with age (Table 5).

Table 5. Prevalence (%) of AHI≥5 and AHI≥15 according to age and gender.

<table>
<thead>
<tr>
<th></th>
<th>Young et al. 1993</th>
<th>Age, years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>30-39</td>
</tr>
<tr>
<td>AHI≥5</td>
<td>17</td>
<td>25</td>
</tr>
<tr>
<td>AHI≥15</td>
<td>6.2</td>
<td>11</td>
</tr>
<tr>
<td>AHI≥5</td>
<td>6.5</td>
<td>8.7</td>
</tr>
<tr>
<td>AHI≥15</td>
<td>4.4</td>
<td>3.7</td>
</tr>
<tr>
<td></td>
<td>Durán et al. 2001</td>
<td>Age, years</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30-39</td>
</tr>
<tr>
<td>AHI≥5</td>
<td>9</td>
<td>25.6</td>
</tr>
<tr>
<td>AHI≥15</td>
<td>2.7</td>
<td>15.5</td>
</tr>
<tr>
<td>AHI≥5</td>
<td>3.4</td>
<td>14.5</td>
</tr>
<tr>
<td>AHI≥15</td>
<td>0.9</td>
<td>8.6</td>
</tr>
<tr>
<td></td>
<td>Hrubos-Strom et al. 2011</td>
<td>Age, years</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;50</td>
</tr>
<tr>
<td>AHI≥5</td>
<td>18</td>
<td>23</td>
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<tr>
<td>AHI≥15</td>
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<td>13</td>
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<tr>
<td>AHI≥5</td>
<td>10</td>
<td>16</td>
</tr>
<tr>
<td>AHI≥15</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Franklin et al. 2012</td>
<td>Age, years</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20-44</td>
</tr>
<tr>
<td>AHI≥5</td>
<td>24</td>
<td>56</td>
</tr>
<tr>
<td>AHI≥15</td>
<td>4.2</td>
<td>17</td>
</tr>
</tbody>
</table>

The reason why OSA is more prevalent in men as compared to women across all age groups is unclear, but as discussed in a review by Young et al. (2002 a), differences in sex hormones, upper airway shape, craniofacial morphology, pattern of fat deposition, and differences in occupational and environmental exposures have been proposed.

There is a marked contrast in the reported prevalence rates with Franklin et al. (2012) reporting the highest figures. As discussed by the authors of this article and as shown in Table 4 some of the differences can be explained by different inclusion criteria, different populations, and the use of different scoring criteria.
Gender differences in OSAS prevalence rates could theoretically be due to differences in the expression of symptoms (i.e. that women remain undiagnosed because their symptoms is different from the more studied male population). Such differences, however, could not be found in a study by Young et al. (1996) where symptoms of 338 women and 551 men from the Wisconsin Sleep Cohort Study were compared.

**A progressive disease?**

Is OSA a progressive disease? Some studies report that progression is mainly dependent on weight gain while others report progression in the absence of weight gain (Table 6, next page). There are also some individual cases where OSA progressed over time despite weight loss (Svanborg and Larsson, 1993). However a major potential confounder in longitudinal studies on OSA progression is weight changes.
Table 6. OSA progression over time.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Subjects n</th>
<th>Age at baseline</th>
<th>Follow up time</th>
<th>AHI/ RDI*/ODI^</th>
<th>BMI</th>
<th>Main finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mason, et al. 1989</td>
<td>32 (m+f)</td>
<td>70.3</td>
<td>4.6 y</td>
<td>16.1*</td>
<td>17.0*</td>
<td>no data                                                                      no data</td>
</tr>
<tr>
<td>Phoha, et al. 1990</td>
<td>11 (m+f)</td>
<td>65.9</td>
<td>3 y</td>
<td>3.4*</td>
<td>5.5*</td>
<td>no data                                                                      no data</td>
</tr>
<tr>
<td>Svanborg, Larsson, 1993</td>
<td>42 (m+f)</td>
<td>55</td>
<td>16 m</td>
<td>10.1^</td>
<td>20.9^</td>
<td>27.1 27.3</td>
</tr>
<tr>
<td>Sforza, et al. 1994</td>
<td>32 (m+f)</td>
<td>51</td>
<td>5.7y</td>
<td>52.2</td>
<td>52.2</td>
<td>30.7 31</td>
</tr>
<tr>
<td>Hoch, et al. 1997</td>
<td>23 (m+f)</td>
<td>69.3</td>
<td>3 y</td>
<td>3.9</td>
<td>8.7</td>
<td>no data                                                                      no data</td>
</tr>
<tr>
<td>Pendlebury, et al. 1997</td>
<td>55</td>
<td>55.8</td>
<td>77 w</td>
<td>21.8</td>
<td>33.4</td>
<td>29.7 29.6</td>
</tr>
<tr>
<td>Lindberg, et al. 1999</td>
<td>29 (m)</td>
<td>50</td>
<td>10 y</td>
<td>2.1</td>
<td>6.8</td>
<td>26.0 26.3</td>
</tr>
<tr>
<td>Peppard, et al. 2000</td>
<td>690 (m+f)</td>
<td>46</td>
<td>4 y</td>
<td>4.1</td>
<td>5.5</td>
<td>29 30</td>
</tr>
<tr>
<td>Young, et al. 2002 (a)</td>
<td>161 (m)</td>
<td>no data</td>
<td>8 y</td>
<td>3.3</td>
<td>6.3</td>
<td>no data                                                                      no data</td>
</tr>
<tr>
<td>Fisher, et al. 2002</td>
<td>40</td>
<td>47</td>
<td>5 y</td>
<td>27*</td>
<td>28*</td>
<td>28.9 29.4</td>
</tr>
<tr>
<td>Redline, et al. 2003</td>
<td>197 (m)</td>
<td>29.5</td>
<td>5 y</td>
<td>3.7* (mdn)</td>
<td>5.4* (mdn)</td>
<td>25.4 27.7</td>
</tr>
<tr>
<td>Newman, et al. 2005</td>
<td>1342 (m)</td>
<td>62.1</td>
<td>5 y</td>
<td>3.4* (∆ change)</td>
<td>2.2* (∆ change)</td>
<td>0.5 (∆ change) 0.6 (∆ change)</td>
</tr>
<tr>
<td>Sahiman, et al. 2007</td>
<td>28</td>
<td>50.2</td>
<td>4 y</td>
<td>9.0</td>
<td>22.3</td>
<td>0.9 (change)</td>
</tr>
<tr>
<td>Berger, et al. 2009</td>
<td>160 (m)</td>
<td>51</td>
<td>5.1 y</td>
<td>23.0</td>
<td>28.9</td>
<td>29.3 30.1</td>
</tr>
<tr>
<td>Silva, et al. 2009</td>
<td>1385 (m)</td>
<td>62.3</td>
<td>5 y</td>
<td>10.5*</td>
<td>13.9*</td>
<td>28.7 29.2</td>
</tr>
</tbody>
</table>

Data are presented as mean if not otherwise indicated. Abbreviations; years (y), months (m), weeks (w)
Cardiovascular disease (including hypertension and stroke) is the most important OSA related morbidity. As reviewed by Bradley and Floras (2009) the prevalence of OSA has been reported to be high in populations with hypertension (30-83%), heart failure (12-53%), ischemic heart disease (30-58%), and stroke (43-91%). Selim et al. (2010) describes in the review *Cardiovascular consequences of sleep apnea* how OSA has been linked to hypertension, stroke, myocardial ischemia, arrhythmias, fatal and nonfatal cardiovascular events, and all-cause mortality. OSA has also been linked to insulin resistance (Tasali and Ip, 2008). The evidence for a link between OSA and cardiovascular disease comes from epidemiological studies, clinical cohorts of sleep apnea patients and from randomized trials of OSA treatment efficacy (Pack and Gislason, 2009).

However, there are and have been opposing views on how to interpret available studies on the associations between OSA and cardiovascular disease. In 1997, Wright et al. concluded that the evidence for a causal association between OSA and a range of poor health outcomes was weak and in 2004 Stradling stated that *Sleep apnea does not cause cardiovascular disease* (2004). In 2007, the authors of a systematic literature review on OSAS (published by the Scandinavian Agencies for Health Technology Assessment) concluded that the available evidence at that time, allowed the conclusion only that OSA co-varies with cardiovascular disease, including stroke and early death in men. There was insufficient evidence concerning relationships between cardiovascular disease and women, OSA and hypertension, or OSA and diabetes mellitus (DM) (SBU, 2007).

As reviewed by Bradley and Floras (2009), there are at least three major pathways through which the cardiovascular system may be negatively affected by OSA. First, apneas and hypopneas cause arousals from sleep which may lead to decreased parasympathetic nervous system activity, increased sympathetic nervous system activity and increased levels of blood catecholamines. Second, the impaired breathing due to obstructive events may negatively affect partial pressures of both blood oxygen and carbon dioxide. Third, breathing against an occluded airway increases the inspiratory negative intra-thoracic pressure. As a result of these changes, the blood pressure may increase, the myocardial oxygen delivery may be decreased and the cardiac oxygen demand may be increased. These changes may also induce oxidative stress, inflammation and endothelial dysfunction, all capable of initiating or exacerbating cardiovascular disease such as hypertension, atherosclerosis, myocardial ischemia, heart failure, cardiac arrhythmias and cerebrovascular disease.

The prevalence of OSA increases with increasing degrees of obesity. In their article *Obstructive sleep apnea and cardiovascular disease: a perspective and future directions*, Pack and Gislason (2009) discuss the scientific challenge in separating the effects of OSA from those of obesity and how much of the cardiovascular consequences of obesity that are mediated by OSA, independently of obesity and other known risk factors. The authors state that both obesity and OSA can activate the same pathogenetic mechanisms with the same endpoints (i.e. insulin resistance, hypertension and cardiovascular disease). The chronic intermittent hypoxia and sleep fragmentation due to arousals in OSA may initiate
oxidative stress, inflammatory pathways and sympathetic activation which in turn lead to increased levels of fatty acids, adipokines, and endothelial dysfunction, all shared pathogenetic mechanisms with obesity.

**Hypertension**

The prevalence of hypertension has been estimated to be about 40% in Europe (Wolf-Maier *et al.*, 2003) and as mentioned above, between 30-83% of patients with hypertension can be expected to have OSA (Bradley and Floras, 2009). There is a great range in these prevalence rates but in a recently published Swedish study, Franklin *et al.* (2012) report an 80% prevalence of OSA (AHI≥5) in women with hypertension aged 20-70 years. For comparison, in a Swedish study from 1994 Carlson *et al.* reports that 34% of patients referred to a sleep lab for evaluation of OSA were either hypertensive on treatment or had undiagnosed hypertension. In this study only apneas were scored, implying that there would be a higher prevalence if also hypopneas were scored. Nevertheless, roughly the same rates were reported from another Swedish study (Sjöström *et al.*, 2002) where 37% of hypertensive men were found to have OSA (AHI>10). Isaksson and Svanborg (1991) found that he prevalence of OSAS among hypertensive therapy resistant patients was 56%, as compared to 19% in the control group of therapy compliant hypertensive patients. Hedner *et al.* (2006) reported OSA prevalence rates (AHI ≥10, PSG) of 83% and 69% in men and women respectively with both hypertension and diabetes.

Blood pressure decreases during sleep in normal subjects, but subjects with OSA sometimes lack this “sleep dipping pattern” (Suzuki *et al.*, 1996; Loredo *et al.*, 2001). Furthermore, OSA subjects have been shown to have a higher risk of both daytime systolic and diastolic hypertension as well as nocturnal systolic hypertension when compared to closely matched controls without OSA (Davies *et al.*, 2000). Hla *et al.* (2008) reports from The Wisconsin Sleep Cohort Study (a prospective study of 328 participants with a mean follow up–time of 7.2 years) a dose-response increased odds of developing systolic non-dipping nocturnal blood pressure in subjects with SDB.

Dúran *et al.* (2001) reported that AHI was associated with hypertension even after adjustment for age, sex, BMI, neck circumference, smoking and alcohol and Bixler *et al.* (2000) reported that SDB (snoring included) was independently associated with hypertension in both genders with the strongest association found in younger subjects with normal weight. Several authors have reported a correlation between the severity of OSA and the severity of hypertension; Lavie *et al.* (2000) reports a relationship independent of age, sex and BMI while Nieto *et al.* (2000) report a relationship where some of the association was explained by BMI. Peppard *et al.* (2000) were able to show a dose-response association between severity of SDB at baseline and presence of hypertension four years later in a prospective population based study (if no SDB at baseline the odds ratio for hypertension after four years was 1.42 and if at least moderate OSA with an AHI ≥15 the odds ratio for having hypertension after four years was 2.89). This relationship was independent of known confounding factors such as hypertension at baseline, BMI, neck- and waist circumference, age, gender, alcohol and smoking.
Faccenda et al. (2001) showed in a randomized (oral) placebo-controlled trial that CPAP can reduce 24-h blood pressure in normotensive OSA patients (especially those who used CPAP >3.5h/night and those with an ODI >20) but the decrease was small. A similar (but rather small; 2.5 mm Hg) effect on mean 24-h blood pressure has been reported from a randomized parallel trial comparing therapeutic and non-therapeutic CPAP in men with OSA (Pepperell et al., 2002). Also in this study the effect was larger in patients with severe OSA. CPAP treatment for three months decreased mean 24-h blood pressure with 1.5 mm Hg compared to sham CPAP-treatment in a study by Dúran-Cantolla et al. (2010). Barbé et al. (2010) report of a similar magnitude of blood pressure decrease (systolic 1.9 mm Hg and diastolic 2.2 mm Hg) after one year of CPAP in non-symptomatic hypertensive patients with OSA, with the most significant reduction occurring in those patients that used CPAP for >5.6h/night. Norman et al. (2006) report a significant decrease in blood pressure already after two weeks of treatment with CPAP compared to sham-CPAP treatment in moderate- to severe OSA patients. This effect was not seen if OSA patients were treated with supplemental oxygen only.

A more substantial effect on blood pressure (a decrease by 10 mm Hg) has been reported by Becker et al. (2003) from their study comparing therapeutic- and non-therapeutic CPAP used for 9 weeks in patients with moderate to severe OSA. Coughlin et al. (2007) found that 6 weeks of CPAP in moderate to severe OSA patients reduced waking systolic- and diastolic blood pressure by 6.7 and 4.9 mm Hg respectively. Jaimchariyatam et al. (2010) report from a retrospective study that blood pressure in mild OSA patients not treated with CPAP increased over a 2- year period while blood pressure slightly decreased in those patients that received CPAP- treatment.

There are also studies that has failed to find an effect on blood pressure with CPAP treatment; both Robinson et al. (2006) and Campos-Rodriguez et al. (2006) report that 4- weeks of CPAP in neither non-sleepy hypertensive OSA subjects (Robinson) nor OSAS subjects with hypertension but on antihypertensive medication (Campos-Rodriguez) did reduce 24-h blood pressure. In a recently published study by Barbé et al. (2012), CPAP treatment on non-sleepy OSA patients did not decrease the incidence of hypertension nor other cardiovascular events (such as myocardial infarction, stroke, TIA, heart failure or cardiovascular death) after 4-years of follow up compared to dietary- and sleep hygiene counseling only.

Even though there are data linking hypertension and OSA it seems that treatment of OSA has a limited effect on blood pressure with the most marked effect in patients with severe degrees of OSA and in patients compliant to CPAP treatment in terms of hours of use/night.

**Cardiovascular disease**

Already in 1987, Koskenvuo et al. reported a doubled risk for ischemic heart disease and stroke in habitual snorers and OSA subjects compared to non-snorers, independent of BMI, hypertension, smoking or alcohol consumption. In 1990 Hung et al. evaluated presence of OSA in patients that had survived a myocardial infarction and found a higher prevalence in these men (after adjustment for age, BMI, hypertension, smoking and cholesterol levels) compared to age matched controls without a history of cardiovascular disease. In 1999, Peker et al. reported a higher prevalence of OSA in men requiring
intensive care for either angina pectoris or myocardial infarction compared to a population matched for age, sex and BMI and data adjusted for hypertension, hypercholesterolemia, diabetes mellitus and current smoking. Peker et al. (2002) have also reported an increased risk for cardiovascular disease independent of BMI, blood pressure, smoking and age (with follow-up time 7 years) in 182 subjects with OSA in a sleep clinic case-control study. Cross-sectional data from 6424 participants in the Sleep Heart Health Study showed an association between OSA and self-reported heart failure, stroke and coronary heart disease even in subjects with relatively mild OSA (Shahar et al., 2001).

Longitudinal studies from cohorts with subjects initially referred for evaluation of OSA have shown that subjects with OSA but without cardiovascular disease at baseline are at higher risk to develop cardiovascular disease than those without OSA at baseline. In 2005 Yaggi et al. presented data on incident stroke and all-cause mortality from 1022 patients with a follow-up time of more than three years (subjects with a history of stroke or myocardial infarction at base-line were excluded). Sixty-eight percent of the cohort had an AHI≥5 and were classified as having OSAS. OSA was found to increase the risk for stroke and all-cause mortality independent of other cardiovascular- and cerebrovascular risk factors (Yaggi et al., 2005). Another study published the same year reported similar findings; Marin et al. (2005) compared fatal- and non-fatal cardiovascular events (mean follow-up 10.1 years) in healthy men, snoring men, men with untreated mild/moderate OSA, men with untreated severe OSA and men with OSA that were treated with CPAP (n= 264, 377, 403, 235 and 372 respectively). Their results showed that untreated severe OSA increased the risk for both fatal- and non-fatal cardiovascular events and that CPAP treatment reduced this risk.

Longitudinal studies with samples from general populations show the same picture. Munoz et al. (2006) studied the risk of ischemic stroke in elderly patients with OSA (n=394, follow-up time 6 years) and found that severe OSA (AHI≥30) increased the risk for stroke independently of other known risk factors. Prospective data (8 years follow-up) from the Sleep Heart Health Study with 5422 participants from the general population, show that moderate and severe OSA at baseline were associated with a threefold increased risk of stroke in men and also that women with AHI >25 had an increased risk for stroke (Redline et al., 2010). Data from the same study (with a median follow-up time of 8.7 years) showed that (after adjustment for risk factors) OSA was a predictor of incident coronary heart disease in men ≤70 years but not in older men or women (Gottlieb et al., 2010). Data from this study also showed that OSA predicted incident heart failure (again only in men).

Cross-sectional as well as longitudinal data from 1475 and 1189 subjects respectively (4-year follow up) from the Wisconsin Sleep Cohort Study show an association with physician diagnosed stroke at baseline in subjects with an AHI>20 compared to those with AHI<5 after adjustment for known confounding factors (Arzt et al., 2005). Prospective data from the same cohort showed an association between OSA and incident stroke within 4 years (Arzt et al., 2005).

**Diabetes and the metabolic syndrome**

As reviewed by Tasali and Ip (2008) in the article *Obstructive sleep apnea and metabolic syndrome* there are both cross-sectional clinical and general population based studies that
have reported an association between the presence and severity of OSA and glucose intolerance, insulin resistance and DM. In a cross-sectional report from the Sleep Heart Health Study both sleep related hypoxemia and the RDI were found to be associated with fasting glucose intolerance independently of age, gender, BMI, and waist circumference at baseline (Punjabi et al., 2004). Reichmuth et al. (2005) reported from the Wisconsin Sleep Cohort Study that both the prevalence and incidence (within 4 years) of DM increased with increased levels of SDB at baseline.

An independent association between frequent snoring and reduced glucose intolerance has been shown in cross-sectional Korean studies including subjects with BMI<25 (Shin et al., 2005; Joo et al., 2006). Theorell-Haglöw et al. (2008) reported an independent association between OSA and decreased insulin sensitivity in Swedish women 20-70 years drawn from the general population. In a longitudinal community based study on Swedish men with a mean follow-up of 11 years Lindberg et al. (2012) report that an ODI>5 at baseline was a predictor of developing diabetes (after adjusting for age, baseline BMI, Δ BMI, hypertension and CPAP use) and all variables of SDB were associated with a deterioration of insulin resistance.

Some authors such as Vgontzas et al. (2005) even argue that sleep apnea might be a manifestation of the metabolic syndrome in obese patients. In a Swedish study on women (20-70 years) measures of OSA (i.e. AHI, ODI, minimal oxygen saturation and time during the night with <90% oxygen saturation) were closely associated with the metabolic syndrome (Theorell-Haglöw et al., 2011). Support for the Syndrome X constellation (metabolic syndrome) was also reported from the retrospective Cleveland Family Sleep Study. In this study AHI, arousal index, percentage of sleep time with oxygen saturation less than 90%, and percentage of slow wave sleep co-aggregated with metabolic features such as insulin resistance, obesity, hypertension, and dyslipidemia (Nock et al., 2009).

**Mortality**

Already in 1988, He et al. reported of an increased mortality risk over 8 years in male subjects with OSA when apnea index was >20 compared to <20, and particularly in subjects <50 years of age (He et al., 1988). Data from an observational sleep clinic cohort study (follow-up time 3.4 years) showed an increased risk for death, adjusted for sex, age, atrial fibrillation, hypertension, BMI, DM, race, smoking, alcohol and hyperlipidemia, already at AHI >5 (Yaggi et al., 2005). Marin et al. (2005) found an increased risk for cardiovascular death, adjusted for BMI, sex, DM, smoking, alcohol, hypertension, cardiovascular disease, lipid lowering- and antihypertensive drugs, when AHI was >30 (follow-up time 10.1 years) in their study on snorers and OSA subjects and matched healthy men from the general population.

Shah et al. (2010) performed an observational cohort study on patients (≥50 years) referred for OSA evaluation and found that an AHI≥5 at base-line increased the risk for death from cardiovascular causes during follow-up (mean 2.9 years). The results were significant even after adjustment for other traditional cardiovascular risk factors. In a prospective observational cohort study on women referred to a sleep clinic with suspected OSA, Campos- Rodriguez et al. (2012) found that severe OSA was associated with cardiovascular death also in women and that CPAP treatment seemed to reduce this risk.
Data from the Sleep Heart Health (follow up time of 8.1 years) showed that OSA was independently associated with both all-cause and cardiovascular disease-related mortality in men aged 40-70 years, but not in men >70 years or in women (Punjabi et al., 2009). Results from the Busselton Health Study showed that moderate to severe sleep apnea was independently associated with an increased risk for all-cause mortality (Marshall et al., 2008). In the Wisconsin Sleep Cohort Study (18-years follow up) there was an association between both all-cause mortality and cardiovascular related mortality and OSA after controlling for covariates such as age, sex, BMI, and other potential confounders (Young et al., 2008).

Strangely, OSA does not seem to be associated with increased mortality in the elderly. In, 2005, Lavie et al. reported declining mortality rates with age in males with moderate to severe sleep apnea compared to the general population. Lavie and Lavie (2009) performed a retrospective study on all-cause mortality in 611 OSA patients ≥65 years (>5 years follow-up) compared to a age-,gender-, and ethnicity- matched national mortality data. The results showed that those with severe sleep apnea had the same mortality as the matched population while individuals with mild- or moderate sleep apnea had lower mortality than the matched population. In a Swedish study, 331 community-dwelling persons aged 71-87 were followed for 7 years. Thirty-eight percent initially had obstructive AHI >5 and OSA was not found to be associated with cardiovascular disease disease or mortality (Johansson et al., 2012).

**Quality of life, depression and insomnia**

Obstructive SDB/OSA has also been associated with impaired quality of life (Finn et al. 1998; Baldwin et al., 2001), depression (Ohayon 2003), and insomnia (Wickwire and Collop, 2010). Finn et al. (1998) evaluated self-reported general health profiles in 421 men and 316 women aged 30-60 years in the Wisconsin Sleep Cohort Study (general community sample), and found that SDB was independently related to lower general health status. The association remained after adjustment for age, sex, BMI, smoking status, alcohol usage and reported cardiovascular conditions. In large, similar findings which were reported from the Sleep Heart Health Study (5816 participants, mean age 63 years) indicated that SDB was associated with poorer quality of life especially when it was moderate to severe (Baldwin et al., 2001). Notable was that in both studies, the decrements in self-reported health status were comparable to other chronic diseases (Baldwin et al., 2001) such as arthritis, angina, hypertension, DM and back problems (Finn et al., 1998).

In another study, quality of life and mood/depression were evaluated in patients with severe OSAS. Not only was quality of life decreased in OSAS patients compared to controls but also strongly correlated to measures of depression (Akashiba et al., 2002). Aloia et al. (2005), report that RDI was related to both BMI and depression scores (Beck Depression Inventory) in a sample of 93 subjects with moderate to severe OSAS but not to ESS score.

Ohayon (2003) performed a telephone-based questionnaire study with 18980 participants on the association between depressive disorders and breathing related sleep-disorders. According to DSM-IV criteria, 18% of those with depressive disorder also had SDB and
17.6% of those with SDB also had depressive disorder. Even after controlling for obesity and hypertension the odds ratio for having a DSM-IV SDB diagnosis was 5.26 for individuals with a depressive disorder. As discussed in a review by Ejaz et al. (2011) symptoms of OSA and depression may overlap and prevalence rates of depression in OSA patients ranging from 5 and 63% have been reported.

According to Wickwire and Collop (2010) insomnia is the most common sleep disorder in the adult population followed by OSA and they often occur together. It is important to recognize that OSA and insomnia may have a shared symptomatology as sleepiness or fatigue, lethargy, anhedonia, decreases in motivation, mood disturbance, or anxiety may be primary complaints of either OSA or insomnia (Wickwire and Collop, 2010). According to these authors, as many as one-third to over one-half of patients referred for evaluation of SDB, may have co-morbid insomnia.

**Accidents in traffic and at work**

Sleepiness and falling asleep at the wheel are common causes of traffic accidents. Since one consequence of OSA is sleepiness and the prevalence of OSA is high in both the general population and especially in commercial drivers (Howard et al., 2004) the question on the association between driving safety and OSA is of great importance. In a review published by the Scandinavian Agencies for Health Technology Assessment on OSAS the authors concluded that OSA co-varies with traffic accidents independent of daytime sleepiness and driving exposure in men (SBU, 2007). This review included 4 studies: Young et al., 1997; Barbé et al., 1998; Teràn-Santos et al., 1999; and Horstmann et al., 2000. Notably, the percentage of women in these studies were: 41%, 2%, 23% and 8% respectively and only Young et al. analyzed gender-specific differences in risk between men and women finding that only men had an increased risk. None of these four studies reports a relationship between sleepiness as measured by the ESS (commonly used in clinical practice to evaluate sleepiness) and increased accident risk. Concerning the association between AHI values and traffic risk, both Young et al. (1997) and Teràn-Santos et al. (1999) reports that already at AHI>5 and AHI≥5 the risk is increased.

In a review by Tregear et al. (2009), 18 articles were analyzed for OSA and crash risk, also in this sample of studies there was a substantial dominance of men. The main conclusion was that untreated sleep apnea is a significant contributor to motor vehicle crashes and that crash predicting characteristics might include BMI, AHI, nightly oxygen saturation, and possibly daytime sleepiness. It should be noted that high BMI with OSA is a risk factor for accident, but also that high BMI alone is as well. Regarding sleepiness and accidents, 8 articles were included using ESS and two using MSLT and none could confirm that increased risk is correlated to higher ESS scores or differences in mean sleep latency. OSA subjects are also at increased risk for work-related accidents. Subjective work performance has been shown to be lower in snorers and OSAS subjects compared to the general population (Ulfberg et al., 1996) and furthermore, subjects referred for evaluation of SDB reported double the risk for being involved in an occupational accident during a 10 year period as compared with the general population (Ulfberg et al., 2000). Lindberg et al. (2001) report from a community based study using questionnaires (follow-up 10 years) that sleepy snorers, in contrast to non-sleepy snorers and sleepy non-snorers had an increased risk for occupational accidents.
TREATMENT

Continuous positive airway pressure
CPAP treatment for OSA was first introduced in 1981 by Sullivan and colleagues (Sullivan et al., 1981). The treatment mechanism consists of a positive air pressure delivered through a mask applied over the nose (or nose and mouth) working as a pneumatic airway splint during sleep. CPAP is regarded as the golden standard for treatment of OSA and it has been proven that CPAP treatment effectively diminishes upper airway obstruction during sleep (SBU, 2007).

CPAP treatment also seems to reduce cardiovascular mortality, for example Young et al. (2008) reported from a study with 18-year follow up that OSA subjects with CPAP treatment had an adjusted all-cause mortality hazard of 3.0 compared to 3.8 for OSA subjects without CPAP treatment. Another study showed that CPAP treatment reduced the risk of fatal and non-fatal cardiovascular events (Marin et al., 2005). CPAP treatment reduces daytime sleepiness regardless of severity of OSA (SBU, 2007). Weaver et al. (2012) showed in a recently published article that CPAP treatment in sleepy patients (ESS>10) even with only mild or moderate OSA (AHI 5-30) improved functional outcome. CPAP treatment also seems to reduce the risk for traffic accidents in OSAS patients (Krieger et al., 1997b; George, 2001).

Mandibular advancement devices
A mandibular advancement device (MAD) for the treatment of OSA was first introduced in 1985 by Soll and George. The MAD protrudes the mandible thus creating both an increased volume of the pharyngeal airway and increased airway stability through an increased muscular tone (Soll and George, 1985).

Even though MADs have been found to have a positive long-term impact on several OSA symptoms such as excessive daytime sleepiness, morning headaches and daytime naps in compliant patients (Marklund and Franklin, 2007) they seem to be somewhat less effective than CPAP in reducing both excessive daytime sleepiness and AHI (SBU, 2007). POSA is a positive predictor for MAD treatment efficacy (Marklund et al., 1998; Chung et al., 2010).

Surgical treatment
In 1981, Fujita et al. introduced Uvulopalatopharyngoplasty (UPPP) as a surgical treatment for OSA. A traditional full UPPP comprises resection of the uvula together with parts of the soft palate and the tonsils. Since it was introduced it has dominated the surgical procedures in the treatment of OSA. The procedure has been reported to be associated with several adverse effects including peri- and postoperative death, bleeding, respiratory compromise, and other postoperative difficulties such as difficulty in swallowing. Additionally the efficacy of the procedure has not been proven (SBU, 2007). The AASM states in their Practice parameters for the surgical modifications of the upper airway for obstructive sleep apnea in adults that UPPP as a sole procedure with or without tonsillectomy, does not reliably reduce the AHI when treating moderate to severe OSAS and therefore both CPAP and MAD should be offered to the patient before UPPP (Aurora et al., 2010).
Tracheostomy is a highly effective surgical treatment to abolish apneas and hypopneas since the tracheostoma bypasses the collapsible pharynx. The AASM recommends that tracheostomy, even though considered very effective, should only be considered when other options do not exist, have failed, are refused or when deemed necessary by clinical urgency (Aurora et al., 2010). The reason for this is of course the significant negative side effects that are associated with a tracheostoma.

Maxillo-mandibular advancement therapy (MMA) includes a surgical reposition of both the mandible and the maxilla in an anterior direction resulting in an increased volume of the airway. There is limited evidence of the effectiveness of this method and therefore (even though published articles with lower quality of evidence shows that the procedure is quite effective) and therefore the AASM states that MMA is indicated only in patients with severe OSA where neither CPAP nor MAD works (Aurora et al., 2010).

**Weight reduction**

Bariatric surgery seems to give substantial reductions in the AHI and in one report surgery resolved or improved OSA in 83.6% (Olson and Courcoulas, 2011). One recently published trial of 60 obese patients randomized to either a conventional weight loss program or bariatric surgery (follow-up 2 years) could not show any significant differences in AHI reduction between groups even though weight loss was markedly greater in the surgery group (Dixon et al., 2012). Other findings from this study were a great variability in the individual effect and that much of the benefit was associated with mild weight loss.

Even though both dietary weight loss and bariatric surgery have been shown to be effective in reducing OSA severity, many patients have residual OSA leading the authors of a recently published meta-analysis to recommend that weight reduction programs should be considered as adjunct rather than curative therapy for OSA (Anandam et al., 2012).

**Positional therapy**

Several methods and devices have been used to hinder POSA patients to sleep in the supine position. In 1985 Cartwright et al. evaluated an auditory supine position warner in 10 men with POSA and found a significant reduction in AHI and number of oxygen desaturations. In another study a “positioner” device- (i.e., a soft vest attached to a board placed under the pillow eliminating the possibility to supine sleep) was tried in 23 patients with POSA. Of these, 18 patients were compliant and a majority lowered their AHI to <10. The mean ESS score decreased but 50% of the patients reported increased snoring (Loord and Hultcrantz, 2007).

Jokic et al. (1999) compared positional treatment (sleep with backpack) with CPAP in 13 patients with POSA and found that CPAP was more effective in lowering the AHI and increasing minimum oxygen saturation. No difference was found concerning sleep architecture, ESS, MWT, or quality of life measures. A thoracic anti-supine band improved AHI in POSA patients but to a lesser extent than CPAP (Skinner et al., 2008). A supine vibration alarm attached to the sternum was found to significantly reduce the AHI albeit with persisting snoring in 15 POSA patients (Bignold et al., 2011).
QUANTITATIVE SENSORY TESTING

Decreased sensory function is a common symptom and characteristic of neuropathic disorders. Sensory modalities such as pain, touch, vibration, and temperature can be affected by disease. These sensory modalities can be assessed and the results used to diagnose and evaluate neuropathic disorders in both clinical practice and research. Historically, several types of tests have been in use, such as the tuning fork or von Frey filaments. These tests have not been standardized (Hagander, 2006), rendering acquired data difficult to reproduce and quantify.

Quantitative sensory testing (QST) is an all-embracing term for different non-invasive methods for the evaluation of sensory function. QST testing uses standardized methods (i.e., standardized stimulus) in order to yield reproducible and quantifiable data and results. Commonly used stimuli to assess sensory function are vibration, cold, warm, cold pain, and warm pain. QST is useful both for the detection and follow-up of diseases affecting the sensory nervous system (Yarnitsky and Pud, 2004). QST evaluates all levels of the sensory pathway, from the peripheral sensory receptor, through the afferent nerves to the sensory cortex in the brain. Thus, the method only tells if there is a decreased function somewhere along the route but not where it is localized (Hagander 2006).

In humans there are different classes of sensory receptors all sensitive to different types of stimulus (such as the bare nerve endings mediating thermal sensations and the mechanoreceptors mediating proprioception). Furthermore, receptors are either of a slowly adapting type or a rapidly adapting type. While the first type signals the magnitude of the stimulus over a longer period of time the latter only signals at the beginning and end of the stimulus. Furthermore there are different types of nerves, and the different sensory nerves have highly specialized ranges of functions. Larger myelinated sensory fibers transmit vibration, touch, pressure, and position-sense. Smaller myelinated (Aδ) and unmyelinated C-sensory nerve fibers transmit thermal sensations (Hagander 2006).

QST is a psychophysical method (Shy et al., 2003), meaning that it is dependent on cooperation as well as expectation and motivation of the tested subject. All QST procedures require that the tested subject responds to a given stimulus either verbally or through pressing a button. Even though the stimulus and the equipment used may be standardized, the subjects’s psychological factors might not be. Therefore it is of great importance that all factors that may affect the psychological aspects of the testing process be controlled and standardized. This includes the environment where testing takes place and the information and instructions be given to the test subject on the procedure.

QST is most commonly performed in the extremities. In clinical practice the two most common sensory modalities to be tested are vibration and cold. Several studies have concluded that both vibration and thermal testing are reliable and reproducible if performed under standardized conditions (Yarnitsky, 1997; Bartlett et al., 1998).
Cold sensory testing

The equipment used for thermal sensory testing contains a computer and an apparatus which delivers different temperatures at the tip of a probe. The rate of temperature change at the tip of the probe can be modulated as well as the time between stimuli. The probe contains a Peltier-element, i.e., a metal interface that change temperature with the directional flow of electric current.

Cold sensory function is measured through cold detection thresholds (CDT). Normally, testing starts at a temperature that ideally should be perceived as neutral (i.e. neither warm or cold). Thereafter different thermal stimuli are delivered. Most commonly the starting temperature when testing CDTs in the extremities is 32°C. The CDT is commonly expressed as the difference between the starting temperature (i.e. adapting temperature) and the response temperature.

Historically, different algorithms for measuring temperature detection thresholds have been used, but more recently two general test algorithms have emerged: the method of levels (MLE) and the method of limits (MLI) (Shy et al., 2003). In MLE, stimuli of predetermined intensities are used and the test subject responds after the stimulus has been given whether it was detected or not. Between stimuli there is a thermo-neutral period where the temperature first returns to the adaptation temperature and then stays at this temperature for a while before the next stimulus. The subsequent stimulus temperature is increased or decreased depending on whether the first stimulus was perceived or not. As a brief example of how the procedure may be performed: the first stimulus could be a decrease of 3°C (i.e. if the starting temperature was 32°C then the stimulus is 29°C). If the subject responds that the stimulus was perceived, the following stimulus steps are decreased (in predetermined step-sizes) until no perception is perceived. On the other hand, if the first stimulus was not perceived the next stimulus is increased until perception is acquired. In this way colder stimuli follows “no” responses and less cold stimuli follows “yes” responses as different thermal stimulus are given (up and down) in order to locate the CDT.

In MLI cold thermal testing, stimulus of continuously increasing (i.e. colder) intensity is used and the test subject is instructed to respond as soon as any sensation of cold is perceived. The MLI algorithm consists of multiple stimuli with thermo-neutral periods between and usually the CDT is taken as the mean of these stimuli. The time interval between stimuli can be varied either with standardized intervals or intervals where the lengths are randomized. In MLI testing the reaction time is of importance since the stimuli keeps increasing during the time it takes for the brain to process the input and then transmit a signal to the hand to press the button. A stimulus change rate of 1 °C/s is common in both MLE and MLI algorithms.

The major differences between these two methods are that MLI also contains a reaction time artifact, which usually results in higher threshold values compared to MLE, but also that MLI is quicker to perform than MLE. The MLI reaction time artifact has led some authors to recommend MLE, but there is little evidence that MLE testing is either more sensitive for pathology or more reproducible than MLI (Yarnitsky and Pud, 2004).
Random dummy stimuli can be used to ensure attention and cooperation of the tested subject in both MLE and MLI and it is recommended to give the tested subject a practice trial since CDT testing is subject to learning and practice effect (Hagander 2006).

**Age and gender**
Increasing age may have an effect on QST results. This has been shown for vibration thresholds, but regarding thermal thresholds it seems that warm sensory thresholds are more affected than CDTs. Sensory function in the distal extremities seems to be more age-sensitive than in more proximal test sites (Hagander, 2006), and there are studies that have shown a significant correlation between CDTs and age for the hand and foot (Bartlett *et al*., 1998; Lin *et al*., 2005) but not for the lip (Dyck *et al*., 1993).

Concerning CDTs and gender Hagander *et al*. (2009) reported a gender difference in soft palate CDTs, as measured by MLE, but this study had a small sample size with only 15 women and eight men. CDTs from other body sites have not been shown to be gender dependent (Bartlett *et al*., 1998; Lin *et al*., 2005).

**Testing conditions**
The results of thermal testing are dependent on probe size, with a larger probe yielding lower thresholds (Hagander, 2006). This phenomenon is due to spatial summation (where the input to different neurons are added together to reach a certain threshold) but also to the fact that a larger stimulated area activates more receptors. Test site temperature (i.e., skin temperature) within the range that normally exists in routine clinical examinations does not affect cold thermal thresholds (Hagander *et al*., 2000). The pressure with which the thermode is applied to the skin does not affect thermal thresholds and it does not affect intra-or inter-subject reproducibility of thermal measurements (Pavlakovic *et al*., 2008).

**Cold thermal testing in the upper airway**
The most common test sites in routine neurophysiological QST examinations are at the hand and feet. However, as reviewed by Hagander (2006), QST in the oral cavity (including the tonsillar pillars) and in other areas with mucosa instead of skin, such as the vagina, has been used in clinical research. At least for the vaginal area, QST has been found to be clinically feasible, valid and repeatable (Vardi *et al*., 2000).
RATIONALE

Why study OSA in subjects with hypertension?
As discussed earlier in this thesis, OSA has been associated with hypertension in both sleep clinic populations and in the general population (Carlson et al., 1994; Bradley and Floras, 2009). Considering the high prevalence rates of both hypertension and OSA in the general population (Young et al., 2002a; Wolf-Maier et al., 2003; Hedner et al., 2006) both diseases can be expected to be common in primary care settings. The ability to identify and treat OSA in primary care may be important for both the individual and the society, as OSA is a treatable risk factor for cardiovascular disease. This could be especially important in patients with hypertension, since OSA may impose an additive cardiovascular risk in these patients.

Furthermore, OSA has been shown to be both associated- and co-occurring with depressive symptoms (Ohayon, 2003), decreased quality of life (Baldwin et al., 2001) and sleep complaints such as insomnia (Wickwire and Collop, 2010). Both depression and insomnia are common problems in primary care populations (Linde et al., 2011; Falloon et al., 2011) and some of their signs and symptoms may mask OSA.

Even though OSA has gained attention among both medical practitioners and in the general population, most subjects with OSA remain undiagnosed (Bradley and Floras 2009) reflecting, the difficulties to identify OSA in affected individuals. In order to simplify identification of OSA patients in primary care hypertension clinics, both updated knowledge on prevalence rates and factors associated with OSA is needed. To the best of our knowledge no previous study has focused on sleep complaints/insomnia, depression, and impaired quality of life as plausible predictors of undiagnosed OSA in a primary care setting.

Why study positional dependency in OSA?
Several studies have reported a significant night to night variability in the AHI (Le Bon et al., 2000; Bittencourt et al., 2001). One of the major factors that may change the AHI from one night to the other is the proportion of supine and non-supine sleep. Oksenberg et al. (1997) report from a sleep clinic population that more than half of the patients had twice as high AHI in the supine position compared to non-supine positions. Based on the assumption that most individuals change their sleeping position several times during the night, yielding different proportions of supine and non-supine sleep, positional dependency may be a potential confounder in both diagnosis, classification of OSA severity and evaluation of treatment efficacy.

Keeping in mind the proposed negative associations between OSA and cardiovascular disease in mind, diagnostic accuracy is of great importance in the decision of whom to treat. Therefore, several aspects of positional dependency in OSA and its potential implications for OSA diagnosis need to be studied. At this point, and to the best of our knowledge, there are no studies that have evaluated the prevalence of POSA in a non-sleep clinic population. Neither are there any studies that have evaluated the impact of POSA on traditional OSA classification.
Why study signs of upper airway neuropathy in OSA?

The pathogenesis of OSA is not fully understood, but as discussed earlier, data indicate that OSA might be a progressive disease. In many cases, patients report years of snoring before witnessed apneas and symptoms occur (Lugaresi and Plazzi, 1997). As described in this thesis there are many factors affecting the patency of the upper airway during sleep, including anthropometric, anatomic, and dynamic factors.

It is known from occupational medicine that long-standing vibrations may cause nervous lesions in tissues, with an exposure–effect relationship between vibration and neuronal damage. (Virokannas, 1995; Strömberg et al., 1996). Based on these observations, the hypothesis was formed on the pathogenesis of OSA that long-standing, snoring-induced vibrations cause neurogenic lesions in upper airway tissues, progressively damaging the reflex circuits responsible for keeping the upper airway open when challenged by inspiratory negative pressure (Svanborg, 2005).

As described earlier in this thesis several studies, using different methods, have demonstrated upper airway sensory neuropathy in patients with OSAS (Larsson et al. 1992; Kimoff et al., 2001; Guilleminault et al., 2002; and Nguyen et al., 2005). However, these previous studies included limited numbers of subjects, clear differentiations of patients with varying degrees of obstructive breathing were not always made, and there were no attempts to correlate the duration of snoring to degree of sensory deficit in the upper airway. Complementary studies are therefore warranted to strengthen the hypothesis.

The prospective design of the Hypersleep study gives us a unique possibility not only to study the factors described above at baseline but also to perform future studies on longitudinal correlations between changes in AHI and degree of sensory impairment. To perform such studies a method with known test-retest repeatability must be used to assess signs of sensory neuropathy. One promising method is QST which has been used to study sensory (vibration and cold) thresholds in the upper airway (Hagander et al., 2009). Cold sensory testing showed several methodological advantages compared to vibration testing (Hagander et al., 2009) but the test-retest repeatability of the method (MLE) was not studied. Therefore, further studies on different methods of cold sensory testing (i.e., MLE and MLI) in the oropharynx with special emphasis on test-retest repeatability are warranted.
AIMS OF THE THESIS

1. To describe the occurrence of undiagnosed OSA and to identify determinants of moderate/severe OSA in a primary care cohort of patients with hypertension.

2. To describe the prevalence of position dependent OSA and its relation to OSA severity classification.

3. To compare two methods for quantitative testing of cold sensitivity in the upper airway with respect to test-retest repeatability, sensitivity of threshold detection and speed of investigation, to decide which would be most suited for testing patients with snoring and OSA.

4. To evaluate signs of upper airway sensory neuropathy in non-snorers, snorers, and snoring OSA subjects with special reference to AHI and duration of snoring history.
METHODS

All subjects in studies I, II and IV were initially recruited as participants in the *Hypersleep study*, initiated in 2007. Therefore, a fundamental description of the aims, design, and methods of this study will be provided as a general introduction. The specific details of each study will then follow.

The general aims of the *Hypersleep study* were:

1. To study the occurrence and characteristics of OSA in hypertensive primary care patients, 18-65 years, with respect to different variables such as gender, weight, co-morbidities, self-perceived health status, depressive- and sleep related symptoms.
2. To compare different methods for the initiation of CPAP treatment with respect to short- and long term compliance.
3. To prospectively (5-year follow up) evaluate the impact of CPAP treatment on morbidity, mortality and quality of life in patients with hypertension and OSA.

*Design of the Hypersleep study*

The registers of four primary care health centers in the community of Jönköping were screened for patients, 18-65 years, with hypertension (140/90 mmHg). Exclusion criteria were terminal disease, current treatment of OSA (CPAP/MAD), severe psychiatric disease, dementia, alcohol/drug abuse or difficulties reading and/or understanding the Swedish language. Participants were evaluated in multiple steps including clinical examinations, questionnaires and a polygraphic recording (Figure 2).

![Diagram of study design](image-url)

**Figure 2.** Design of the *Hypersleep* study.
Clinical variables

The following clinical variables were collected: age, gender, systolic- and diastolic blood pressure in the supine position after 5 minutes of rest, BMI, neck circumference, and waist circumference. Data on co-morbidities, smoking habits and alcohol consumption were also collected. Co-morbidities were defined as follows: ischemic heart disease (IHD) was defined as a history of angina pectoris, myocardial infarction, coronary angioplasty or coronary artery by-pass surgery. DM was defined as current treatment with insulin or anti-diabetic pharmaceuticals or repeated fasting blood glucose values ≥7mmol/l. Respiratory disease was defined as a history of asthma, chronic obstructive pulmonary disease or current treatment with β-agonists or inhalation corticosteroids. Transient ischemic attack (TIA)/stroke was defined as a history of either events. Data on medication affecting the cardiovascular system, hypnotic drugs and antidepressants were also collected as well as data on blood cholesterol levels (the latter from the primary care register).

Questionnaires and self-rating scales

Data on the following variables were collected through a specially designed questionnaire: difficulties initiating sleep, presence of loud and disturbing snoring, breathing interruptions during sleep, dry mouth on awakening, morning headaches, daytime tiredness, involuntary sleep spells during the daytime, difficulties staying awake behind the wheel. All questions were evaluated with a likert scale (never, seldom, sometimes, often, always). In the same questionnaire participants were also asked about their normal sleep length (hours) and if and how many years they had suffered from disturbing snoring. Self-perceived sleep efficiency was evaluated through the quotient of self-estimated sleep time/desired sleep time.

The Berlin Sleep Apnea Questionnaire (BASQ) was also used (Netzer et al., 1999). The BASQ includes 11 items in three categories. Category 1 (5 questions) focuses on the frequency and severity of snoring and apneas; category 2 (4 questions) focuses on daytime symptoms (i.e., tiredness, and sleepiness related to driving) and category 3 the occurrence of hypertension and obesity. Patients are classified as “positive” for OSA if they have 2 or more responses indicating high frequency/severe problems in each of the first two categories. The third category is “positive” if the patient has hypertension and/or a BMI >30 kg/m². In total, 2 or more “positive categories” indicates a high risk of OSA. The sensitivity and the specificity of BASQ for OSA among patients with coronary artery disease have been reported to be 70% and 48%, respectively; the positive and negative predictive values are 56% and 64% (Martinez et al., 2012).

The ESS (Johns, 1991) was used to assess excessive daytime sleepiness. In this questionnaire the respondents are asked how likely they are to doze off (0 = no chance of dozing/1 = slight chance of dozing/2 = moderate chance of dozing/3 = high chance of dozing) in different situations: sitting and reading, watching TV, sitting inactive in a public place (e.g. a theater or a meeting), as a passenger in a car for an hour without a break, lying down to rest in the afternoon when circumstances permit, sitting and talking to someone, sitting quietly after a lunch without alcohol, in a car while stopped for a few minutes in traffic. EDS was defined as ESS >10.
The Minimal Insomnia Symptoms Scale (MISS) (3 items) was used to measure difficulties initiating sleep, difficulties maintaining sleep, difficulties with non-restorative sleep, as well as occurrence of clinical insomnia (Broman et al., 2008). The subjects grade their sleeping difficulties on scales ranging from no problems (0), to very great problems (4). A total score of 0-3 indicates no clinical insomnia; 4-6 sub-clinical insomnia; 7-9 moderate clinical insomnia and 10-12 severe clinical insomnia. Reliability, as assessed with Cronbach’s alpha for the whole scale was 0.81 in an elderly Swedish population. Sensitivity and specificity for at least moderate clinical insomnia were 93% and 84%, respectively (Hellström et al., 2010).

The well validated Hospital anxiety and depression scale (HAD) (14 items) was used to measure anxiety and depressive symptoms (Bjelland et al., 2002). The total score of the seven depression items range from 0-21, the higher score the more depressive symptoms. A cut-off of ≥7 was used to indicate depressive symptoms. The seven anxiety items work the same way, and a cut-off of ≥9 can be used to indicate anxiety (Zigmond and Snaith 1983).

Finally, self-perceived health status was measured through the first question of the SF-36 questionnaire where subjects are asked to rank their perceived health as either poor (1), fair (2), good (3), very good (4), or excellent (5) (Ware and Sherbourne, 1992).

**Polygraphic recordings**

All participants underwent a full-night PG recording in their homes, which included digitized recordings (Embletta recording system, Somnologica software, ResMed Inc., Trollhättan, Sweden) of nasal airflow (nasal air-pressure), pulse oximetry, respiratory movements (thorax and abdomen), and body position. Sleep time was estimated from a combination of several factors. First, all participants were asked to record estimated sleep onset, wake periods during the night, and wake-up time. Second, all recordings were analyzed for a stabilization of breathing patterns (nasal airflow and thoraco-abdominal movements) and absence of awake-type body movements. Periods during the night showing awake-type respiration and body movements were excluded from index time. Periods during the night were the above mentioned factors were in favor of sleep were considered as sleep.

Apneas, hypopneas and blood oxygen desaturations were manually scored. An apnea was scored if the nasal pressure signal amplitude dropped ≥90% of baseline, the event lasted more than 10 s., and at least 90% of the events duration met amplitude reduction criteria. A hypopnea was scored if the nasal pressure signal amplitude dropped ≥30% of baseline, oxygen saturation dropped ≥4% from pre-event baseline, the event lasted more than 10 s., and at least 90% of the events duration met amplitude reduction criteria. Desaturations were scored if oxygen saturation dropped ≥4% from baseline and were not related to a change in sleeping position. All subjects had at least 4 h of estimated sleep (otherwise another recording was performed). Recordings were scored blinded to other data. The AHI and the ODI was calculated. Furthermore, the lowest point of oxygen desaturation during the night was recorded as well as the mean oxygen saturation level and the percentage of time spent in <90% of oxygen saturation. Subjects were defined as having mild OSA or moderate/severe OSA if they had AHI≥5-<15 or ≥15 respectively.
**Clinical examination**

All participants with an AHI≥5 (and those included in the non-snorer group of study IV) underwent a standard examination (post-polygraphy) of the upper airways: inspection of the anterior part of the nose and the oral cavity with a head lamp and nasal specula/tongue spatula and a fiber-endoscopic examination of the epipharynx, oropharynx and hypopharynx/larynx. Subjects in study IV were classified according to tonsil size (Friedman *et al.*, 2004).

**Intervention**

All participants with an AHI ≥15 were offered CPAP treatment. Participants with an AHI between ≥5-<15 were invited to be randomized to either a control group with no intervention or to be offered CPAP treatment (randomization in 1:2 mode between groups to compensate for expected treatment failures). All patients (despite initial AHI) that accepted intervention with CPAP-treatment were randomized to either standard CPAP installation or CPAP installation combined with intensified patient education in the form of group studies in a problem based learning mode.
Population and methods study I-IV

**Study I:** Population and methods as described for the *Hypersleep Study*.

**Study II:** The PG recordings of last 265 subjects from the *Hypersleep study* were specially evaluated for AHI in the supine- versus the non-supine positions. Before the final analysis, it was decided to exclude subjects that spent less than 10% or more than 90% of the night in the supine position, as it was judged that the time for the less used position would be too short to allow any assessment of positional tendency. Since all subjects had at least 4 hours of estimated sleep these percentages would yield at least 24 min in either the supine- or the non-supine position. We defined POSA as a supine AHI twice the non-supine AHI with the additional criteria of an AHI ≥5.

Subjects were classified both according to traditional/AASM classification and degree of POSA. The latter classification was based on the relation between supine and non-supine AHI. Subjects with a supine AHI≥5 and normal non-supine AHI (<5) were classified as mild, moderate or severe exclusively supine POSA (supine AHI≥5, ≥15, ≥30 respectively). POSA subjects but with elevated AHI (≥5) also in the non-supine position were classified as a separate group.

Thus, in total, six different groups were formed:
1. No OSA/POSA
2. Mild exclusively supine POSA (supine AHI ≥5–<15, non- supine AHI <5)
3. Moderate exclusively supine POSA (supine AHI ≥15–<30, non- supine <5)
4. Severe exclusively supine POSA (supine AHI ≥30, non- supine AHI <5)
5. POSA (position dependent, but with supine AHI≥5 and non- supine AHI ≤5)
6. OSA (non position dependent, total AHI ≥5)

The relation between supine and non-supine AHI were analyzed as follows. Groups were compared with respect to age, gender, BMI, ESS, supine time (%) and total, supine- and non-supine AHI. The outcome of classification by POSA group was compared to the outcome of a standard classification of OSA severity as recommended by the AASM (Epstein *et al.*, 2009). We also analyzed the percentage of sleep time in the supine position for each position dependent OSA group sub-divided by group based on AASM classification. Predictors for POSA were assessed.

**Study III:** Forty healthy volunteers were recruited from the School of Health Sciences in Jönköping and from the staff at the County Hospital in Jönköping. Exclusion criteria included past or present snoring or sleep apnea (as verified by partners), smoking, obesity (BMI >30), tonsillar disease, upper airway or lip surgery, and diseases or medications known to cause peripheral neuropathy.

All CDTs were measured with a Medoc TSA–2001 (Medoc Ltd., Ramat Yishai, Israel). An intra-oral thermode with a 6 mm diameter Peltier element at the tip was used (Figure 3).
All subjects were informed of the procedures in a standardized manner. The tests were performed in a quiet room secluded from external stimuli. A standardized test protocol was used. Two sets of test were done with a mean time between first and second test of 45 days (range 15–90 days). The order of tests administered on both occasions was; MLI soft palate, MLI lip, MLE soft palate, and MLE lip. Before each test, subjects were given a set of trial stimuli (the results were not recorded). The tested sites were centrally at the outer surface of the lower lip and centrally at the left side of the soft palate.

The apparatus was set to deliver 37°C and 33°C for the soft palate- and lip testing respectively (in order to deliver 36° and 32°C, respectively, according to the instruction manual). When testing the lip, the subjects held the thermode themselves with the investigator visually ensuring that the probe was held in place so that the indentation of the thermode on the lip was constant. When testing the soft palate the thermode was held by the investigator for the same reasons.

The MLE algorithm consisted of consecutive stimuli of predetermined steps. The subjects were asked to respond whether they perceived a sensation of cold or not through pressing switches on a hand-held computer mouse button (“yes/no”). When the subject responded, the temperature of the probe returned to starting temperature. Then, after a thermo-neutral period a new stimulus was given. The first stimulus step size was 3 °C (colder than starting temperature). If the subject did not perceive the first stimulus the next stimulus would be increased with the same step size until the subject responded (first stimulus 3°C, second stimulus 6°C, third stimulus 9°C etc.). If the subject first perceived a sensation of cold at for example 6°C, a new stimuli, with the subtraction of half the step size of the previous round, would be repeated until a “no” response was given (4.5, 3, 1.5°C etc.). If the subject then perceived cold at for example 1.5°C the intensity of the next stimulus would increase again in steps half the size as in the previous round (2.25, 3, 3.75°C etc.) until a “yes” response was given. In this way colder stimuli followed “no”
responses and less cold stimuli followed “yes” responses. Step sizes were halved, at
direction changes. The test was terminated when step size was 0.1°C. The mean of the
last “yes” and the last “no” responses was taken as threshold. The MLI algorithm
consisted of four continuously increasing stimuli. The subject was asked to press a hand-
held computer mouse button as soon as they perceived a sensation of cold. The time
intervals between the four stimuli were randomized to last between 4–6 s. The average of
the four stimuli was taken as threshold value. A stimulus change rate of 1°C/s was used in
both MLE and MLI algorithms. All CDTs are presented as the difference between
starting and detection temperatures.

**Study IV:** Subjects were consecutively recruited from the *Hypersleep study*. Exclusion
criteria were previous tonsil or soft palatal surgery, central sleep apnea, position
dependent OSA, medications known to affect peripheral nerves, as well as cases where
snoring history could not be confirmed or denied, i.e. when there was no partner. All
subjects underwent a polygraphic recording (as described previously) to establish the
AHI.

Sensory function in the upper airway was measured by MLI-CDT with the same
equipment as used in study III. The apparatus was set at 36°C starting temperature for
soft palate testing, and 32°C for lip testing. The MLI algorithm consisted of four
continuously increasing stimuli. The subject was asked to press a hand-held computer
mouse button as soon as they perceived a sensation of cold. The time intervals between
the four stimuli were randomized to last between 4 and 6 seconds. The average of the
four stimuli was taken as threshold value. A stimulus change rate of 1°C/sec was used.
CDTs were calculated as the difference between starting temperature and mean detection
temperature in °C.

The soft palate was chosen as test site for two main reasons. First, this tissue is probably
the site in the upper airway most subjected to the stretching and vibration that occurs
during snoring and second this site is accessible by mouth. The lip was chosen because it
is not affected by snoring and suitable in size for the intra-oral probe.

Subjects were grouped based on a combination of self reported snoring history and AHI
as follows:
1) Non-snorers, with partner-verified absence of past or present snoring and AHI ≤5
2) Snorers, with partner-verified habitual snoring and AHI <10
3) OSA subjects, with partner-verified habitual snoring and AHI ≥10.
STATISTICAL METHODS

In study I statistical analyses were performed with the PASW statistics 18 (IBM Inc., USA). In study II-IV statistical analyses were performed with SPSS statistical software version 15.0 (SPSS Inc, Chicago, IL, USA). The significance level was set to p<0.05 in all studies (I-IV).

Study I
Categorical data were described with numbers, percentages, and 95% confidence intervals (CI). Continuous data were described with means, standard deviation and 95% CI. Normal distribution was assessed by histograms. Normally distributed data were analyzed with a t -test, ANOVA, or Pearson correlation. Non-normally distributed data and dichotomous variables were analyzed with Mann–Whitney test, Kruskal–Wallis test, chi-square test, or Spearman rank correlation test.

Bivariate correlation analyses were performed to evaluate associations between different variables and AHI≥15. All variables that showed an association of p<0.20 were used as predictors in a logistic regression analysis.

Study II
Categorical data were presented with numbers, medians, maximum-minimum and percentages. Continuous data were presented with means, 95% CI or standard deviation. Cross-tabulation was used to show relation between groups based on positional dependency and AASM classification. Box-plots were used to illustrate the amount of supine time according to both POSA based groups and AASM classification based groups.

Normal distributions were assessed by histograms. Normally distributed data were analyzed with ANOVA, chi-square test or paired sample t-test. Non-normally distributed data were analyzed with Mann-Whitney test, Kruskal Wallis test or Spearman rank correlation test. Ordinal regression analysis was used to investigate predictors for POSA.

Power calculation was performed with the G*Power 3.1.3 (Faul et al., 2009). With a sample size of 189 subjects as in the present study, assuming a medium-sized effect (0.25) and an alpha level of 0.05, the power to detect significant differences between POSA groups was approximately 75%.

Study III
Normal distributions were assessed with histograms. CDT results were described by CDT intersession means and intersession mean differences for each site and method. Mann–Whitney test was used for analysis of CDT gender differences. Correlations between CDTs and age, as well as between CDTs for each body site obtained with the MLE and MLI methods were evaluated with Spearman rank correlation test. Test-retest repeatability was evaluated according to the methodology described by Bland and Altman (1986). Results acquired at first and second test occasions were analyzed with one sample T-test (for each method and site). Bland-Altman plots of the intersession difference
against intersession mean were created for each test algorithm and body site. The repeatability coefficient ($r$) for each algorithm and test site was defined. The repeatability coefficient is the minimal required difference between two repeated measurements made on the same subject under the same conditions that would designate a true change with 95% confidence (Yarnitsky and Sprecher, 1994).

**Study IV**
Categorical data were presented with numbers. Continuous variables were described with means and maximum-minimum values. Normal distributions were assessed with histograms. A plot with error-bars (95% CI and mean) was used to show relations between CDTs for soft palate and lip by group. Correlations between soft palate CDTs and age, AHI, and self-reported snoring years were evaluated with Spearman rank correlation test. Group analysis was performed using Mann-Whitney test and Kruskal-Wallis test.

**ETHICS**
All studies were approved by the Regional Ethical Review Board in Linköping, Sweden (diary numbers M 29-07, M173-9, M24-08). All participants, in all studies, gave informed consent.
RESULTS

Study I
Of the 918 eligible subjects, 394 subjects (187 men and 207 women) passed all criteria for inclusion and exclusion and had a satisfactory PG recording (Figure 4).

<table>
<thead>
<tr>
<th>Step 1</th>
<th>Screening of subjects at 4 hypertension primary care clinics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eligible: 918 subjects</td>
<td>Excluded: 109 subjects</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Step 2</th>
<th>Clinical assessment and self-rating scales</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eligible: 480 subjects were assessed regarding weight, height and blood pressure. Data regarding medication and co-morbidities were collected. Self-rating scales for OSA symptoms, sleep, insomnia, daytime sleepiness, depressive symptoms and perceived health were answered.</td>
<td>Did not want to perform polygraphy: 69 subjects</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Step 3</th>
<th>Polygraphic recordings during sleep</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eligible: 411 subjects were screened for OSA with a full night polygraphic recording</td>
<td>Excluded: 17 subjects Causes for exclusion: recording failures: 10 subjects, could not accept the equipment: 7 subjects</td>
</tr>
<tr>
<td>Final study population: 394 subjects</td>
<td></td>
</tr>
</tbody>
</table>

Figure 4. Description of the Hypersleep study from screening of eligible participants to final population.

The occurrence of an elevated AHI was high. A majority, 234/394 (total 59%, men 68% and women 52%), of the subjects had AHI ≥5 (Table 7). Forty-nine percent of the subjects would also be diagnosed as having OSA according the ICSD, i.e. when using comparable variables as those used as criteria for OSA in the 2nd edition of ICSD 2005; AHI ≥15 or AHI ≥5+symptoms complaints of unintentional sleep episodes during wakefulness, daytime sleepiness, unrefreshing sleep/non-restorative sleep, fatigue, insomnia, awakenings with breath holding, gasping, or choking, loud snoring, or breathing interruptions. No less than 31% (121/394) had AHI ≥15 and of the 29% (113/394) subjects with an AHI ≥5<15, 64% (72/113) had one or more symptoms qualifying them for an OSA diagnosis (Table 8).
Table 7. AHI levels in the Hypersleep population

<table>
<thead>
<tr>
<th>AHI</th>
<th>All n=394</th>
<th>Women n=208 (52.8)</th>
<th>Men n=186 (47.2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5</td>
<td>160 (40.6)</td>
<td>100 (48.1)</td>
<td>60 (32.3)</td>
</tr>
<tr>
<td>≥5-&lt;15</td>
<td>113 (28.7)</td>
<td>56 (26.9)</td>
<td>57 (30.6)</td>
</tr>
<tr>
<td>≥15-&lt;30</td>
<td>64 (16.2)</td>
<td>34 (16.3)</td>
<td>30 (16.1)</td>
</tr>
<tr>
<td>≥30</td>
<td>57 (14.5)</td>
<td>18 (8.6)</td>
<td>39 (21.0)</td>
</tr>
</tbody>
</table>

Data are presented as numbers and (%)

Table 8. Presence of OSA related symptoms in subjects with AHI of ≥5-<15 (n=113).

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Percentages (numbers)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>total</td>
</tr>
<tr>
<td></td>
<td>Women n=56</td>
</tr>
<tr>
<td></td>
<td>Men n=57</td>
</tr>
<tr>
<td>Partner report of loud snoring (often or always)</td>
<td>33% (37)</td>
</tr>
<tr>
<td></td>
<td>28% (16)</td>
</tr>
<tr>
<td>Daytime sleepiness (ESS&gt;10)</td>
<td>24% (27)</td>
</tr>
<tr>
<td></td>
<td>26% (15)</td>
</tr>
<tr>
<td>Unrefreshing sleep/ non-restorative sleep (great or very great problems)</td>
<td>23% (26)</td>
</tr>
<tr>
<td></td>
<td>21% (12)</td>
</tr>
<tr>
<td>Fatigue during the day (often or always)</td>
<td>22% (25)</td>
</tr>
<tr>
<td></td>
<td>18% (10)</td>
</tr>
<tr>
<td>Insomnia (great or very great problems to fall asleep)</td>
<td>13% (15)</td>
</tr>
<tr>
<td></td>
<td>14% (8)</td>
</tr>
<tr>
<td>Witnessed apneas (sometimes, often or always)</td>
<td>12% (14)</td>
</tr>
<tr>
<td></td>
<td>11% (6)</td>
</tr>
<tr>
<td>Unintentional sleep episodes during wakefulness (often or always)</td>
<td>6% (7)</td>
</tr>
<tr>
<td></td>
<td>2% (1)</td>
</tr>
<tr>
<td>One or more of the above symptoms</td>
<td>64% (72)</td>
</tr>
<tr>
<td></td>
<td>61% (35)</td>
</tr>
</tbody>
</table>

Therefore, the total prevalence of OSA according to the principles of the 2005 ICSD was 49% (193/394), 56% and 43% for men and women respectively. A diagnosis of OSAS defined as AHI≥5 and ESS score >10 (common in both clinical practice and research) would yield a prevalence rate of 19.5% (77/394) in the studied population.

There was no significant difference for gender, systolic-or diastolic blood pressure, IHD, respiratory disease or TIA/Stroke between OSA severity groups. Obesity (BMI >30 kg/m²) was more prevalent in groups with elevated AHI and DM was significantly more prevalent in subjects with AHI≥5 (Table 9).

Table 9. Characteristics and co-morbidities across OSA severity groups.

<table>
<thead>
<tr>
<th>AHI</th>
<th>&lt;5 (n=160, 41%)</th>
<th>≥5-&lt;15 (n=113, 29%)</th>
<th>≥15 (n=121, 30%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age: mean (95% CI)</td>
<td>57.3 (56.3-58.4)</td>
<td>57.8 (56.4-59.1)</td>
<td>58.8 (57.4-59.1)</td>
</tr>
<tr>
<td>Gender: % males</td>
<td>38</td>
<td>50</td>
<td>58</td>
</tr>
<tr>
<td>BMI: mean (95% CI)</td>
<td>27 (26.4-27.7)</td>
<td>29 (28.2-30.0)</td>
<td>31 (29.8-31.7)</td>
</tr>
<tr>
<td>Systolic blood pressure: mean (95% CI)</td>
<td>138.8 (136.0-141.5)</td>
<td>142.8 (139.9-145.7)</td>
<td>140.6 (137.1-143.8)</td>
</tr>
<tr>
<td>Diastolic blood pressure: mean (95% CI)</td>
<td>86.4 (84.9-87.9)</td>
<td>87.8 (85.9-89.7)</td>
<td>87.5 (85.4-89.7)</td>
</tr>
<tr>
<td>Diabetes mellitus: % (number)</td>
<td>13 (20)</td>
<td>20 (22)</td>
<td>21 (25)</td>
</tr>
<tr>
<td>Ischemic heart disease: % (number)</td>
<td>72 (112)</td>
<td>72 (82)</td>
<td>77 (92)</td>
</tr>
<tr>
<td>Respiratory disease: % (number)</td>
<td>6 (10)</td>
<td>5 (6)</td>
<td>7 (8)</td>
</tr>
<tr>
<td>TIA/ Stroke: % (number)</td>
<td>2 (3)</td>
<td>2 (2)</td>
<td>3 (3)</td>
</tr>
</tbody>
</table>
There were no differences between groups for estimated sleep need, sleep sufficiency index, insomnia, EDS, or depressive symptoms. Among all the studied variables a logistic regression analysis showed that only male gender, BMI >30 kg/m², snoring, reports of witnessed apneas, and sleep duration >8 hours were significant predictors of an AHI ≥15 (Table 10).

Table 10. Odds ratio for AHI≥15 predictors in the Hypersleep study population.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>1.7</td>
</tr>
<tr>
<td>BMI &gt;30</td>
<td>4.0</td>
</tr>
<tr>
<td>Snoring</td>
<td>3.9</td>
</tr>
<tr>
<td>Witnessed apneas</td>
<td>3.2</td>
</tr>
<tr>
<td>Sleep duration &gt;8 hours</td>
<td>3.6</td>
</tr>
</tbody>
</table>

Study II

Of the 265 included subjects, 4 were excluded due to technical failure of the recordings and 72 were excluded because they slept <10% or >90% in the supine position. Of these 72 excluded subjects, 17 had no supine sleep at all (total AHI 0-26) while 6 slept exclusively in the supine position (total AHI 0-36). Forty subjects slept in the supine position between 1 and 9% of the night (total AHI 0-81) and 9 subjects slept between 90- and 99% in the supine position (total AHI 0-45). The excluded subjects did not significantly differ from the included subjects by age, gender, or BMI. All 189 subjects included in the final analysis had predominantly obstructive apneas and hypopneas. A total of 154 subjects (81%) had more obstructive events in the supine position compared to non-supine positions and 100 subjects (53%) had POSA according to our definition. The characteristics according to POSA groups are shown in Table 11.

Table 11. General characteristics and classification according to POSA group

<table>
<thead>
<tr>
<th>No OSA/POSA</th>
<th>Mild exclusively supine POSA</th>
<th>Moderate exclusively supine POSA</th>
<th>Severe exclusively supine POSA</th>
<th>POSA with elevated AHI also in the non-supine positions</th>
<th>OSA (non-position dependent)</th>
<th>Total number of subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects n (%)</td>
<td>47 (25)</td>
<td>42 (22)</td>
<td>18 (10)</td>
<td>10 (5)</td>
<td>30 (16)</td>
<td>42 (22)</td>
</tr>
<tr>
<td>Males n (%)</td>
<td>17 (36)</td>
<td>17 (40)</td>
<td>10 (56)</td>
<td>8 (80)</td>
<td>22 (73)</td>
<td>21 (50)</td>
</tr>
<tr>
<td>Age, years</td>
<td>57 (55-59)</td>
<td>56 (54-58)</td>
<td>59 (57-62)</td>
<td>57 (54-61)</td>
<td>58 (56-60)</td>
<td>59 (57-60)</td>
</tr>
<tr>
<td>BMI</td>
<td>27 (25-28)</td>
<td>28 (27-29)</td>
<td>27 (25-29)</td>
<td>30 (27-33)</td>
<td>30 (28-32)</td>
<td>31 (30-33)</td>
</tr>
<tr>
<td>ESS, total score</td>
<td>7 (0-14)</td>
<td>9 (1-18)</td>
<td>6 (1-18)</td>
<td>6 (5-18)</td>
<td>8 (0-18)</td>
<td>8 (1-18)</td>
</tr>
<tr>
<td>Supine time (%)</td>
<td>42 (36-48)</td>
<td>42 (36-48)</td>
<td>38 (26-49)</td>
<td>32 (17-47)</td>
<td>35 (28-43)</td>
<td>36 (32-41)</td>
</tr>
</tbody>
</table>

Age, BMI and supine time values are given as means with confidence intervals. ESS values are given as medians with maximum-minimum. AHI values are given as means with SD.

Mean supine AHI was more than twice the mean non-supine AHI 21.6 (range 0-122) versus 9.9 (range 0-140) for the group as a whole (p<0.001). The discrepancy between supine- and non-supine AHI for each individual is illustrated in Figure 5.
There were no significant differences between POSA groups for age, ESS, or supine time but the group with non-POSA had significantly higher BMI than no OSA/POSA, mild exclusively supine POSA, and moderate exclusively supine POSA groups (p<0.01). No correlation was found between supine time and waist circumference.

A cross tabulation of AASM classification and POSA classification reveals that of the 53 classified as mild OSA by AASM classification, 16 (30%) would have changed to moderate- severe OSA (by AASM classification), and of the 29 subjects classified as moderate OSA 4 (14%) would have changed from moderate to severe OSA (by AASM classification) if their sleep had been exclusively supine. Thirty-six (33%) of the 108 subjects that could have been diagnosed as having OSA (AHI≥5) would have been classified as normal if they had avoided supine sleep (Table 12).

Table 12. Cross tabulation of AASM classification versus position dependent OSA classification.

<table>
<thead>
<tr>
<th>Position dependent OSA classification</th>
<th>AASM classification</th>
<th>Total number of subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No OSA</td>
<td>Mild OSA</td>
</tr>
<tr>
<td>1. No OSA/POSA</td>
<td>47</td>
<td>0</td>
</tr>
<tr>
<td>2. Mild exclusively supine POSA</td>
<td>29</td>
<td>13</td>
</tr>
<tr>
<td>3. Moderate exclusively supine POSA</td>
<td>4</td>
<td>12</td>
</tr>
<tr>
<td>4. Severe exclusively supine POSA</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>5. POSA</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>6. OSA</td>
<td>0</td>
<td>16</td>
</tr>
<tr>
<td>Total number of subjects</td>
<td>81 (43%)</td>
<td>53 (28%)</td>
</tr>
</tbody>
</table>

Note: POSA groups are marked with dark grey fields in the figure.
Figure 5. Individual relation between supine AHI and non-supine AHI for each subject, showed by group classified by total AHI. Y-axis shows AHI, each subject is represented by a line with left y-axis showing supine AHI and right y-axis showing non-supine AHI.
An ordinal regression analysis was performed to investigate predictors for positional dependency. Age (regression coefficient, 0.07; p<0.01), gender (regression coefficient, 0.91; p<0.01), and BMI (regression coefficient, 0.18; p<0.01) were found to be significant predictors but not systolic or diastolic blood pressure.

A sub-group analysis of subjects with mild exclusively supine POSA showed that differences in supine time, supine-AHI and non-supine AHI between subjects that classified as either no OSA or mild OSA (by AASM classification) were statistically significant. The splitting of the material in groups as shown in Table 12, makes statistical comparisons between groups impossible. However, and as shown in Figure 6, a visual analysis shows the impact of supine sleep on OSA classification based on total AHI. The amount of supine time in POSA subjects (but not for non-POSA subjects) increases with OSA severity (according to AASM classification).

Study III

Forty healthy volunteers were included. The mean age was 30 years (range 19–45 years) and 42% were men. All subjects tolerated the tests well. CDTs were lower at the lip compared to the soft palate for both methods and the intersession means were lower with the MLE method at both sites compared to MLI. The intersession mean differences were larger for MLE at both sites but no significant intersession biases were found for any of
Concerning the repeatability coefficient, there was a larger difference between the two tested sites than between the two methods (Table 13).

Table 13. Repeatability and intersession characteristics of cold detection thresholds.

<table>
<thead>
<tr>
<th>Site</th>
<th>Method</th>
<th>Repeatability (r)</th>
<th>CD intersession mean (°C)</th>
<th>CD intersession mean difference (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lip Levels</td>
<td>0.6</td>
<td>0.7</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>Lip Limits</td>
<td>0.6</td>
<td>0.9</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>Soft palate Levels</td>
<td>2.6</td>
<td>3.2</td>
<td>0.4</td>
<td></td>
</tr>
<tr>
<td>Soft palate Limits</td>
<td>2.2</td>
<td>4.2</td>
<td>0.2</td>
<td></td>
</tr>
</tbody>
</table>

The distribution of intersession means, as well as intersession difference showed a markedly narrower distribution for the lip data compared to soft palate (Figure 7).

There were no gender differences for either MLE/MLI at the soft palate or for lip MLI. The only significant gender difference found (p <0.05) was for the second test of lip MLE (women increased thresholds). CDTs were not correlated to age. All four pairs
(MLE-MLI lip first test, MLE-MLI lip second test, and MLE-MLI soft palate first test, MLE-MLI soft palate second test) of CDT measurements were correlated (p <0.05). Lip MLI was the fastest test taking approximately 30 seconds, followed by soft palate MLI 60 seconds, lip MLE 2.5 min and soft palate MLE 5 min.

Study IV
A total of 101 subjects met inclusion criteria, were invited and underwent CDT testing. Eight subjects, (three women, five men) could not participate in CDT testing due to strong gag reflexes, and three subjects (all men) had technically unsatisfying recordings. Characteristics of the remaining 25 non-snorers, 32 snorers, and 33 OSA subjects included in the analysis are summarized in Table 14.

Table 14. Subject characteristics and results

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of subjects</th>
<th>Total</th>
<th>M</th>
<th>F</th>
<th>Age</th>
<th>AHI</th>
<th>Snoring years</th>
<th>ESS</th>
<th>BMI</th>
<th>CDT (°C) Soft Palate</th>
<th>CDT (°C) Lip</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-snorers</td>
<td>25</td>
<td>8</td>
<td>17</td>
<td></td>
<td>59 (51-65)</td>
<td>2</td>
<td>0</td>
<td>7</td>
<td>26 (21-38)</td>
<td>2.8 (1.0-5.0)</td>
<td>0.9 (0.4-1.4)</td>
</tr>
<tr>
<td>Snorers</td>
<td>32</td>
<td>14</td>
<td>18</td>
<td></td>
<td>60 (41-65)</td>
<td>4</td>
<td>13 (4-30)</td>
<td>8</td>
<td>28 (21-34)</td>
<td>5.1 (1.0-13.2)</td>
<td>1.1 (0.4-2.1)</td>
</tr>
<tr>
<td>OSA subjects</td>
<td>33</td>
<td>18</td>
<td>15</td>
<td></td>
<td>59 (42-66)</td>
<td>30</td>
<td>15 (4-40)</td>
<td>8</td>
<td>31 (22-43)</td>
<td>6.6 (1.7-16.6)</td>
<td>1.1 (0.5-2.2)</td>
</tr>
</tbody>
</table>

Values are given as means (maximum- minimum).

No significant differences were found between groups for tonsil size (Friedman et al., 2004), ESS score, or age. Non-snorers had significantly lower BMI than the other groups, but BMI did not differ between the snorers and OSA subjects. In the non-snorong group neither soft palatal nor lip CDT was correlated to age or gender difference. There were significant differences between groups for soft palate- (p<0.01) but not lip CDTs. There were significant differences in soft palatal CDTs between non-snorers as compared to both snorers (p<0.01) and OSA subjects (p<0.05). There were also differences between snorers and OSA subjects (p<0.05) (Figure 8).

Scatter plots with CDTs plotted against self-reported snoring years and AHI showed in both plots a considerable amount of scatter, but correlation analyses indicated that the degree of neuropathy increased with both duration of snoring and AHI (p<0.01, r_s 0.41 and r_s 0.47, respectively).
Figure 8. Cold detection thresholds for the soft palate and lip by groups.
METHODOLOGICAL CONSIDERATIONS AND LIMITATIONS

Polygraphy
One potential limitation in study I, II and IV is the use of PG devices in the evaluation of the AHI. The use of PG means that we lack wake/sleep data and thus are at risk of underestimate variables such as the AHI (Epstein et al., 2009). The potential pitfalls with the use of PG have been thoroughly discussed in this thesis. To minimize the risks, we used both subjective sleep time and respiratory trace patterns to improve our estimation of sleep and wake time. In fact, subjective sleep time has been shown to correlate fairly well with PSG-measured sleep time (Franklin and Svanborg, 2000) and analysis of respiratory trace patterns have been shown to allow a fairly correct calculation of ODI compared to PSG (Lysdahl, 2002).

But there are also potential strengths with the use of a PG device. To sleep with a PSG equipment attached to the body and head may predispose subjects to sleep in the supine position, which increases the risk to overestimate AHI in POSA subjects. Metersky and Castriotta (1996) reported that subjects spent more time in the supine position during a PSG night than during a night when pulse oximetry only was recorded. It is therefore possible that full PSG causes more supine sleep than the limited PG equipment used in our studies.

Populations
In the Hypersleep study a considerable amount of subjects choose not to participate. Of all eligible subjects, 12% fell into the exclusion criteria and almost 40% declined participation. One of the reasons to decline participation in a research project on OSA may be that clinical signs of OSA such as snoring or witnessed apneas is lacking. Since at least snoring and witnessed apneas were found to be predictors of OSA in our study, the results should be interpreted with some caution due the risk for over-inclusion of OSA subjects. On the other hand, there were no differences in demographic variables for participants and non-participants.

Despite the large decline rate, the results are comparable to those found in a study by Drager et al. (2010). This is a Brazilian study on characteristics and predictors of OSA in patients with hypertension. In this study only 5 of 104 (<5%) subjects that met inclusion criteria declined participation and the prevalence rate of OSA, 56% (AHI>5), is comparable to ours of 59% (AHI≥5). Other studies that at least indicate that our prevalence rates are not overestimated due to selection bias are the ones by Hedner et al. (2006) and Franklin et al. (2012) who both report substantially higher OSA prevalence rates in subjects with hypertension.

Study II comprised the last 265 subjects in the Hypersleep study. The reason for this was that AASM (Iber et al., 2007) criteria for the scoring of apneas and hypopneas were not used for the first 129 recordings in the Hypersleep Study. Thus, when the work with the manuscript of study II was performed 265 recordings scored according to AASM criteria were available. The first “non-AASM” scored 129 recordings were later re-scored according to AASM criteria and included in the manuscript of study I. A power
calculation on the final sample in study II of 189 subjects (with 76 subjects excluded) with the G*Power 3.1.3 (Faul et al., 2009) assuming a medium-sized effect (0.25) and an alpha level of 0.05, revealed that the power to detect significant differences for the POSA groups was approximately 75%.

When planning study III we decided that at least 40 healthy, non-snoring participants needed to be included to allow parametric testing. Participants were mainly recruited through flyers and personal communication at the County Hospital Ryhov and at the School of Health Sciences in Jönköping. Recruitment was slow which may have been due to the nature of the tests (repeated intra-oral tests) and our inclusion/exclusion criteria. Thus, when 40 subjects were included we stopped the inclusion.

In study IV only about 25% (101/394) of subjects from the total Hypersleep cohort were included. The reasons for this were: inclusion in the Hypersleep study started before study IV was initiated, and continued during collection of data for study III. Furthermore, the inclusion criteria of partner verified history of snoring and non-POSA decreased the number of potential candidates.

Starting temperature
The attentive reader might note that we used 37°C and 33°C (for the soft palate and the lip respectively) as starting temperatures in study III compared to 36°C and 32°C in study IV. Other studies have used either 36°C (Hagander et al., 2009) or 37°C (Pigg et al., 2010) for intra-oral testing, while 32°C is the most used starting temperature in both clinical practice and research for skin surfaces.

In order to check whether our routines for cold thermal testing were feasible, we performed a pilot-study using MLI using approx. 30 participants from the Hypersleep study. In these measurements we used 32°C for the lip and 36°C for the soft palate as these temperatures were used in the somewhat similar study by Hagander et al. (2009). When our pilot-study was finished, we learned that the temperature settings of the software differed from the temperature delivered at the tip of the probe. The apparatus had to be set at 37°C and 33°C in order to come as close to 36°C and 32°C as possible. Since we believed that the preferable starting temperatures were 36°C and 32°C we changed the settings for study III. When the results in study III showed that MLI was the method of choice we had to choose whether to throw away the results achieved with the original settings. Several series of tests with different starting temperatures were performed to control whether comparable results, as those reported in study III, would be achieved (at both higher and lower starting temperatures). The results (unpublished) indicated that within a certain temperature range the starting temperature is of minor or no importance. Therefore we decided that we could use the first settings and safely include data from the pilot study.

QST is in many aspects a vulnerable method as the results may be affected by many factors, not least test algorithms, equipment etc. Therefore some authors even recommend that (ideally) reference values should be established for each lab to reflect the specific conditions under which testing takes place (Shy et al., 2003).
DISCUSSION AND CLINICAL IMPLICATIONS

Study I
The main finding of this study was that a majority (59%) of hypertensive primary care patients with previously undiagnosed OSA had objective evidence of OSA (AHI ≥5). For men and women the prevalence was 68% and 52% respectively. If OSA was defined according to the principles of the 2005 ICSD the prevalence was 49%, and if defined as an AHI ≥5+ESS ≥10 the prevalence was 19.5%. Thus, depending on definition, prevalence rates ranged from 19.5%-59% in the studied population.

Compared to another Swedish study on subjects with hypertension (from a primary care population) our prevalence rates were lower. Hedner et al. (2006) reported OSA prevalence rates (AHI ≥10, PSG) of 83% and 69% in men and women with hypertension and DM, though the latter being a strong predictor for OSA, Drager et al. (2010). In a study by Franklin et al. (2012), 80% of the women that reported hypertension also had OSA (AHI ≥5). Some of the discrepancies may be due to different methods (PSG/PG) and/or different scoring criteria for apneas and hypopneas.

When comparing our results with other relatively recently published Scandinavian studies (using general populations), a divergent picture emerges. The prevalence of an AHI ≥5 in the women of our sample, 52%, is comparable to the prevalence rate (50%) in women reported by Franklin et al. (2012) but our rates for both genders are higher than those reported from Norway by Hrubos-Strøm et al. (2011). In the latter study OSA prevalence (AHI ≥5) was 21% and 13% for men and women respectively. The mean age in our population was 57 years, while a mean age of 47 years were reported from both other studies.

No relationship between OSA severity and blood pressure or anti-hypertensive treatment was seen in our population. This is in contrast to earlier reports where hypertension has been found to be independently related to OSA (Baguet et al., 2009; Franklin et al., 2012). The lack of relationship in our study may be due to the fact that our subjects were already treated for hypertension, mostly successfully. Another reason maybe our cut-off at AHI ≥15 as the association may become significant at more severe forms of OSA (Lavie et al., 2000).

Of all the analyzed potential predictors of OSA only BMI ≥30 kg/m², snoring, sleep duration >8 hours, witnessed apneas, and male gender were found to be significantly correlated to AHI ≥15. In this aspect our findings are on the whole comparable to the reports from the Sleep Heart Health Study where male gender, higher age, BMI, self-reported snoring and breathing pauses were found to be associated with AHI ≥15 (Young et al., 2002 b). Drager et al. (2010) studied 99 hypertensive patients with previously undiagnosed OSA and found that hypertensive patients with OSA were older, more obese, had greater neck/waist circumferences, higher blood pressure, a greater percentage of DM, dyslipidemia, obesity, resistant hypertension, and metabolic syndrome. We could not reproduce these findings in our study except for DM and BMI.
We hypothesized that both depressive symptoms and insomnia would be predictors of OSA as earlier studies have shown an association and co-occurrence with OSA (Ohayon, 2003, Wickwire and Collop, 2010). Both depressive symptoms and insomnia were common, but not associated with OSA. In our study the prevalence rates of difficulties initiating or maintaining sleep were 28% and 51% respectively and with 20% showing signs of depression. The insomnia rates are somewhat comparable to the rates (32%) of insomnia in primary care reported by Kushida et al. (2000). The prevalence of depressive symptoms in our population was quite high: 13-19% (depending on the severity of OSA), compared to an estimated 4-10% general prevalence of depression (SBU 2004). The discrepancy is probably due to differences in the definition of depression and depressive symptoms and in instruments used to measure these factors. Another reason to the relatively high prevalence of depressive symptoms may be co-occurring IHD. Coronary artery disease and depression often occur together (Zellveger et al., 2004) and as many as 72-77% (depending on AHI levels) were classified as having IHD in our population. OSA has been associated with impaired quality of life in other studies (Finn et al., 1998, Baldwin et al., 2001) but we could not find such an association in our sample.

EDS was common (ESS≥10 in approx. 1/3 of the sample) but was not associated with OSA. This is in accordance with other studies that have failed to find such an association (Dúran et al., 2001; Franklin et al., 2012), but in contrast to others (Young et al., 1993; Chervin, 2000; Kapur et al., 2005). However, our finding that self reported sleep duration of ≥8 hours was significantly correlated to OSA might be an indirect sign of sleepiness (need for longer sleep duration to avoid sleepiness during the day).

Our findings are in most respects consistent with known facts on OSA. Even though some factors are more associated with OSA than others, screening for OSA in a hypertensive care population should not be restricted to obese men. It is important to acknowledge that a substantial amount of patients in primary care hypertension clinics without previously diagnosed OSA may benefit from OSA treatment. Today there is no consensus on which sleep apnea patients should be treated. According to AASM guidelines both subjects with AHI ≥5 + symptoms and asymptomatic subjects with an AHI ≥15 should be offered CPAP treatment (Epstein et al., 2009). This would mean that 49% (56% of the men and 43% of the women) of primary care patients with hypertension not yet evaluated for OSA could be considered. Other authors recommend a more conservative approach. Pack and Gislason (2009) recommend that subjects with AHI ≥30 should be offered treatment regardless of symptoms to reduce cardiovascular risk, which in our sample would concern 14% of subjects.

**Study II**

The major finding in this study was that 81% of the subjects had more obstructive events in the supine position compared to non-supine positions and that 53% of the studied population had POSA. The severity of OSA, as defined by AASM, could therefore be dependent on supine time in a substantial amount of subjects.

Compared to other aspects of obstructive SDB there is a scarcity of published papers (at least to our knowledge) on how body position affects the diagnostic process of OSA. This is somewhat surprising since Cartwright already in 1984 reported that sleep in the supine
position worsened the degree of sleep apnea. Although a small study, 24 of 30 patients had twice the AHI in the supine position compared to side positions (Cartwright, 1984).

The far largest study so far on this topic is the one by Oksenberg et al. published in 1997. They studied positional dependency in a sample of 574 subjects with an RDI > 10, age > 20 years, and BMI > 20, initially referred to a sleep clinic. Fifty-six percent of these patients had POSA. The prevalence rate of POSA in our study is in line with the report of Oksenberg et al. (1997). We also found that POSA subjects were less overweight (lower BMI) and had having milder forms of OSA than non-POSA subjects. Also these findings are consistent with the findings of Oksenberg et al. (1997) who reported that a thin, young patient with mild-to moderate OSA was more likely to have POSA than an older, obese patient with severe OSA. However, one difference between our studies is that we could not show that POSA subjects were generally younger than non-POSA subjects.

Pevernagie and Shepard (1992) reported that subjects with POSA spent less sleep time (in relation to the supine AHI severity) in the supine position than non-POSA subjects, implying a spontaneously developed strategy of sleeping in the non-supine positions. We could not reproduce these data, as we could not find any difference in time spent in the supine position between POSA groups or any correlation between positional dependency and time spent in the supine position. The mean percentage of supine time in our study (39%) is comparable to the findings of Sahlin et al. (2009) who reported a mean supine sleep time of 41% in a study of 400 Swedish women from the general population.

The results of our study illustrate how, for the majority of subjects, the amount of time spent in the supine position during sleep has the potential to influence the total AHI. This is of importance since total AHI is used to decide both OSA diagnosis and suggested treatment in both clinical practice and research. Our study also show that differences in time spent in the supine position between nights may explain why other studies have found a significant night to night variability in AHI (Le Bon et al., 2000; Aarab et al., 2009; Ahmadi et al., 2009).

In clinical settings, knowledge of positional dependency gives the opportunity to individualize OSA treatment. MADs have been found to be effective especially in non-obese patients with POSA (Marklund et al., 1998; Chung et al., 2010) and could therefore be offered as primary treatment to such patients. According to our data and the data of Sahlin et al. (2009) it seems that most subjects spend a substantial amount of time in the supine position during sleep. Therefore also positional therapy (Loord and Hulterantz, 2007; Bignold et al., 2011) may be an alternative either as adjunctive therapy or when other treatment fails in POSA subjects. Furthermore, our study shows that treatment efficacy (CPAP, MAD, surgery) must be assessed in light of positional data in order to avoid wrong conclusions based on total AHI.

**Study III**

The main finding of this study was that MLI showed a better test-retest repeatability than MLE for the soft palate ($r = 2.2$ vs. 2.6) and therefore should be used in longitudinal studies. The performance of MLI is also faster than MLE. CDT testing with MLI is a safe
and reliable method suitable for longitudinal studies of peripheral neuropathy in OSA pathogenesis.

The repeatability coefficient is defined such that there are 95% confidence that two determinations made on the same subject under the same conditions would differ by less than $r$ (Yarnitsky and Sprecher, 1994). This means that a repeated measurement of CDT should differ with more than $0.6^\circ C$ for both lip MLE and MLI, and more than $2.2^\circ C$ for MLI and $2.6^\circ C$ for MLE at the soft palate to indicate a true change with 95% certainty.

As shown in the differences between the lip and soft palate in our study, the performance of MLE and MLI may be body site dependent. To our knowledge the only comparable data concerning test–retest repeatability of cold thermal testing using the same statistical approach and the same methodology are those published by Yarnitsky and Sprecher (1994). These authors investigated the repeatability for CDTs at the hand and foot and found that MLE had better test-retest repeatability than MLI for both sites (approx. $r$ for MLE hand 1.0, MLI hand 2.0, MLE foot 3.0, and MLI foot 3.8). When comparing the repeatability coefficients from our study with these coefficients, the lip performs “better” while the soft palate seems to be intermediary to the hand and foot. It should be noted that in Swedish neurophysiological routine, MLI of hand and foot is most commonly used method in the assessment of painful neuropathic disorders (personal communication, professor Svanborg).

However, the results from the Yarnitsky and Sprecher (1994) study, makes our finding that MLI performed better than MLE in the soft palate somewhat surprising. The explanation may be the long duration of intra-oral MLE testing. We hypothesize that the long testing time in soft palate MLE is explained by the relatively low sensitivity in this area. In order to sound out the CDT with an MLE algorithm a large amount of stimuli have to be given. This demands a prolonged opening of the mouth which dries the mucosa and impairs concentration, both factors having potential negative effects on MLE test-retest repeatability.

CDT did not correlate with age in our study, which may be explained by the limited number of participants and narrow age span in our sample. Both Bartlett et al. (1998) and Lin et al. (2005) have reported a significant correlation between CDTs and age for the hand and foot but Dyck et al. (1993) did not find such an association for the lip.

We did not find any differences in CDTs according to gender in soft palate CDT. This is discordant with the findings of Hagander et al. (2009) who reported a gender difference in non-snoring subjects’ soft palate CDT, measured by MLE, but this study had a small sample size. However, no CDT differences according to gender has been reported from other body sites such as the hand and foot (Bartlett et al., 1998; Lin et al., 2005).

**Study IV**

The main finding of this study was that snorers without significant OSA and subjects with OSA showed a gradual decrease in sensitivity to cold (soft palate CDTs 5.1 and 6.6 respectively), compared to non-snorers (soft palate CDT 2.8), indicating a progressive sensory nervous lesion.
Our findings are consistent with previous findings indicating a snoring-induced damage to upper airway tissues (Friberg et al., 1998; Lindman and Ståhl, 2002; Svanborg, 2005) and in particular previous findings of upper airway sensory neuropathy in subjects with obstructive SDB (Larsson et al., 1992; Kimoff et al., 2001; Guilleminault et al., 2002; Nguyen et al., 2005; Hagander et al., 2009).

Furthermore, our data showed significant but weak correlations between the degree of impaired cold sensory function and both estimated duration of snoring ($r_s 0.47$) and AHI ($r_s 0.41$). The rather weak correlations might be due to uncertainties when estimating snoring years and that other factors than impaired sensory function influences the severity of AHI (e.g. anatomical and anthropometric factors).

Several studies (as reviewed by White, 2006) have showed activation of upper airway dilating muscles in response to inspiratory negative pressure and that this reflex may be impaired in OSA subjects. In addition to negative pressure, cold air has been proposed as an activating factor of these dilating reflex circuits (Basner et al., 1990). Negative pressure is considered a stronger stimulus for pharyngeal dilation than cold (Svanborg, 2005), and therefore a sensory neuropathy concerning mechanical stimuli can be the more important pathologic feature in OSA compared to cold sensory neuropathy.

Considering that Basner et al. (1990) showed that cold air stimuli increased the activity of the genioglossus muscle in humans, the findings by Valham et al. (2012) that OSA patients had more obstructive events when ambient room temperature was 16°C and 18°C compared to 24°C was unexpected. It is known that cold stimuli may have negative effects on the airways as cold air has been shown to produce both nasal congestion (which could be a predisposing factor for SDB) and broncho-constriction (Koskela, 2007). Therefore the question of whether cold air reflexes are involved in maintaining the patency of the upper airway during sleep remains unanswered.

That snoring vibration may have other deleterious effects than the disturbed regulation of upper airway patency described above, was discussed already in 1994 by Hedner et al. These authors hypothesized that snoring vibrations may be transmitted through the surrounding tissues to the carotid artery wall and later it has been hypothesized that vibratory stimuli may cause damage to the arterial wall leading to atherosclerosis (Lee et al., 2008). In fact, Lee et al. (2008) reports that heavy snoring increased the risk of carotid atherosclerosis after adjustment for other risk factors such as smoking, hypertension, age, sex, and independent of nocturnal hypoxia and OSA.

Our results strengthen the hypothesis that snoring vibrations may cause a neuropathy in the upper airway, which may contribute to the progression and development of OSA. Most often “simple snoring” is looked upon as a harmless but unpleasant condition. However, untreated habitual snoring may not only be a risk for progression of obstructive SDB but also for the development of carotid artery atherosclerosis. Therefore early identification and treatment of snoring may be an important preventive act in order to reduce both the incidence of OSA and of carotid atherosclerosis. Oro-pharyngeal cold sensory testing of snorers may have a role in such a setting.
FUTURE DIRECTIONS

Even though PG recordings are relatively available in Sweden today, most centers have long waiting lists. With the high prevalence of OSA in mind, especially in populations with cardiovascular disease, there is still a need to facilitate the identification of patients with undiagnosed OSA. Therefore studies evaluating efficient screening methods are needed, one example could be combinations of questionnaires and automatically scored simple two-channel recording devices. Furthermore, large, well-designed studies are needed to further explore symptom profiles in different populations, not least hypertensive patients with undiagnosed OSA in primary care settings.

Future studies could also investigate whether POSA is a distinct entity compared to non-POSA. Is the cardiovascular risk associated with OSA different depending on whether the subject has apneas in all positions (non-POSA) compared to subjects that breathes freely in the non-supine positions? Is cardiovascular risk in OSA coupled to time spent with repetitive obstructive events during the night or not? Is it, especially from a cardiovascular perspective, equally important to treat non-POSA and POSA?

The assumption that variations in sleeping position causes night to night AHI variability, presupposes that individuals vary their amount of supine time between nights. To the best of my knowledge, no such studies have been performed and the design of this study with only one night of data collection falls short of answering the question. Future studies should evaluate long-term patterns of variations in sleeping positions in both normal subjects and subjects with POSA. In subjects with POSA, studies should include the evaluation of long term associations between position and AHI.

Another topic that warrants further research is whether POSA is an intermediary state in the progression from snoring to OSA. Oksenberg et al. (2012) recently reported that POSA patients that became non-POSA patients over a mean period of 6.2 years, have had a significant gain in weight and a significant increase in AHI, mainly in lateral AHI. On the contrary, non-POSA patients who became POSA patients had a significant decrease in weight and a decrease in the AHI (again mainly in lateral AHI). By following the participants in the Hypersleep study for a planned 5 years, we will have the opportunity to evaluate these aspects of OSA progression and see whether the results of Oksenberg et al. (2012) may be reproduced.

Another important question to pursue is whether untreated habitual snoring is a risk for incidence or progression of obstructive SDB. By following the subjects in the present study with repeated measurements of CDTs and AHI, we hope to shed light on this question. Hopefully we will be able to evaluate whether changes in local sensory neuropathy and AHI are related to each other, and also if termination of upper airway tissue vibration through CPAP treatment can hinder the progression or even regress the degree of local sensory neuropathy found in the soft palate at base-line.
CONCLUSIONS

Undiagnosed OSA is common in Swedish primary care patients with hypertension, but only male gender, BMI>30 kg/m², and a clinical history of snoring and witnessed apneas are predictors of an AHI≥15.

Position dependent OSA is common both in subjects that by AASM classification had OSA as well as those without OSA. The severity of OSA, if based on total AHI, could be dependent on supine time in a substantial amount of subjects.

CDT is easily performed in the oropharynx, with acceptable test–retest repeatability. MLI was considerably faster to perform and had a slightly better repeatability than MLE. Therefore MLI should be the used method for cold thermal testing at the soft palate.

Both self-reported snoring years and OSA severity are correlated to the degree of cold sensory impairment in the upper airway. Our results strengthen the hypothesis that snoring vibrations may cause a neuropathy in the upper airway, which may contribute to the progression and development of OSA.
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