Psychometric aspects of obstructive sleep apnea syndrome

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Linköping 2013
To my family
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ABSTRACT

Introduction Obstructive sleep apnea (OSA) is a common chronic disorder consisting of episodes with impaired breathing due to obstruction of the upper airways. Treatment with Continuous Positive Airway Pressure (CPAP) is a potentially effective treatment, but adherence is low. Several potential factors affecting adherence, e.g., subjective sleepiness and personality, are only quantifiable through questionnaires. Better knowledge about psychometric properties of such questionnaires might improve future research on CPAP adherence and thus lead to better treatment options.

Aim Study I: To describe the development and initial testing of the Side Effects of CPAP treatment Inventory (SECI) questionnaire. Study II: To describe the prevalence of Type D personality in OSAS patients with CPAP treatment longer than 6 months and the association with self-reported side effects and adherence. Study III: To study whether any of the items in the Epworth Sleepiness Scale (ESS) exhibit differential item functioning and, if so, to which degree. Study IV: To examine the evolution of CPAP side effects over time; and prospectively assess correlations between early CPAP side effects and treatment adherence.

Patients and Methods In study I, SECI items were based on a literature review, an expert panel and interviews with patients. It was then mailed to 329 CPAP-treated OSAS patients. Based on this, a principal component analysis was performed, and SECI results were compared between adherent and non-adherent patients. In study II, the population consisted of 247 OSAS patients with ongoing CPAP treatment. The DS14 was used to assess the prevalence of type D personality, and SECI and adherence data from medical records were used to correlate Type D personality to side effects and adherence. In study III, the population consisted of pooled data from 1167 subjects who had completed the ESS in five other studies. Ordinal regression and Rasch analysis were used to assess the existence of differential item functioning for age and gender. The cutoff for age was 65 years in the Rasch analysis. In study IV, SECI was sent to 186 subjects with newly diagnosed OSAS three times during the first year on CPAP. SECI results were followed over time within subjects, and were correlated to treatment dropout during the first year and machine usage time after 6 months.

Results SECI provides a valid and reliable instrument to measure side effects, and non-adherent patients have higher scores (i.e., were more bothered by side effects) than adherent patients (study I). Type D personality was prevalent in approximately 30% of CPAP treated OSAS patients, and was associated to poorer objective and subjective adherence as well as more side effects (study II). Differential item functioning was present in items 3, 4 and 8 for age in both DIF analyses, and to gender in item 8 the Rasch analysis (study III). Dry mouth and increased number of awakenings were consistently associated to poorer adherence in CPAP treated patients. Side effects both emerged and resolved over time (study IV).

Conclusions Differences in previous research regarding side effects and CPAP adherence might be explained by differences in how side effects and adherence are defined. While some side effects are related to adherence, others are not. Side effects are furthermore not stable over time, and might be related to personality. ESS scores are also related to CPAP adherence according to previous research, but might be affected by other factors than sleepiness, such as age and possibly gender.
<table>
<thead>
<tr>
<th>ABBREVIATIONS</th>
<th>Definition</th>
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<tbody>
<tr>
<td>AASM</td>
<td>American Academy of Sleep Medicine</td>
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<tr>
<td>AHI</td>
<td>Apnea Hypopnea Index</td>
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<td>AI</td>
<td>Apnea Index</td>
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<tr>
<td>CPAP</td>
<td>Continuous Positive Airway Pressure</td>
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<td>CVD</td>
<td>Cardiovascular Disease</td>
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<td>DIF</td>
<td>Differential Item Functioning</td>
</tr>
<tr>
<td>EEG</td>
<td>Electroencephalography</td>
</tr>
<tr>
<td>EMG</td>
<td>Electromyography (surface EMG if not otherwise specified)</td>
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<tr>
<td>EOG</td>
<td>Electrooculography</td>
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<td>ESS</td>
<td>Epworth Sleepiness Scale</td>
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<td>HR</td>
<td>Hazard Ratio</td>
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<td>MSLT</td>
<td>Multiple Sleep Latency Test</td>
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<td>MWT</td>
<td>Maintenance of Wakefulness Test</td>
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<td>ODI</td>
<td>Oxygen Desaturation Index</td>
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<tr>
<td>OR</td>
<td>Odds Ratio</td>
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<tr>
<td>OSA</td>
<td>Obstructive Sleep Apnea</td>
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<tr>
<td>OSAHS</td>
<td>Obstructive Sleep Apnea Hypopnea Syndrome</td>
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<td>OSAS</td>
<td>Obstructive Sleep Apnea Syndrome</td>
</tr>
<tr>
<td>PG</td>
<td>Polygraphy</td>
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<td>PSG</td>
<td>Polysomnography</td>
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<tr>
<td>RDI</td>
<td>Respiratory Disturbance Index</td>
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<tr>
<td>RERA</td>
<td>Respiratory Effort-Related Arousal</td>
</tr>
<tr>
<td>RIP</td>
<td>Respiratory Inductance Plethysmography</td>
</tr>
<tr>
<td>RR</td>
<td>Risk Ratio</td>
</tr>
<tr>
<td>SD</td>
<td>Standard Deviation</td>
</tr>
<tr>
<td>SDB</td>
<td>Sleep-Disordered Breathing</td>
</tr>
<tr>
<td>SECI</td>
<td>Side Effects to CPAP treatment Inventory</td>
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<tr>
<td>UARS</td>
<td>Upper Airway Resistance Syndrome</td>
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INTRODUCTION
Obstructive sleep apnea (OSA) is a disorder characterised by repeated events of impaired ventilation during sleep, caused by obstruction of the upper airways (American Academy of Sleep Medicine, 2005). These events can be total (apneas) or partial (hypopneas), and are often associated to episodes of decreased arterial blood oxygenation level (i.e., desaturations) and brief arousals from sleep. The term OSA syndrome (OSAS) is often used to denote symptomatic OSA, e.g., OSA with daytime sleepiness. The diagnosis is made based on a polygraphic recording of physiological signals related to breathing (e.g., nasal airflow, chest and abdominal movement, heart rate and blood oxygen saturation) during sleep. Sleep can either be measured directly by polysomnography (PSG), consisting of electroencephalography (EEG), surface electromyography (EMG) and electrooculography (EOG), or it can be inferred indirectly from movements and breathing patterns or from time in bed (SBU, 2007). OSA severity is often based on the number of apneas and hypopneas per hour or sleep (the Apnea Hypopnea Index, AHI) and the number of oxygen desaturation events per hour of sleep (the Oxygen Desaturation Index, ODI).

OSAS has been associated to hypertension, cardiovascular disease (Parati et al., 2013), traffic accidents (De Mello et al., 2013), obesity and hyperglycaemia/type II diabetes mellitus (Shaw et al., 2008). The main treatment for OSAS is Continuous Positive Airway Pressure (CPAP), where a device is used to create a positive air pressure of the upper airways. If efficient, CPAP might alleviate symptoms and reduce the risk of negative health consequences. However, adherence rates tend to be non-satisfactory. The reasons are not completely clear, although a number of factors have been identified that are associated to treatment adherence.

Many patients cite side effects as a reason for non-adherence, but earlier research has been contradictory with regard to the effects that side effects actually have on adherence. There are also indications that symptoms and symptom reduction from the treatment might affect adherence. The most commonly reported symptom of OSAS is daytime sleepiness, which is often measured using the Epworth Sleepiness Scale (ESS; Johns, 1991).

There are three main approaches that are commonly used when studying CPAP adherence. One approach focuses on technical development, such as various forms of masks and humidifiers (Rose et al., 1993). Another approach focuses on physiological factors, such as disease severity (e.g., as measured by AHI and ODI; Kohler et al., 2010). A third approach is to explore various psychological and social factors related to personality, self efficacy, attitudes to treatment, beliefs about treatment etc (e.g., Wild et al., 2004; Stepnowsky et al., 2002).
Especially for the third approach, i.e., the social/psychological approach to CPAP adherence, questionnaires are commonly used. This is also true for side effects, which technological interventions often aim to reduce. For side effects, different studies have defined side effects differently and used different approaches to assess their prevalence. For sleepiness, the ESS has an almost hegemonic position as the main questionnaire, despite having psychometric problems (reviewed in Chervin, 2000).

In order to approach adherence it is important to have measurement instrument with sound methodological properties. This thesis focuses on developing ways to measure three potentially important constructs that might affect CPAP adherence, i.e., sleepiness, side effects and personality.

**DEFINING SLEEP RELATED OBSTRUCTIVE BREATHING DISORDERS**

*Definitions of specific syndroms*

Since OSAS was first described, the definitions have changed with various terms being used, sometimes with different meaning in different studies.

Guilleminault et al. (1976) described OSAS as a syndrome consisting of daytime hypersomnolence and polysomnographically proven obstructive apneas. The initial description of hypopneas is often accredited to Kurtz and Kryger (1978), but it is not certain whether they actually described obstructive hypopneas or central hypopneas, as they could not measure respiratory effort. Block et al. (1979) and Gould et al. (1988) described hypopneas having the same clinical consequences as apneas, and the term Obstructive Sleep Apnea Hypopnea Syndrome (OSAHS) was coined for patients having both apneas and hypopneas. Another group of patients identified by Guilleminault et al. (1993) had neither apneas nor hypopneas, but still suffered from the same symptoms as had been described earlier in OSAS patients. Despite the absence of overt apneas/hypopneas, these patients suffered from episodes of increased esophageal pressure, indicating increased upper airway resistance. This is referred to as Upper Airway Resistance Syndrome (UARS). When a task force formed by the American Academy of Sleep Medicine (AASM) and the American Thoracic Society set out to develop a standardised terminology and outcome measures for sleep-related breathing disorders, they recommended that UARS should be included in the OSAHS category, as there was not enough evidence to suggest a specific pathophysiology behind UARS. Instead, a new respiratory event, the Respiratory Effort
Related Arousal (RERA) was defined as a sequence of breaths characterized by progressively more negative esophageal pressure, terminating in either an arousal or a sudden change in pressure to a less negative level, lasting for at least 10 s. (Quan et al., 1999).
The AASM Task force recommends the following definition of OSAHS (ibid.):

**Box 1:** Definition of OSAHS suggested by AASM in 1999.

<table>
<thead>
<tr>
<th>The individual must fulfill criterion A or B, plus criterion C:</th>
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<tbody>
<tr>
<td><strong>A.</strong> Excessive daytime sleepiness that is not better explained by other factors;</td>
</tr>
<tr>
<td><strong>B.</strong> Two or more of the following that are not better explained by other factors:</td>
</tr>
<tr>
<td>- choking or gasping during sleep.</td>
</tr>
<tr>
<td>- recurrent awakenings from sleep.</td>
</tr>
<tr>
<td>- unrefreshing sleep.</td>
</tr>
<tr>
<td>- daytime fatigue.</td>
</tr>
<tr>
<td>- impaired concentration; and/or</td>
</tr>
<tr>
<td><strong>C.</strong> Overnight monitoring demonstrates five or more obstructed breathing events per hour during sleep. These events may include any combination of obstructive apneas/hypopneas or respiratory effort related arousals.</td>
</tr>
</tbody>
</table>

Guilleminault et al. (1976) had originally used a cutoff AI (Apnea Index, as hypopneas were not defined) of 30 apneas during seven hours of sleep, based on a study of presumably normal sleepers. When hypopneas are added, the index naturally is higher, although it has been questioned whether it is clinically relevant to distinguish between hypopneas and apneas (Meoli et al., 2001). Quan et al., (1999) used an AHI cutoff criterion of 5/h or higher in adults, which is the most commonly used cutoff value (Kripke et al., 1997). This was motivated by the fact that earlier research had found an increased risk for traffic accidents in people with an AHI between 5 and 15/h (Young et al., 1997), a positive effect of CPAP treatment in patients with AHI between 5 and 15/h (Engleman et al. 1997), and a dose-response relationship between severity of even mild sleep-disordered breathing and prevalence of hypertension (Young et al., 1996).

In 2005, the AASM revised the diagnostic criteria and classification of OSA again, in the International Classification of Sleep Disorders, 2nd edition (AASM 2005). OSAS was renamed...
to "Obstructive Sleep Apnea, Adult", and the occurrence of daytime symptoms was removed as a mandatory diagnostic criterion:

**Box 2: ICSD 2 definition of “Obstructive Sleep Apnea, Adult”**

A, B and D or C and D satisfy the criteria:

A. At least one of the following applies:
   i) The patient complains of unintentional sleep episodes during wakefulness, daytime sleepiness, unrefreshing sleep, fatigue or insomnia,
   ii) The patient wakes with breath holding, gasping, or choking,
   iii) The bed partner reports loud snoring, breathing interruptions, or both during the patient’s sleep.

B. Polysomnographic recording shows the following:
   i) Five or more scoreable respiratory events (i.e., apneas, hypopneas, or RERAs) per hour of sleep.
   ii) Evidence of respiratory effort during all or a portion of each respiratory event (in the case of a RERA, this is best seen with the use of esophageal manometry).

OR

C. Polysomnographic recording shows the following:
   i) Fifteen or more scoreable respiratory events (i.e., apneas, hypopneas, or RERAs) per hour of sleep.
   ii) Evidence of respiratory effort during all or a portion of each respiratory event (in the case of a RERA, this is best seen with the use of esophageal manometry).

D. The disorder is not better explained by another current sleep disorder, medical or neurological disorder, medication use, or substance use disorder.

Different studies have used different scoring and diagnostic criteria, which is important to keep in mind when going through OSA/OSAS literature.

**Definitions of events**

An apnea has been defined, since its first description (Guilleminault et al., 1976), as a total cessation of breathing lasting for at least ten seconds. No reason is given for the ten-second rule. Regarding hypopneas, various definitions have been given, differing in which measurement
technique is recommended (Berg et al., 1997; Thornton et al., 2012), what amount of airflow reduction is required (Redline et al., 2007), whether an ensuing arousal is required, whether a desaturation is required, and, in that case, how pronounced it has to be. For example, Fietze et al. (1999) required a 50 % decrease in thoracoabdominal inductive plethysmography but did not require any decrease in SaO₂. Mooe et al., 1996 defined a hypopnea as a bout where a two per cent decrease of SaO₂ was required together with a 50 % decrease of airflow, while Shahar et al. (2001) required a four per cent decrease in SaO₂ together with a 30 % reduction of airflow.

The AASM Criteria of 1999 (Quan et al., 1999) define an obstructive hypopnea as either a ≥50 % of airflow reduction from a previous baseline of the last two minutes preceding the event, or a ”clear amplitude reduction” together with a desaturation of ≥3 % or an arousal, lasting for at least ten seconds. Thus, there are two ways in which a respiratory event can qualify as a hypopnea. These criteria have been referred to as the Chicago criteria (Thornton et al., 2012). The clear amplitude reduction was specified further by the AASM in 2001 to be at least 30% with a ≥4 % reduction in arterial oxygen saturation (Meoli et al., 2001). There were two main arguments for this definition: the 30% reduction criterion had been used in the Sleep Heart Health Study, a large, multicenter study aiming at relating cardiovascular disease with PSG findings (Redline et al., 1998); and Tsai et al. (1999) had found that combining the 30 % reduction in airflow with an oxygen desaturation criterion increased inter-rater reliability.

In 2007, the AASM revised its criteria for scoring hypopneas, and offered two possible ways to define them (Iber et al., 2007). One is termed the ”recommended” criteria and consists of a 10 s or longer episode of which at least 90 % of the duration of the event shows a ≥30% drop from baseline together with a ≥4% reduction in SaO₂. The other possible definition is termed the ”alternative” criteria, which require a ≥50 % reduction in airflow for at least 90 % of the duration of an episode lasting at least 10 s, in association with a ≥3% reduction in SaO₂ or an arousal. This has led to much criticism (e.g., Ruehland et al., 2009). Ruehland et al. (2009) found that the the median AHI in a sample consisting of 328 consecutive suspected OSA patients referred for PSG was only 30% of the AHI according to Chicago criteria when hypopneas were defined according to the ”recommended” criteria. Applying the ”alternative” criteria resulted in a median AHI of 60 % of the AHI according to Chicago criteria. The reason to allow two different definitions of hypopnea was that while many clinicians favoured the ”alternative” criteria, the ”recommended” criteria are endorsed by the Center for Medicare and Medicaid Services, and are thus important for reimbursement purposes in the USA (Berry et al., 2012).
Sleep-related breathing disorders are diagnosed by recording breathing and physiological phenomena related to breathing (e.g., arterial oxygen saturation, transcutaneous partial pressure of carbon dioxide, heart rate) during sleep. Sleep can either be detected using EEG, EOG and surface EMG and scored according to standard criteria (Rechtschaffen & Kales 1968, Iber et al., 2007), or it can be deduced indirectly from movements and from the clinical interview after the examination.

Depending on the clinical setting and the type of data recorded, clinical studies of sleep disordered breathing are often classified into four levels (American Sleep Disorders Association, 1994):

**Box 3: Diagnostic levels for SDB**

**Level I: In-lab polysomnography**, including EEG, EOG, surface EMG from the chin, ECG, airflow, respiratory effort, oxygen saturation and body position, the latter either by observation or objective measurement. The PSG should be performed at a manned sleep lab with trained personnel constantly present.

**Level II: Outpatient polysomnography**
Heart rate might substitute ECG and trained personnel is not required for all studies. Apart from this, the same data should be collected as for a level I study.

**Level III: Modified portable sleep apnea testing**
Apart from preparing the study, presence of trained personnel is not required. The device should record ventilation (at least two channels of respiratory effort, or airflow and one respiratory effort channel). ECG or heart rate and oxygen saturation should also be recorded.

**Level IV: Continuous single or dual bioparameter recording**
This is not further specified apart from that it should consist of continuous recording of at least one physiological parameter. Personnel is not required to attend or intervene.

There has been some discussion regarding what kind of measurement should be used to detect apneas and hypopneas. In their 2007 scoring rules, the AASM recommended an oronasal thermistor to detect apneas, and a nasal air pressure transducer to detect hypopneas (Iber et al., 2007). While thermistors are relatively good at detecting apneas, they are not able to provide the kind of quantitative information about air flow that would be used to score hypopneas according
to criteria based on relative decreases in airflow (Redline et al., 2007). Berg et al. (1997) studied three different thermistors, inductance plethysmography and nasal airflow in awake subjects simulating hypopneas by voluntarily reducing their tidal volume, and found only weak correlations between thermistors and plethysmography. In an experimental study using an artificial nose, Farré et al. (1998) showed that thermistors underestimated reductions in airflow caused by simulated hypopneas and were also sensitive to differences in the waveform of the airflow that affected the thermistor signal but not the actual airflow. At the same time, thermistors outperform nasal pressure sensors in detecting low levels or airflow, especially through the mouth, thus making it possible that some events that are registered as apneas when using a nasal pressure transducer might actually be hypopneas (Hérnandez et al., 2001).

Nasal pressure transducers and respiratory inductive plethysmography (RIP) are recommended as alternative ways of detecting apneas. In RIP, the tidal volume is assessed by measuring the movements of the chest wall and abdominal wall during the respiratory cycle (Cohn et al., 1982). Most studies that have validated the use of RIP in respiratory event detection have done so without differentiating apneas from hypopneas (Thurnheer et al., 2001; Heitman et al., 2002). The currently recommended sensor for detecting apneas is thus a combined oronasal thermistor, while nasal pressure and RIP are alternative methods. For hypopneas, the recommended method is nasal air pressure, while oronasal thermistor and RIP are alternative methods (Berry et al., 2012).

There are large differences between centres as to whether full PSG or one of the simplified PG recording methods are used to assess sleep-related breathing disorders (Hedner et al., 2011). The American Sleep Disorders Association (ASDA) reviewed PG and its potential role in the diagnosis of OSA (Collop et al., 2007), and stated that it may be used in populations where there is a high pre-test probability of OSA. They recommended against the use of PG in patient populations with comorbid sleep disorders, mainly due to paucity of studies validating PG in these populations. The patients that are included in the studies presented in this thesis have been examined mainly using the portable Embletta system (ResMed). It has been validated against PSG with good results (Dingli et al., 2003; Ng et al., 2010).

In the Nordic countries, there is an agreement that manually scored recordings including measurement of airflow, respiratory movements and pulse oximetry during a full night recording may be used for diagnostic purposes, since they have been found to identify pathologic AHI with high sensitivity and specificity compared to PSG (i.e., recordings also comprising EEG) (SBU, 2007).
EPIDEMIOLOGY

Prevalence in various populations

After the initial description, OSA was believed to be a relatively rare disorder, but it is now known that a significant proportion of the population has sleep disordered breathing. Young et al. (1993) used a multiple step design, where a telephone survey of state employees in Wisconsin was followed by a questionnaire that was sent to all self-described snorers and a random sample of the non-snorers from the telephone interview. In-hospital PSG was then performed with thermocouples for apnea/hypopnea detection. The definition of a hypopnea was any discernible reduction in airflow associated with a desaturation of 4 % or more. Daytime sleepiness was assessed using three questions about how often the subjects felt excessively sleepy during daytime, how often they woke up unrefreshed regardless of the duration of prior sleep and how often they had uncontrollable sleepiness that interfered with daily living. Responses were given on a five-point scale. After invalid registrations (e.g., total sleep time less than 4 hours) had been excluded, 602 subjects remained. They concluded that 9% of the women and 24 % of the men had sleep-disordered breathing (defined as an AHI≥5/h), and 2% of the women and 4% of the men had both sleep-disordered breathing and hypersomnolence.

Kripke et al. (1997) studied the prevalence of SDB in middle-aged adults (40-64 years). In a first step, people were randomly selected for a telephone interview. Of 1,467 identified subjects, 1084 subjects were interviewed, and of those, 34 % accepted a home interview and sleep study. The sleep study consisted of actigraphy and oximetry, but no airflow parameters were recorded. The ODI4, i.e., the number of desaturations of at least 4% per hour of sleep, was used to assess patients, and these data were analysed by a computer. They found an ODI≥20/h in 7.2 % of the total population (9.3 % for men and 5.2 % for women, but the gender difference was not significant).

Bixler et al. (2001), in a community-based study, screened 12,219 women and 4,364 men by telephone interviews, and then selected a semi-random (patients with more risk factors or potential symptoms of sleep-disordered breathing were more likely to be selected) subsample who underwent a PSG. A hypopnea was defined as a 10 s or longer episode of a ≥50% drop of airflow by at least in combination with a ≥4 % desaturation. OSA was defined as AHI≥10/h and clinical symptomatology, e.g., daytime sleepiness, hypertension or other cardiovascular complications. Prevalence data in the background population were extrapolated using various weights to take the oversampling of subjects with higher pre-test probability of sleep-disordered
breathing into consideration. Defined as stated above, 1.2 % of women and 3.9 % of men were found to have OSA. If an \( \text{AHI} \geq 15 \text{/h} \), regardless of daytime symptoms or negative health consequences, was used to define cases, 2.2 % of women and 7.2 % of men were found to have OSA.

Durán et al. (2001) invited 2,794 subjects between 30 and 70 years of age in Spain to a two-step study consisting of a preliminary screening recording (i.e., in-home recording of heart rate, snoring, oxygen saturation and body position) followed by PSG in patients that were considered to have a high risk of OSA and a random subsample of those who were considered to have a low risk. A hypopnea was defined as a 50% or more reduction of the airflow followed by a desaturation of at least 4 % or an arousal. 2,148 subjects completed the first phase, and 555 underwent PSG. OSA was defined as \( \text{AHI} \geq 5 \text{/h} \), and OSA syndrome as OSA combined with daytime symptoms. Daytime sleepiness was defined as sleepiness at least 3 days/week during the last 3 months in at least one of the following situations: after awakening, during free time, at work or driving, or during daytime in general. In both men and women, irrespective of which \( \text{AHI} \) cutoff value was used (i.e., 5, 10, 15, 20 or 30), sleep-disordered breathing increased with age. Based on a cutoff value of 10/h, they estimated the prevalence of sleep-disordered breathing to be 19 % in men and 15 % in women. OSA with daytime sleepiness was found in 3.4 % of men and 3 % in women.

In the Sleep Heart Health Study (Quan et al., 1997; Young et al., 2002), patients were recruited from other ongoing cohort studies. They were examined using home PSG. A hypopnea was defined as a decrease of airflow to 70% or less from baseline, lasting for at least 10 s. Both apneas and hypopneas had to be associated to a desaturation of at least 4 % to be counted. They found an \( \text{AHI} \) of 5-15/h in 33% of 2648 men and in 26 % of 2967 women. When using a cutpoint of 15/h, they found a prevalence of sleep-disordered breathing of 25% of men and 11% of women. It is important, however, to notice, that the Sleep Heart Health Study actually explicitly excluded patients who had been treated for sleep-disordered breathing. They also oversampled young habitual snorers (Quan et al., 1997). Both these factors might influence the prevalence data that they report.

Hrubos-Ström et al. (2011) studied the prevalence of obstructive sleep apnea in a Norwegian population-based sample. The Berlin Sleep Apnea Questionnaire (BSAQ; Netzer et al., 1999) was used for an initial screening of 29,258 Norwegians between 30 and 65 years. 55.7 %
responded. From the responses, a stratified randomisation was performed based on age, sex, BSAQ risk (in the BSAQ, respondents are classified as having either a high or a low risk of OSA). The high risk strata were further stratified according to previous otitis media surgery or diabetes. Based on this, 518 subjects were selected for in-lab PSG. Oronasal thermocouples were used for airflow recording. A hypopnea was defined as a 30 % reduction in airflow for at least 10 s combined with a ≥4 % desaturation. The prevalence for an AHI exceeding 5/h was found to be 21 % in men and 13 % in women. Using a cutoff at 15/h the figures were 11% and 6%, respectively.

Franklin et al. (2013) examined a randomised sample of 10,000 women in Uppsala, Sweden. In an initial step, a questionnaire was sent by mail to the sample. From the respondents 400 subjects were randomly selected for PSG, with an oversampling of habitual snorers as identified by the questionnaire (i.e., patients who had answered "often" or "very often" on the question "How often do you snore loudly and disturbingly?"). Apneas and hypopneas were recorded with oronasal thermosensor and air pressure transducer. A hypopnea was defined as a 50% reduction in both the thermistor and air pressure transducer signal for at least 10 s together with either a ≥3% desaturation or an arousal. Obstructive sleep apnea was found in 50 % when an AHI cutoff of 5/h was used, 20 % when an AHI cutoff of 15/h was used and 5.9 % when an AHI of 30/h was used. There was a general increase of the prevalence with increasing age.

Most studies have had a similar design, where a general screening has been performed to identify patients with a high risk of sleep-disordered breathing, and then objective examinations in a selected subsample of the screened patients (Lindberg & Gislason 2000). The prevalence figures differ somewhat between the studies. This might be due to differences in the background population with regard to risk factors (e.g., age, smoking and BMI). Another reason might be the differences in how sleep-disordered breathing was defined.

In some special populations, the prevalence of sleep-disordered breathing is higher. In elderly patients, for example, Ancoli-Israel et al. (1991) randomly selected 1865 elderly subjects (i.e., older than 65 years), of which 1,526 agreed to be interviewed by telephone. 427 subjects performed a sleep study. Respiration was assessed by RIP, and sleep was recorded from actigraphy. Obstructivity was assessed from phase difference between the abdominal and thoracic respiratory movement channels. Hypopneas were defined as a ≥50% decrease in the respiratory signal. There is no explicitly stated duration criterion for hypopneas. They found that
81 % had an RDI (Respiratory Disturbance Index; in this case defined as the number of apneas and/or hypopneas per hour of sleep, i.e., the AHI) of 5/h or higher, 62 % had an RDI of 10/h or higher and 44 % had an RDI of 20/h or higher. Somewhat strangely, they state that the highest reported RDI was 349.8/h, which is indeed very high. It would mean that of an average hour, at most 102 s would consist of normal breathing. This is not discussed.

Johansson et al. (2009) examined the prevalence of sleep-disordered breathing in a sample of community-dwelling elderly in the municipality of Kinda, Sweden. The study was performed on the CoroKind cohort (all inhabitants aged 65-82 years old and living in the municipality of Kinda). Of 1130 available subjects, 876 inhabitants accepted inclusion, and of those, 346 agreed to a home PG study. Nasal airflow for apneas and hypopneas were assessed by an airway pressure transducer and RIP. Hypopneas were defined as a \( \geq 10 \) s episode of either a 50 % reduction of airflow or a 30 % reduction of airflow in combination with a desaturation exceeding 3%. 55 % of the subjects had sleep-disordered breathing when it was defined as an AHI \( \geq 5/h \), of which most patients (i.e., 32 % had an AHI between 5/h and 15/h).

In hypertensive subjects, sleep-disordered breathing is highly prevalent. Among patients with drug-resistant diastolic hypertension, defined as a diastolic blood pressure exceeding 95 mmHg despite triple antihypertensive drug therapy for at least six months, Isaksson & Svanborg (1991) found a much higher prevalence of OSAS, defined as AI and ODI>5/h (56%) than among age and BMI matched controls with well controlled hypertension (19%). Goncalves et al. (2007) performed a case-control study where cases were defined as patients having a blood pressure exceeding 140/90 mmHg in two consecutive visits and were on at least three antihypertensive drugs including a diuretic. They were consecutively enrolled from patients at a hypertension clinic in Porto Allegre, Brazil, between 2004 and 2006. Controls were receiving drug treatment for hypertension but did not have a blood pressure exceeding 140/90 mmHg. Cases and controls were matched with regard to age, gender and BMI. 63 cases and 63 controls enrolled in the study. Breathing was analysed using a level III PG device. An air pressure transducer was used to assess airflow. A hypopnea was defined as a 10 s or longer decrease in airflow to 50% or less of baseline values, followed by either a desaturation of at least 3 % or an arousal, defined as an increase of the heart rate by at least 6 beats per minute for at least two seconds following the episode. 71 % of the patients and 38 % of the controls had an AHI of at least 10/h (p<0.001), but both cases and controls had hypertension. The study thus indicates a high prevalence of sleep-
disordered breathing in drug-resistant hypertension. This has also been shown in other studies (e.g., Logan et al., 2001).

Broström et al. (2012) examined 480 consecutive patients with hypertension at four primary care centres in Jönköping, Sweden. Of these, 394 patients underwent a technically acceptable PG recording. Airflow was assessed by nasal air pressure and RIP. A hypopnea was defined as an airflow reduction of at least 30 % for at least 90 % of the duration of an event lasting at least 10 s in combination with a desaturation of at least 4 %. OSA was defined as an AHI of 5/h or higher. Moderate and severe OSA were defined as AHI exceeding 15/h and 30/h, respectively. 59 % had OSA, and half of them had moderate or severe OSA.

**Risk factors for obstructive sleep apnea**

Several factors have been associated to an increased risk for OSA. Among the most significant ones are obesity, age and male gender.

**Obesity**

Obesity or overweight is a significant risk factor for obstructive sleep-disordered breathing. 40 % of obese men have OSAS and 70 % of OSAS patients are obese (Parati et al., 2007). In cross-sectional studies, the odds for having OSAS increases with increased body weight (Young et al., 1993; Franklin et al., 2013). In longitudinal population-based studies, an increase in AHI has been associated to an increased BMI, and a decrease in BMI has been associated to a decrease in AHI. The Wisconsin Sleep Cohort Study found that a 10 % weight gain led to an average 32 % increase in AHI and a six-fold increase in the odds of developing at least moderate (i.e., AHI>15/h) OSA (Peppard et al., 2000). Another approach has been to study weight-changing interventions in overweight or obese patients, and their influence on the degree of sleep-disordered breathing. The published studies have been relatively small with short follow-up times. Johansson et al. (2009b) randomized 63 obese men with moderate to severe OSA (AHI≥15/h) and CPAP to either receive weight loss therapy (Very low calorie diet, 2.3 MJ/day) or no treatment. Both groups had similar AHI at the beginning of the intervention, but the intervention group lost 20 kg more than the control group over 9 weeks, and had, at the end of the intervention, a lower AHI (in average 23/h lower than
the control group with 17% disease free (i.e., AHI<5/h) and 50% with an AHI between 5 and 15/h). In the control group, in contrast, only one subject had an AHI below 15/h at the end of the intervention. Gastric bypass surgery has been associated to a decrease in sleep respiratory parameters as well as daytime sleepiness in 100 consecutive obesity patients undergoing weight-reduction surgery (Rasheid et al., 2003).

While there is a clear possible pathogenetic mechanism that links obesity to OSA by narrowing of the upper airways due to fat depositions around the upper airways (Mortimore et al., 1998), and/or by increasing the collapsibility of the upper airways (Schwartz et al., 1991), it is also possible to see OSA as a risk factor for obesity. Patients with OSA were more likely to gain weight than control subjects with the same BMI but without OSA (Philips et al., 2000). The problem with this study is, however, that weight gain data was collected retrospectively (i.e., patients reported their weight change during the year preceding the diagnosis of OSA). Thus, it is hard to tell whether they increased in weight due to their OSA, or whether an unrelated increase in weight was the cause of their OSA. Patients with OSA also have higher levels than normal controls of the appetite-stimulating hormone ghrelin, and this is reduced by effective CPAP treatment (Harsch et al., 2003). It is also possible, that sleepiness and other daytime symptoms caused by sleep-disordered breathing lead to less physical activity.

**Age**

The OSA that is seen in children is probably a somewhat different disease with regard to causes etc. than the OSA seen in adult subjects (Young et al., 2002b). The prevalence of sleep-disordered breathing is high in older populations (Ancoli-Israel et al., 1991; Johansson et al., 2009). There is also some evidence that obstructive sleep apnea might be a part of a spectrum starting with snoring and then slowly progressing over the cause of years or decades (e.g., Svanborg & Larsson 1993; Young et al., 2002). There is a possibility that this might be due to a snoring vibration-induced nerve damage to the upper airways (Friberg et al., 1998; Svanborg 2005; Hagander 2006; Sunnergren 2012). With increasing age, it has been hypothesized that structural changes in upper airway and changes in muscle tone (e.g., Worsnop et al., 2000) and decreased respiratory effort in response to obstructive events (Krieger et al., 1997) act together to increase the risk for and duration of apneas and hypopneas. After 60 to 65 years of age, however, there seems to be a plateau or even a decrease (Young et al., 2002b; Bixler et al., 1998; Bixler et al., 2001).
**Gender**

Male gender has been associated to an increased prevalence of OSA. In women, OSA becomes more prevalent after menopause (Bixler et al., 2001). The gender difference is seen both in clinical and population-based samples (Lindberg & Gislason, 2000). In early epidemiological research, it was assumed that OSA was much more common in men than in women (e.g., Block et al., 1979). Later research has downgraded the gender difference. Still, OSA is believed to be approximately two to three times as common in men (Young et al., 2002b). One reason might be that both patients and doctors are less likely to suspect that a woman suffers from OSA. In sleep clinic populations, the male predominance is higher than in population-based samples (Lindberg & Gislason, 2000), which could support this hypothesis. Lindberg & Gislason (2000) speculate that this might be, at least partly, due to different symptom profiles among men and women. In a sleep clinic sample, Ambrogetti et al. (1991) found that women were more likely to report morning headache and fatigue than men. Some studies have indicated that postmenopausal women on hormone replacement therapy have a lower prevalence of OSA (e.g., Bixler et al., 2001; Shahar et al., 2003), but the results are not conclusive (see Young et al., 2002b).

**Consequences of obstructive sleep apnea**

**Mortality**

The main problem with relating mortality and morbidity to obstructive sleep apnea is that there is a strong comorbidity with obesity, which is a known risk factor for several cardiovascular disorders.

All-cause mortality has been studied both in population-based samples and certain clinical samples. Prospective studies using objective measurements are summarized in Table 1.
Table 1: Prospective studies of mortality in obstructive sleep apnea.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study population</th>
<th>Sleep study</th>
<th>Results</th>
<th>Comment</th>
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</thead>
<tbody>
<tr>
<td>Bliwise et al., (1988)</td>
<td>198 subjects who had undergone PSG (35% men), dichotomized for age (cutoff age 65 years) and BMI (median, i.e., cutoff BMI 35 kg/m²)</td>
<td>PSG. OSA was defined as RDI≥10/h.</td>
<td>Mortality was 222.2/1000 person years among high-RDI subjects vs 83.3/1000 person years among low-RDI subjects.</td>
<td>Age was a major confounder, and there was no significant association between RDI and death after adjusting for it.</td>
</tr>
<tr>
<td>Campos-Rodriguez et al., (2012)</td>
<td>1116 patients (only women) referred to sleep study for suspected OSA were followed for a median of 6 years.</td>
<td>PSG or PG. AHI&lt;10 (controls), 10-29 or ≥30. OSA patients were subdivided into treated or untreated groups.</td>
<td>After adjustment for age, BMI, hypertension, diabetes and previous cardiovascular events, HR for cardiovascular death was 3.50 (1.23-9.98) among untreated patients with AHI&gt;30 vs controls.</td>
<td>No risk increase in CPAP treated patients or in milder disease.</td>
</tr>
<tr>
<td>He et al., (1988)</td>
<td>385 patients (only men) referred for suspected sleep apnea</td>
<td>PSG. AI&gt;20</td>
<td>Probability of cumulative 8-year survival was 96% among patients with AI&lt;20/h and 63% among patients with AI&gt;20/h (p&lt;0.05).</td>
<td>Only 22 deaths.</td>
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</tbody>
</table>
Table 1: Prospective studies of mortality in obstructive sleep apnea (continued)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study population</th>
<th>Sleep study</th>
<th>Results</th>
<th>Comment</th>
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</thead>
<tbody>
<tr>
<td>Korostovtseva et al., (2011)</td>
<td>147 patients (61 % men) with hypertension and high risk for OSAHS were followed for a median of 3.9 years.</td>
<td>PG. AHI &lt;5, 5-15, 15-30 and &gt;30.</td>
<td>After adjustment for sex, age, BMI, duration of hypertension, alcohol, smoking, physical activity, heredity, coronary artery disease, glucose metabolism, OR for cardiovascular fatal events was 9.2 (1.2-72) in AHI&gt;30 vs &lt;5.</td>
<td>Patients with AHI 5-30 had no significantly increased cardiovascular mortality.</td>
</tr>
<tr>
<td>Lavie et al., (2005)</td>
<td>14589 patients (only men) referred to a sleep clinic for suspected or definite OSAS. Median follow-up was 4.6 years.</td>
<td>PSG. OSA was defined as RDI≥10/h.</td>
<td>All-cause mortality increased with RDI and BMI.</td>
<td>RDI was related to mortality only in younger (&lt;50 years) subjects.</td>
</tr>
<tr>
<td>Mant et al., (1995)</td>
<td>163 retirement village residents over 70 years (21 % men) were followed for 4 years</td>
<td>PG. RDI&gt;15</td>
<td>No association between RDI and mortality.</td>
<td>Few cases with high RDI.</td>
</tr>
<tr>
<td>Marin et al., (2005)</td>
<td>1387 patients (only men) vs 264 controls matched for age and BMI followed for 10 years.</td>
<td>PSG. AHI&gt;30/h</td>
<td>Untreated severe OSA adjusted OR 2.87 (1.17-7.51) for fatal cardiovascular events</td>
<td></td>
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</table>
| Marshall et al., (2008)       | Busselton Health Study. 380 subjects from Busselton, WA, Australia (73 % men) underwent a home sleep study. Mean follow-up was 13.4 years. | PG. RDI<5, RDI 5-15 and RDI>15 groups were compared. | HR 6.24 (2.01-19.39) for death after adjustment for age, gender, BMI, smoking status, total cholesterol, HDL, diabetes, angina and mean arterial pressure. | Mean arterial pressure was defined as 2/3*systolic blood pressure + 1/3*diastolic blood pressure, which is not the standard definition (i.e., 1/3*systolic blood pressure + 2/3*diastolic blood pressure; Sesso et al., 2000).
Table 1: Prospective studies of mortality in obstructive sleep apnea (continued)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study population</th>
<th>Sleep study</th>
<th>Results</th>
<th>Comment</th>
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</thead>
<tbody>
<tr>
<td>Martinez-Garcia et al., (2012b)</td>
<td>939 elderly (&gt;64 years; 64 % men) patients with a suspicion of OSA. Mean follow-up was 5.8 years.</td>
<td>PSG or PG. AHI&lt;15 (controls), AHI 15-30, AHI&gt;30 without treatment, AHI&gt;30 with treatment.</td>
<td>Adjusted HR(for age, BMI, sex, sleepiness, smoking, co-morbidities) for all-cause mortality was 1.99 (1.42-2.81), fatal stroke HR was 4.63 (1.03-20.8), fatal heart failure HR was 3.93 (1.13-13.65) when comparing untreated AHI&gt;30 to controls.</td>
<td>No increased risk for fatal ischaemic heart disease. No increased risk in the AHI 15-30 group. CPAP treated patients had no increased HR for death.</td>
</tr>
<tr>
<td>Punjabi et al., (2009)</td>
<td>Sleep Heart Health study, 6,441 subjects (47 % men). Average follow-up was 8.2 years.</td>
<td>PSG. AHI&lt;5/h vs AHI&gt;30/h</td>
<td>AHI&gt;30 in 40-70-year old men HR for death was 2.09 (1.31-3.33) after adjusting for age, race, BMI, smoking, blood pressure, hypertension, diabetes and CVD.</td>
<td>For older men, and for women irrespective of age, there was no significant association between AHI and mortality.</td>
</tr>
<tr>
<td>Tang et al., (2010)</td>
<td>93 peritoneal dialysis patients (52 % men). Median follow-up was 41 months.</td>
<td>PSG. AHI&lt;15 vs AHI ≥15</td>
<td>Adjusted HR for all-cause mortality in the AHI&gt;15 group was 1.72 (1.03-2.88) after adjusting for age, gender, diabetes, minimum SaO2 and kidney function.</td>
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<tr>
<td>Yaggi et al., (2005)</td>
<td>1,022 patients (71 % men) referred to a sleep clinic, aged at least 50 years and no previous stroke or TIA. Median follow-up was 3.4 years.</td>
<td>PSG. AHI&gt;5/h</td>
<td>After adjusting for age, sex, race, smoking status, alcohol, BMI, diabetes, hyperlipidemia, atrial fibrillation, and hypertension the HR for stroke or death was 1.97 (1.12-3.48).</td>
<td>Combined end-point</td>
</tr>
<tr>
<td>Young et al., (2008)</td>
<td>1522 subjects (55 % men) from the Wisconsin Sleep Cohort were followed for 18 years.</td>
<td>PSG. AHI &lt;5, 5-15, 15-30 and &gt;30.</td>
<td>Adjusted HR for all-cause mortality (AHI&gt;30 vs &lt;5) was 3.0 (1.4-6.3) after adjusting for age, sex and BMI.</td>
<td>No significant risk increase among those with AHI&lt;30, but significant p for trend (p=0.008).</td>
</tr>
</tbody>
</table>
OSA has also been associated to increased risk of death in patients with stroke (Sahlin et al., 2008; Martinez-Garcia et al., 2009) and coronary artery disease (Peker et al., 2000). In a study on 3,100 Swedish 30 to 69-year-old men, Lindberg et al. (1998) found the adjusted HR for death within 10 years to be 2.2 (95% CI 1.3-3.8), but only in subjects younger than 60 years. That study, however, used questionnaires to assess sleep-disordered breathing.

**Hypertension**

Lugaresi et al. (1980) described an association between systemic arterial hypertension and snoring. Especially so called 'non-dipping' hypertension, i.e., hypertension that does not decrease during the night, is associated to obstructive sleep apnea (Davies et al., 2000). Brooks et al. (1997) induced increased night-time blood pressure in dogs by inducing intermittent obstruction of the upper airways, and Troncoso Brindeiro et al. (2007) exposed rats to a chronic intermittent hypoxia protocol, which increased their blood pressure. Hardy et al. (1994) showed that experimentally induced hypoxia causes increased blood pressure in humans. Not only desaturations, but also disturbed sleep, may affect blood pressure.

Both age and BMI are risk factors for obstructive sleep apnea, but they also increase the risk of hypertension. There was therefore initial concerns whether hypertension was actually an effect of OSA, or whether obesity and/or age were confounders, creating a spurious relationship. The same is true for alcohol consumption and tobacco use. Caffein has been proposed as a potential confounder as it increases norepinephrine excretion, but Bardwellet al. (2000) did not find it to be a likely major confounder.

Several cross-sectional studies have described either a higher prevalence than expected of sleep-disordered breathing among hypertensive patients (e.g., Hedner et al., 2006; Broström et al., 2012) or a higher than expected degree of hypertension among patients with obstructive sleep apnea (e.g., Davies et al., 2000; Carlson et al., 1994; Levinson et al., 1993). In a population-based cross-sectional study of a subsample of the Sleep Heart Health Study, Javier Nieto et al. (2000) found a successive increase in blood pressure in parallel with higher SDB indices, which was partially, but not totally, explained by BMI. These studies generally are not able to discern causative relationships.
Table 2: Prospective studies of associations between OSA and hypertension using objective measurements.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Subjects</th>
<th>Sleep study</th>
<th>Results</th>
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</thead>
<tbody>
<tr>
<td>Marin et al., (2013)</td>
<td>1889 normotensive patients (76% men) referred for sleep study were followed for a median time of 12.2 years.</td>
<td>PSG. AHI 5-14.9/h was mild, AHI 15-29.9 was moderate and higher AHI was severe OSA.</td>
<td>Adjusted HR (AHI, age, sex, SBP, DBP, BMI, alcohol, smoking, medication, glucose, lipids, menopausal status, BMI change) for patients who declined CPAP was 1.96 (1.44-2.66), and for CPAP treated patients 0.71(0.53-0.94).</td>
</tr>
<tr>
<td>O’Connor et al., (2009)</td>
<td>Sleep Heart Health Study. Prospective study of 2470 non-hypertensive subjects (44.7% men), mean age 59.6 years. 5 years follow-up.</td>
<td>PSG</td>
<td>No significant association between baseline AHI and hypertension after adjustment for BMI.</td>
</tr>
<tr>
<td>Peker et al., (2002)</td>
<td>182 30-69-year-old men investigated for sleep apnea followed for 7 years.</td>
<td>PG. &gt;30 oxygen desaturations/night</td>
<td>Adjusted OR (adjusted for BMI, blood pressure and age) for cardiovascular disease (hypertension, angina, myocardial infarction, stroke, cardiovascular death, heart failure) was 4.9 (1.8-13.6) and for hypertension 3.7 (1.1-13.1).</td>
</tr>
</tbody>
</table>
Table 2: Prospective studies of associations between OSA and hypertension using objective measurements (continued).

<table>
<thead>
<tr>
<th>Reference</th>
<th>Subjects</th>
<th>Sleep study</th>
<th>Results</th>
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<tbody>
<tr>
<td>Peppard et al.,</td>
<td>Prospective study of the Wisconsin Sleep Cohort. 709 subjects (55% men)</td>
<td>PSG. No OSA (AHI 0), AHI 0.1-4.9, AHI 5-14.9 or AHI 15 and higher</td>
<td>Adjusted OR (baseline hypertension, age, sex, BMI, waist and neck circumferences, menopause, exercise, alcohol and smoking) for hypertension: AHI 0: 1.0, AHI 0.1-4.9 1.42 (1.13-1.78), AHI 5-14.9 2.03 (1.29-3.17), AHI≥15 2.89 (1.46-5.64). P for trend 0.002.</td>
</tr>
<tr>
<td>(2000b)</td>
<td>followed for 4 years.</td>
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Two of the larger studies, by Peppard et al., (2000b) and by O’Connor et al., (2009) are contradictory. There are several differences between the Peppard and O’Connor studies, that might explain the differences (Peppard, 2009). The Sleep Heart Health cohort was older, the control population was defined differently (i.e., the Wisconsin cohort defined healthy subjects as subjects with no respiratory events while the Sleep Heart Health cohort definition was AHI≤5/h). Also, the baseline prevalence of hypertension and the gender distribution differed between the two studies.

Several intervention studies have examined the effects of CPAP on patients with OSA. The findings are inconclusive in most (early) trials, which were mostly small and of poor quality. Some found a decrease in ambulatory blood pressure (e.g., Engleman et al., 1996 in non-dipping hypertensives; Guilleminault et al., 1996), while other studies were unable to find any significant effect of the treatment (e.g., Ali et al., 1992). This is also shown in a placebo-controlled trial, where daytime blood pressure was lowered in both patients on active and sham CPAP treatment (Dimsdale et al., 2000), and incident hypertension was not lower in the treatment group among non-sleepy OSA patients that were randomized to CPAP or placebo (Barbé et al., 2013), and a meta-analysis of studies with oral appliances in OSA patients found modest effects on some, but not all, measures of hypertension (Iftikhar et al., 2013).
Other cardiovascular diseases

Several studies have indicated an association between obstructive sleep apnea and ischemic heart disease. In a cross-sectional examination of the Sleep Heart Health study cohort (n=6,424, of which 5,250 were used in the full model mainly due to missing data), subjects belonging to the highest quartile regarding AHI had a higher relative odds for having had a heart failure or stroke, but the relative odds was not significantly increased for coronary artery disease (Shahar et al., 2001). Similar findings, i.e., an increased prevalence of prior stroke (OR 2.57, 95 % CI 1.03-6.42) but not coronary artery disease was found by Rice et al., (2012) among diabetic men in a cross-sectional study. Mooe et al., (1996) and Peker et al., (1999) both found that sleep-disordered breathing was significantly associated to ischemic heart disease in case-control studies. Koskenvuo et al., (1987) found self-reported frequent or habitual snoring to increase the relative risk of a combined end-point of stroke and ischemic heart disease.
Table 3: Prospective studies of other cardiovascular outcomes with objective recordings

<table>
<thead>
<tr>
<th>Reference</th>
<th>Subjects</th>
<th>Sleep study</th>
<th>Results</th>
<th>Comment</th>
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<tbody>
<tr>
<td>Arzt et al.,</td>
<td>Wisconsin sleep cohort. 1189 subjects (55% men) followed for 4 years.</td>
<td>PSG. AHI&gt;20 vs AHI&lt;5</td>
<td>After adjusting for age, sex, BMI, smoking and hypertension, OR for stroke was 3.83 (1.17-12.6) in a cross-sectional analysis and 3.08 (0.74-12.8) in a prospective analysis.</td>
<td>Few strokes, underpowered</td>
</tr>
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<td>(2005)</td>
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<tr>
<td>Marin et al.,</td>
<td>1387 patients (only men) referred for sleep apnea and 264 controls matched for age and BMI.</td>
<td>PSG. Untreated severe OSA (i.e., AHI&gt;30)</td>
<td>After adjusting for BMI, sex, diabetes, smoking, alcohol, cholesterol, triglycerides, hypertension, cardiovascular disease, lipid lowering and antihypertensive drugs, the OR for non-fatal cardiovascular events for patients were 3.17 (1.12-7.51).</td>
<td></td>
</tr>
<tr>
<td>(2005)</td>
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<tr>
<td>Marshall et al.,</td>
<td>Busselton Health Study. 380 subjects from Busselton, WA, Australia (73% men) underwent a home sleep study.</td>
<td>PG. Snoring sounds were recorded.</td>
<td>No association between snoring and stroke or cardiovascular events.</td>
<td>Hypothesis: snoring injures carotid arteries by vibration (Amatoury et al., 2006).</td>
</tr>
<tr>
<td>(2012)</td>
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</tr>
<tr>
<td>Mooe et al.,</td>
<td>407 patients with coronary artery disease (68% men) were followed for a median of 5.1 years.</td>
<td>PG. AHI&gt;10 or ODI&gt;5</td>
<td>Adjusted hazard ratio (adjusted for diabetes, left ventricular ejection fraction, coronary intervention, age, sex, BMI and hypertension) for stroke was 2.98 (1.43-6.20) for AHI&gt;10.</td>
<td></td>
</tr>
<tr>
<td>(2001)</td>
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</tr>
</tbody>
</table>
Table 3: Prospective studies of other cardiovascular outcomes with objective recordings (continued)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Subjects</th>
<th>Sleep study</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Munoz et al., (2006)</td>
<td>394 stroke-free subjects from the general population aged 70 to 100 years (57% men) were followed for 6 years.</td>
<td>PSG. AHI&gt;30/h vs &lt;30/h</td>
<td>After adjustment for sex, the HR for stroke was 2.52 (1.04-6.01) in the AHI&gt;30 group.</td>
</tr>
<tr>
<td>Peker et al., (2002)</td>
<td>182 30-69-year-old men investigated for sleep apnea followed for 7 years</td>
<td>PG. &gt;30 oxygen desaturations/night</td>
<td>Adjusted OR (adjusted for BMI, blood pressure and age) for cardiovascular disease (hypertension, angina, myocardial infarction, stroke, cardiovascular death, heart failure) was 4.9 (1.8-13.6)</td>
</tr>
<tr>
<td>Redline et al., (2010).</td>
<td>5422 subjects (45% men) aged &gt;40 years in the Sleep Heart Health Study (all were stroke-free at inclusion) were followed for an average of 8.7 years.</td>
<td>PSG. Patients were grouped in AHI quartiles.</td>
<td>Among men in the highest obstructive AHI quartile (&gt;19.13/h) the adjusted HR for stroke was 2.86 (1.10-7.39) after adjusting for age, BMI, race, smoking, systolic blood pressure, antihypertensive medication, and diabetes. No significant risk increase in the highest quartile was found for women.</td>
</tr>
<tr>
<td>Tang et al., (2010)</td>
<td>93 peritoneal dialysis patients (52% men). Median follow-up was 41 months.</td>
<td>PSG. AHI was used as a continuous variable.</td>
<td>HR for a +1/h increase in AHI for cardiovascular events was 1.02 (1.01-1.03) after adjusting for age, gender, diabetes and creatinine clearance.</td>
</tr>
</tbody>
</table>
Table 3: Prospective studies of other cardiovascular outcomes with objective recordings (continued)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Subjects</th>
<th>Sleep study</th>
<th>Results</th>
<th>Comment</th>
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<tr>
<td>Yaggi et al., (2005)</td>
<td>1022 patients referred to a sleep clinic, aged at least 50 years and no previous stroke or TIA. Median follow-up time was 3.4 years.</td>
<td>PSG. AHI&gt;5/h</td>
<td>After adjusting for age, sex, race, smoking status, alcohol, BMI, diabetes, hyperlipidemia, atrial fibrillation, and hypertension the HR for stroke or death was 1.97 (1.12-3.48)</td>
<td>Combined end-point</td>
</tr>
</tbody>
</table>

It has also been shown that stroke patients with OSA who do not tolerate CPAP have a higher degree of non-fatal cerebrovascular events than those who do (Martinez-García et al., 2012) and that they require a longer post-stroke hospitalization (Kaneko et al., 2003). Functional outcomes are better in some studies in CPAP-treated patients compared to untreated patients (e.g., Ryan et al., 2011), but some studies have not found an effect on outcome (reviewed in Tomfohr et al., 2012).

Almost every type of cardiac arrhythmia has been described in OSA, especially in more severe cases. This also includes severe forms of cardiac arrhythmias (Guilleminault et al., 1983). In the Sleep Heart Health study, 228 subjects with severe OSA (AHI≥30/h) were compared to healthy controls. After adjusting for age, sex, body mass index, and prevalent coronary heart disease, there was a higher prevalence of atrial fibrillation, nonsustained ventricular tachycardia, and complex ventricular ectopy in patients with OSA (Mehra et al., 2006). Atrial fibrillation has also been associated to obstructive sleep apnea in other studies (reviewed in Goyal & Sharma 2013). There seems to be an increased risk of relapse of atrial fibrillation after AF catheter ablation in OSA patients (Ng et al., 2011). There are also some studies that indicate that CPAP treatment might alleviate cardiac arrhythmias (Harbison et al., 2000; Abe et al., 2010). Many studies (e.g., Harbison et al., 2000) have only found an increased prevalence of nocturnal arrhythmias, but Namtvedt et al., (2011) found an increased prevalence of daytime arrhythmias as well.
Diabetes mellitus

Type 2 diabetes mellitus and impaired glucose tolerance have been associated to OSA in cross-sectional studies. Insulin resistance as measured by oral glucose tolerance tests has been associated to oxygen desaturations (Tiihonen et al., 1993). Lindberg et al., (2007) found in a population-based sample of 6,779 women that self-reported snoring and daytime sleepiness were associated to diabetes, at least in older women (i.e., ≥50 years old). In the Nurses' Health Study (Al-Delaimy et al., 2001), self-reported snoring was associated with an increased risk of diabetes during a ten-year follow-up period. OSA is independently associated with dyslipidemia and higher fasting insulin (Coughlin et al., 2004). A higher prevalence of insulin resistance was also found in a clinical sample of patients referred to a sleep clinic for suspected OSA. Patients with OSA (defined as AHI ≥ 5/h) were more insulin resistant than non-OSA subjects (Ip et al., 2002).

A high prevalence of OSA has been shown in clinical samples of patients with type 2 diabetes mellitus. In the SleepAHEAD study, Foster et al., (2009) found that 86% of type 2 diabetic subjects suffered from OSA, and 22.6% had severe OSA, defined as an AHI ≥ 10/h, with obesity explaining the link.

Prospective studies have indicated that OSA might be an independent risk factor of diabetes. In an observational cohort study, 544 diabetes-free consecutive patients referred to a sleep clinic for suspected OSA between 2000 and 2005 were included. Mean follow-up time was 2.7 years. There was a higher incidence of diabetes in patients with OSA, with a dose-response relationship when patients were divided into quartiles depending on their AHI after adjusting for age, gender, race, baseline fasting blood glucose, BMI, and change in BMI (Botros et al., 2009). Diabetes patients with OSA have worse glycemic control than those without OSA with a dose-response relationship with regard to OSA severity (Aronsohn et al., 2010).

Studies of effects of CPAP treatment on insulin resistance and type 2 diabetes have yielded inconsistent results. West et al., (2007) randomized 42 diabetic newly diagnosed OSA patients (ODI ≥ 10/h) to receive either therapeutic or sham CPAP with follow-up after three months. Although patients in the therapeutic group improved significantly with regard to daytime sleepiness, they did not improve with regard to HbA1C or insulin resistance. Dawson et al., (2008) compared nocturnal glucose during the diagnostic PSG and a night on CPAP in type 2 diabetic patients with newly diagnosed OSA after on average 41 days and found an improved glucose control on CPAP than during the diagnostic study. The patients in that study had a more well-regulated diabetes than those in the study by West et al., (2007).
Sleepiness

When a differentiation is made between OSA and OSAS, it is usually based on the prevalence of daytime sleepiness. To measure subjective acute sleepiness, single-item instruments are usually used, such as KSS (Åkerstedt & Gillberg, 1990) or SSS (Hoddes et al., 1973). Most often, sleepiness over a longer time period is assessed using the Epworth Sleepiness Scale (ESS). Both ESS and KSS and SSS have been validated against physiological measures of sleepiness. The ESS was developed by Johns (1991), and consists of eight items, describing situations where the respondent is asked to rate the probability of falling asleep on a four-level Likert-type scale, ranging from 0 to 3, where higher scores indicate a higher probability of falling asleep. There has been criticism regarding the items in the ESS, based on the fact that the item generation and selection process is not described in detail. Two questions (item 3, about the probability of falling asleep in a public meeting, and item 4, about the probability of falling asleep as a passenger in a car for an hour), have been published as a poster (Miletin & Hanly, 2003), but there is no information about the generation and selection process for the other items. Item 8 asks for the probability of falling asleep “in a car, that has stopped for a few minutes in traffic”. It does not state whether the respondent drives the car or is a passenger, despite the fact that this is likely to affect the soporificity (i.e., sleep-inducing potential) of the situation. In the pictorial ESS (Ghiassi et al., 2011), which is an ESS version where all items and response alternatives are described using cartoon-like pictures, item 8 is shown with a passenger in the backseat falling asleep. As a part of the development process of the pictorial ESS, a version with the driver falling asleep was also shown, and this was found to decrease the respondents’ scores on the item (Ghiassi, personal communication). The passenger version was chosen to enable more people to answer the questionnaire.

Physiological measurements of sleepiness are usually based on EEG-derived indices, usually the sleep latency during various conditions and after having received various instructions. The Multiple Sleep Latency Test (MSLT; Richardson et al., 1978) and the Maintenance of Wakefulness Test (MWT; Mitler et al., 1982) are both based on this principle, but differ in which instructions are given and the specific details (e.g., the duration of each specific trial). In the MSLT, patients are asked to lie down with closed eyes in a dark room and try to go to sleep (Carskadon et al., 1986), while the MWT instructs patients to try to remain awake for 40 minutes in a semi-supine position. Other physiological measurements of sleepiness include EEG alpha
power, which increases in sleepy drivers (Kecklund & Åkerstedt, 1993), and blink duration, which also increases with increasing sleepiness (Åkerstedt et al., 2005).

The Epworth Sleepiness Scale has been validated against MSLT and MWT, with varying results. Fong et al., (2005) compared ESS and MSLT in patients with OSAS and found that while MSLT sleep latency was significantly shorter in severe OSAS than in mild or moderate OSAS, no significant differences were found for ESS scores between different severity groups. ESS scores were, however, significantly correlated to MSLT, albeit weakly. Chervin et al. (1997) found a negative correlation (rho=-0.37) between ESS and MSLT in one study, but in another study they did not find any correlation at all (Chervin & Aldrich 1999). Olson et al., (1998) found no correlation between the ESS and AHI, or between MSLT and AHI. However, their study sample was a mixed sample with SDB, narcolepsy, chronic fatigue syndrome, circadian rhythm disorders and hypersomnia of other causes. When only patients with OSA were included, the findings were similar (i.e., no significant correlation). Johns (1993) found a correlation between ESS and AHI in patients with SDB. Findings are, in other words, contradictory.

Treatment studies have indicated that CPAP treatment might alleviate sleepiness in patients with OSAS. Hardinge et al., (1995) found that CPAP treatment improved ESS scores both after two months and one year on treatment in patients with OSA. There was, however, no control group. Kribbs et al., (1993b) compared subjective sleepiness (SSS), objective sleepiness (MSLT) and psychomotor consequences of sleepiness (psychomotor vigilance task, PVT) prior to, during and after one night without CPAP after treatment initiation. They found that MSLT improved on CPAP treatment, and worsened after a night without it. The PVT and SSS showed similar trends, but they were not fully significant. However, only 15 patients were studied. In another study, Engleman et al. (1998), found a significant decrease in sleepiness, measured by both ESS and MSLT in OSAS patients with an AHI≥15/h. That study consisted of 23 subjects with an AHI of at least 15/h. Engleman et al. (1994b) also found improvements in MSLT and ESS when compared CPAP to placebo.

**Cognitive deficits**

In the Sleep Heart Health Study, word fluency, digit-symbol substitution and delayed word recall were studied. There was no consistent pattern between OSA severity indices and neuropsychological test results after adjusting for gender, age, education, occupation, field centre, diabetes, hypertension, BMI, use of CNS medications, and alcohol drinking status (Boland et al., 2002).
Several studies have examined neuropsychological sequelae of OSAS, but many of the studies contain methodological weaknesses (Aloia et al., 2004). These include failure to control for learning effects from repeated uses of psychometric tests, failure to account and control for adherence, inconsistent methods for controlling for demographic factors and making the diagnosis. Besides, different studies use different tests and measure different constructs. In a meta-analysis, Beebe et al., (2003) reported that vigilance and executive functions were most clearly affected by OSA, in contrast to general intelligence and verbal ability. Antic et al. (2011) found a dose-response relationship between hours of nightly CPAP use and daytime sleepiness as measured by the ESS, and a significant effect on executive functioning and verbal memory, but no significant dose-response effect for the latter two.

Accidents

Young et al. (1997) studied traffic accidents in a sample of subjects from the Wisconsin Sleep Cohort study. Men who had an AHI ≥ 5/h had three to four times as high odds of having been involved in a traffic accident during the last five years, and men and women combined, with an AHI of at least 15/h, had an adjusted odds ratio of 7.2 compared to normal sleepers for having had multiple accidents. The models were adjusted for gender, age and miles driven per year. Interestingly, adding sleepiness to the models did not improve them. Sleepiness has, however, been associated to driving performance in several other studies (e.g., Åkerstedt et al., 2001; Åkerstedt et al., 2013).

In a case-control study, Teràn-Santos et al. (1999) included 102 patients who sought emergency treatment to 152 controls that were matched for age and gender but with no history of traffic accidents for the two years prior to enrolment. Data were adjusted for use or nonuse of alcohol, visual-refraction disorders, BMI, years of driving, medications causing drowsiness, work and sleep schedule (work during the day and sleep at night or some other pattern), kilometers driven per year, and presence or absence of arterial hypertension. The adjusted odds ratio for having had a traffic accident during the last two years was 7.2 for cases having an AHI of at least 10/h compared to controls.
TREATMENT

Treatment of OSA focuses on alleviating the symptoms of sleep-disordered breathing and on counteracting the potential health hazards that might follow from it. The main treatment approach, at least in more severe cases of OSA, is CPAP, in which a device is used to produce a positive air pressure of the upper airways to keep them unobstructed during sleep. Another approach is to advance the mandible using an oral appliance, thereby preventing the soft tissues to fall back and obstruct the airways (Soll & George, 1985). Surgery where soft tissue of the upper airways is removed has also been used.

Surgery

Surgery was popular in the beginning of the 1990’s, but lost momentum as the relapse rate, at least in overweight subjects and in those with severe disease, was very high (Larsson et al., 1991) and due to lack of evidence of efficacy (SBU, 2007). However, in patients that did not relapse in four years after surgery, the treatment is effective even after long time (Browaldh et al., 2011), and it has recently been shown that UPPP is efficacious in reducing the AHI from severe to moderate levels in selected patients as compared to untreated controls (Browaldh et al., 2013). The main surgical approach to OSA in adults is removal of soft tissues surrounding the upper airways (Fujita, 1984). Due to the relationship between obesity and OSA, surgery aiming primarily at weight reduction has been studied more extensively due to its potential effects on OSA. Several studies (reviewed in Sarkhosh et al., 2013) have examined the effects of OSA disease severity measures. In summary, weight reduction is a potentially effective treatment, with malabsorptive surgical approaches probably more efficient than purely restrictive approaches. Interestingly, sleep-disordered breathing might improve relatively early postoperatively (Varela et al., 2007).

Mandibular advancement devices

Regarding mandibular advancement devices, Gotsoupolos et al., (2002) compared the effect of devices to an untreated control condition in a randomized, cross-over design. They found that in 73 consecutive patients with OSA, both respiratory indices and sleepiness (measured both by the ESS and MSLT) improved on active treatment, as compared to placebo. In another cross-over trial, Barnes et al., (2004) compared 114 OSA patients with mild to moderate disease (AHI 5-30/h) who were assigned to CPAP, a mandibular advancement device or placebo (in the form of a pill). Evaluation was performed by the Maintenance of Wakefulness Test (MWT) and ESS on
the last day of each treatment (patients used each treatment for three months), neurocognitive tests, quality of life and daytime symptoms and blood pressure. Daytime sleepiness was more common when measured subjectively (i.e., ESS) than objectively (i.e., MWT). Subjective sleepiness decreased with treatment, compared to both placebo and baseline conditions. There was no similar effect on objective sleepiness. Regarding neurocognitive function, both CPAP and the oral device improved vigilance and paced serial addition, but not other neurocognitive tests used. Quality of life improved with both active treatments, and nocturnal diastolic blood pressure improved slightly by the oral device, but no other effects on blood pressure were found. There were no outcome differences between sleepy and nonsleepy subjects. An effect of oral devices on diastolic blood pressure was also found by Gotsopoulos et al. (2004), in a randomized cross-over trial were patients were using an active oral device and a control oral device.

Continuous Positive Airway Pressure

Sullivan et al., (1981) first described CPAP treatment in five patients with OSA. CPAP works like a splint, preventing the collapse of the upper airways. A mask is fitted to cover either the nose or the nose and the mouth. The air pressure is titrated, either manually or automatically, to a level where breathing is unobstructed. Ayas et al., (2004) found no significant differences between auto-CPAP and traditional CPAP with a constant pressure that had been titrated manually with regard to treatment adherence or effects on daytime sleepiness or breathing-related parameters.

Several studies have examined the effect of CPAP on sleep parameters, such as AHI. CPAP treatment has been found effective in improving these (e.g., Jenkinson et al., 1999; Barnes et al., 2004). Daytime sleepiness also improves by CPAP treatment, both when assessed subjectively (e.g., Jenkinson et al., 1999; Barnes et al., 2004; Siccoli et al., 2008) and objectively (e.g., Engleman et al., 1998; Siccoli et al., 2008). However, Barnes et al. (2004) did not find any improvement in objective daytime sleepiness as assessed by MWT. In non-sleepy patients, the benefits from treatment might be smaller (Barbé et al., 2001).

Patients with OSA are more likely to be sleepy drivers. CPAP might improve driving performance, at least partly, in driving simulator situations (Vakulin et al., 2011). This has also been shown with mandibular advancement devices (Hoekema et al., 2007) and with surgery (Haraldsson et al., 1991).
Adherence to CPAP treatment

Adherence is defined by the World Health Organization as “The extent to which a person's behavior (in terms of taking medications, following diets, or executing lifestyle changes) coincides with medical or health advice”. Early studies indicated good adherence, at least subjectively (Sanders et al., 1986). In the beginning of the 1990s, studies indicated that adherence to CPAP treatment was poor. For example, several studies with objective measurement of machine time (e.g., Reeves-Hoche et al., 1994; Engleman et al., 1994) found a mean CPAP usage time of 4.7 h/night, with no correlation to OSA severity indices. This led to a definition of CPAP adherence as using the machine for at least four hours/night at least 70 % of the nights (Sawyer et al., 2011). Patients tend to over-report their adherence (Kribbs et al., 1993). Several studies have indicated that there is a dose-response relationship between adherence (measured as machine usage) and treatment effect on outcomes such as subjective daytime sleepiness (Antic et al., 2011; Weaver et al., 2007), but with more contradictory findings regarding objective daytime sleepiness. Antic et al. (2011) did not find a dose-response effect of MWT, but Weaver et al. (2007) found it with regard to MSLT. Zimmerman et al., (2006) found a dose-response relationship between CPAP use and memory impairment when patients were divided into three groups (i.e., <2 hours/night, 2-6 hours/night and >6 hours/night), and in a retrospective study, Campos-Rodriguez et al. (2005) found a dose-response relationship between CPAP adherence and survival, with highest mortality among those using CPAP for less than one hour per night compared to those using it 1-6 h/night and >6 h/night, respectively.

Mask leakage was early on identified as a potential cause of problems with CPAP (Richards et al., 1996). Interventions were mainly aimed as technical and device-related factors, such as heated humidification (Massie et al., 1999) and various mask types (Massie & Hart 2003). A more recent intervention along similar (i.e., device-related) lines is the development of auto-titration, where the CPAP device continuously adjusts the delivered pressure to what is needed to counteract apneas. No significantly superior effect has been conclusively shown from auto-CPAP compared to fixed-pressure CPAP (Ayas et al., 2004). Bi-PAP, where a different pressure is exerted during expiration than during inspiration (Hörmann et al., 1994), has been tested, but without any certain effect on adherence (Smith et al., 2009).

Regarding side effects, findings are somewhat contradictory. It is quite common that patients report side effects as a reason for non-adherence or treatment dropout (Nino-Murcia et al., 1989), but other studies have given less clear results. For example, Pépin et al., (1995) found no
correlation between side effects and adherence in a cross-sectional study, but Janson et al., (2000) found an increased risk of dropout in patients with nasal side effects.

**Patient characteristics**

Socioeconomic status is related to adherence, at least in healthcare providing systems where patients pay a significant amount of the treatment by themselves (Brin et al., 2005; Simon-Tuval et al., 2009; Billings et al., 2011). Patients with a lower income and/or socioeconomic status are less likely to obtain a CPAP device. Adherence might also be associated to spousal support (Broström et al., 2010), especially collaborative support (Glazer Baron et al., 2012).

Regarding age and gender, findings have been somewhat inconsistent. Woehrle et al. (2011) found that, among experienced users, high age were associated to a higher adherence, measured both as nights per week and hours per night. Males were slightly more adherent than females when adherence was measured by average nightly use, but the gender difference was small and of uncertain significance. Higher age was also found to be associated to better adherence by Simon-Tuval et al., (2009). Among new patients, when adherence was assessed during the first week of treatment, Ye at al., (2012), found that neither age, gender nor socioeconomic status (measured as education level and employment status) were associated to CPAP adherence, although married subjects used the CPAP more and black subjects used the CPAP less. Tzischinsky et al., (2011) found no correlation between age and gender and the decision to get a CPAP or not. Sin et al., (2002) found women to be more adherent than men, and older patients to be more adherent than younger patients.

CPAP use tends to be stable in long-term users with a slight increase over time (Sucena et al., 2006).

Early research on factors related to treatment focused on disease characteristics, such as AHI and oxygen saturation levels prior to treatment, as well as improvement when on CPAP (Engleman et al., 1996b; Sin et al., 2002). Sin et al. did, however, not find any relationship between total sleep time, AHI, BMI, oxygen saturation and PLM index to CPAP mean use time.

McArandle et al. (1999) found, however, that patients with an AHI exceeding 15/h were more likely to be adherent than patients with an AHI below 15/h. Snoring and subjective sleepiness were also associated to a higher degree of CPAP adherence. In univariate analyses, gender, age, BMI, arousal index, CPAP pressure and driving problems were associated to adherence, but these findings disappeared in the multivariate analysis. Regarding driving problems (patients experiencing sleepiness during driving were more likely to be adherent), there is always a
possibility that non-adherent patients under-report driving problems as to justify continued driving despite poor adherence.

**Psychological factors**

Various psychological constructs have been associated to CPAP adherence, some of which are known from other medical fields, such as the Health Belief Model (Rosenstock et al., 1988) and the Social Cognitive Theory (Bandura, 1989). The main components of the Health Belief Model model are a concern for health issues; a perceived threat or a belief that one is particularly vulnerable to a certain health outcome; and a belief that one can affect this outcome by following a specific treatment regime. The ultimate behavior is seen as the result of weighing pros and cons of the treatment with the perceived risk and effectiveness of the treatment. The Health Belief Model has been applied to CPAP treatment in OSA patients by Olsen et al., (2008). In a prospective study, 77 consecutive OSA patients where a decision to initiate CPAP treatment had been made on clinical grounds were included. Prior to initiating treatment, they were asked to complete various questionnaires to assess constructs of the Health Belief Model (symptoms by the ESS and the Functional Outcomes of Sleepiness Scale; self-efficacy, risk perception and outcome expectancy by the Self Efficacy Measure for Sleep Apnea). Outcome was adherence defined as meter reading after approximately four months on CPAP. The Health Belief Model constructs together with biomedical indices (i.e., RDI, AI, BMI, ESS score, nadir of oxygen saturation and percentage of TST at <80% oxygen saturation) prior to treatment could explain 31.8 % of adherence after four months.

The Social Cognitive Theory has also been used to explain CPAP adherence by Stepnowsky et al., (2002). According to SCT, the decision to engage in treatment is a result of a health concern, expectations about the outcome of the treatment as well as the potential consequences of abstaining and social support and self-efficacy. Stepnowsky et al., (2002) examined constructs related to social cognitive theory in 51 patients with newly diagnosed OSA, who completed ESS and SCT (Self-efficacy, Outcome expectations, social support and knowledge; a questionnaire that was developed specifically for that study). The questionnaires were completed at treatment initiation and after one week and one month on CPAP, respectively. Together with ESS and CPAP pressure, self-efficacy, social support and knowledge could explain 31 % of the variance in cross-sectional CPAP adherence after one week and 40 % after one month.

A person’s personality might affect his or her behavior, but this has not been extensively studied in obstructive sleep apnea. Type D personality (the ‘D’ stands for ‘distressed’; Denollet, 2000) is used to describe a personality type consisting of a combination of social inhibition and negative
affectivity. Social inhibition is defined as a tendency to inhibit expressions and behaviours in social situations. Social inhibition is related to, but not identical to, introversion. It correlates with extraversion in the Eysenck Personality Questionnaire (Denollet, 1998) in congestive heart failure patients. The other component is negative affectivity, which is a tendency to experience negative emotions more often and more strongly than positive ones. Type D personality has been associated to worse outcome in several diseases, mainly cardiovascular disorders (for a review, see Pedersen & Denollet, 2003). Most mechanistic studies have focused on physiological phenomena relating stress to inflammatory responses etc., but it is also conceivable that a negative affectivity might increase the likelihood of experiencing side effects to a treatment, and in combination with a lower likelihood of seeking help due to social inhibition, this might affect the long-term adherence to prescribed treatments. This might also be true for CPAP users. Denollet has developed an instrument, DS14 (Denollet, 2005) to classify people as having a type D personality or not.

In conclusion, OSA is a common disorder, with several potentially severe adverse consequences. There is effective treatment, but problems with CPAP adherence have been known to sleep medicine for the last 20 years. While progress has been made, there are still significant open questions regarding the causes of poor adherence. Answering those might help in developing clinical routines to improve patient care. Psychosocial factors are getting more attention. However, regarding side effects and sleepiness, previous research has given conflicting results. Regarding personality and its impact on CPAP adherence, it has largely been overlooked in previous research. These factors are often subjective and must therefore be analyzed using questionnaire data. In order to obtain reliable and valid data, there is a need for reliable and valid questionnaires. The overall aim of the thesis is thus to develop and/or validate questionnaires to examine various factors that are related to CPAP adherence.
AIMS

The overall aim of the thesis was to develop and/or validate questionnaires to examine various factors that may be related to CPAP adherence. Specific aims were as follows:

1. To describe the development and initial testing of a new instrument, the Side Effects of CPAP Inventory (SECI);
2. To measure the frequency and magnitude of CPAP side effects, as well as their impact on CPAP use;
3. To describe the prevalence of Type D personality in OSAS patients with CPAP treatment longer than 6 months and the association to self-reported side effects and adherence;
4. To examine whether any of the items in the ESS exhibit differential item functioning with regard to age or gender, and if so, to which degree;
5. To examine the evolution of CPAP side effects over time; and
6. To prospectively assess correlations between early CPAP side effects and treatment adherence.
Paper I: Development and initial testing of SECI

**Rationale for paper I**
SECI stands for Side Effects of CPAP Inventory. The rationale behind developing the questionnaire was that side effects are common (Weaver & Grunstein, 2008), and are often reported by patients to be significant causes of treatment non-adherence (e.g., Broström et al., 2010). Prior to the development of the SECI, however, there was no validated instrument to assess or quantify CPAP side effects in a systematic way.

**Methods**

**Item generation**
Items (i.e., potential side effects) were generated by a literature review and in-depth interviews with 23 patients using CPAP for OSAS. Based on these, a primary list of twenty side effects was generated. This list was reviewed by a multi-professional panel consisting of physicians, nurses and nurse researchers with experience from CPAP and sleep apnea research. Five of the side effects were removed from the initial list (e.g., claustrophobia, which was thought to be covered by “anxiety during treatment”). The resulting list thus contained the following fifteen side effects:

**Box 4: Side effects included in the SECI**

| 1. Blocked up nose. |
| 2. Runny nose.     |
| 3. Nose bleed.     |
| 4. Dry throat.     |
| 5. Irritated eyes. |
| 6. Irritated bowl. |
| 7. Transient deafness. |
| 8. Feeling uncomfortable because of wearing the CPAP in front of others. |
| 9. Increased awakenings. |
| 10. Uncomfortable pressure of the mask. |
| 11. Mask leaks.    |
| 12. Cold air.      |
As it was not clear which aspects of a side effect would affect the patients (e.g., whether a rare but severe side effect would affect adherence differently than a frequent but less severe side effect), three questions were used for each side effect. They cover frequency (“How frequently does this side effect occur?”), magnitude (“How great a problem does this side effect cause?”) and perceived impact on adherence (“How does this side effect decrease your use of CPAP?”). Each question is answered on a five-point Likert-type scale, ranging from one (least concern) to five (most concern). An example item with all three questions and response alternatives is presented below:

**Box 5:** Item 1 in SECI, as it is presented to patients.

<table>
<thead>
<tr>
<th>Blocked up nose</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>How frequently does this side effect appear?</td>
<td>Never</td>
<td>Seldom</td>
<td>Sometimes</td>
<td>Often</td>
<td>Very often</td>
</tr>
<tr>
<td>How great a problem does this side effect cause you?</td>
<td>No problems</td>
<td>Small problems</td>
<td>Some problems</td>
<td>Great problems</td>
<td>Very great problems</td>
</tr>
<tr>
<td>How does this side-effect decrease your adherence?</td>
<td>Not at all</td>
<td>A little</td>
<td>Moderately</td>
<td>Much</td>
<td>Very much</td>
</tr>
</tbody>
</table>

Three scores were initially calculated for the SECI. They consisted of the sum scores of all frequency, magnitude and impact questions, respectively. The total score for each of the scales (i.e., frequency, magnitude and impact) thus ranged from 15 to 75, with lower scores indicating less problems. A pilot test was performed on 20 CPAP treated OSAS patients to assess readability, clarity and layout.

**Data collection**

To assess reliability and validity of SECI, consecutive OSAS patients from three sleep centres were included in a cross-sectional study. The centres were located in Linköping, Jönköping and Stockholm. The Linköping centre is located at a university hospital, the Jönköping centre at a county hospital and the Stockholm centre is a private care clinic where the care provided is reimbursed by the County Council of Stockholm. Inclusion criteria were age ≥ 18 years and a diagnosis of OSAS (clinical symptoms and AHI ≥ 10/h) and CPAP-treatment for at least 2 weeks. Patients were diagnosed using in-home PG comprising airflow, respiration movements, pulse...
oximetry and body position. Exclusion criteria were life-threatening disease with short expected survival, severe psychiatric disease, dementia, communication problems or inability to read or speak Swedish. 350 patients fulfilled the eligibility criteria, and were mailed questionnaires as well as general background questions pertaining patient demographics. Clinical background variables, i.e., co-morbidities, blood pressure, BMI, ESS and OSAS severity variables (AHI and ODI) as well as objective data on adherence (machine usage time) were taken from medical records.

**Statistical processing and analysis**
Statistical analyses were performed in SPSS, version 15.0.1.1 (SPSS Inc, Chicago, IL, USA). Reliability was assessed by item-total correlations adjusted for overlap and Cronbach’s alpha if item deleted (Nunnally & Bernstein, 1994). Relationship among items as well as scales were analysed by Spearman’s correlation coefficient.

To test construct validity, principal component analysis (PCA) was performed. Prior to this, the data had been examined by Bartlett’s test of sphericity and measure of sample adequacy, both in each variable and overall (Kayser-Meyer-Olkin measure). Principal components with eigenvalues of 1.0 or greater were extracted in a first analysis (five components), and in an analysis based on the scree plot, two components were extracted. Varimax rotations were applied on all analyses. Factor loadings ≥ 0.4 were considered significant. Cross-validation was performed on a random split of the sample into two groups. Known group validity was examined using a dichotomization of the sample into two groups, with a cutoff adherence of 4 hours/night of CPAP use. Non-parametric statistics was used to compare the two groups.

**Results**

**Study population**
After one reminder, 329 out of the 350 patients responded, resulting in a response rate of 94 %. The non-responders did not differ significantly from the responders with regard to age, education, marital status, co-morbidities, disease severity measures or duration of CPAP treatment. The duration of treatment ranged from 2 weeks (i.e., the minimum time on CPAP to be eligible for inclusion in the study) to 182 months, with an average of 39 months. All patients used fixed-pressure devices and 21 % had humidifiers.
Validity and reliability of the SECI
Internal consistency and item-total correlation were both satisfactory. Nose bleed, however, had somewhat weaker item-total correlation, and "disturbing noise" and "feeling uncomfortable wearing the CPAP in front of others" had lower item-total correlations in the frequency scale. Generally, the frequency scale showed the least item-total correlation, and had higher scores than the other scales.

The scree plot criterion was used for the final principal component analysis, after a component extraction based on the Kaiser criterion (i.e., eigenvalues ≥ 1.0). The latter led to a five-component solution for the frequency scale and four-component solutions for the magnitude and impact scales, and several items loading on multiple questions. The scree plot, however, gave two components, and when extraction was fixed at two components in a new analysis, the two principal components extracted could be said to represent device-related and symptom-related side effects, respectively. The cross-validation validated the components for the impact and magnitude scales, but not for the frequency scale.

The non-adherent patients, i.e., the patients who used the CPAP less than four hours per night, scored significantly higher on all scales (i.e., frequency, magnitude and impact) and four of six subscales (i.e., all except for the frequency/device subscale and the magnitude/symptom subscale).
Paper II: Type D personality

Rationale for paper II
Type D personality has been described as a risk factor for cardiovascular disease, and it was speculated that poor adherence to treatment could be a part of the link (Denollet et al, 1996). One of its main components, i.e., negative affectivity, has been related to health complaints (Watson & Pennebaker, 1989). It is reasonable to expect that there could be a correlation between perceived side effects and type D personality, but it had not been studied. Given the fairly high prevalence of type D personality in other populations (e.g., Denollet, 2005), an association between type D personality and adherence would need to be taken into consideration when designing interventions to improve CPAP adherence.

Methods

Data collection
All CPAP treated OSAS patients at the department of Clinical Neurophysiology, University hospital of Linköping, with OSAS defined as an AHI≥10/h and clinical symptoms, age≥18 years and CPAP duration of at least six months were invited. Patients were excluded if they suffered from other life-threatening diseases with short survival time, severe psychiatric disease, dementia, communication problems or inability to read and speak Swedish. 350 patients fulfilled the eligibility criteria. Questionnaires were sent to them by mail about demographics, side effects (i.e., SECI) and a Swedish translation of the DS14 (Denollet, 2005). Data about objective adherence (i.e., machine usage time) were collected from their medical records.

Questionnaires
DS14 consists of 14 items, and are answered using a five-point Likert-type scale, with scores ranging from 0 to 4 for each item. The test is divided into two subscales, termed negative affectivity (NA) and social inhibition (SI). Each scale consists of seven items. The result of DS14 is a sum score for each scale, after reversal of two reversely worded items in the SI scale. To be defined as having a type D personality, a person must score at least ten points on each of the two subscales. For each subscale, it is also possible to categorize respondents into seven groups, depending on their score (very low, low, below average, average, above average, high and very high). A Swedish translation of the DS14 was made for the study. DS14 was originally
developed in Dutch, and translated to English by Denollet (2005). The English translation was used as a basis for the Swedish version. The Swedish translation was back-translated into English and approved by Denollet.

SECI was used to assess side effects to CPAP treatment. Daytime sleepiness was measured using ESS (Johns, 1991).

Statistical processing and analysis
All statistical calculations were performed in SPSS (SPSS Inc, Chicago, IL, USA). Patients were classified, based on the criteria from Denollet (2005) (i.e., scores of at least 10 on both subscales of the DS14), as having or not having type D personality. Both parametric and non-parametric statistics were used, as appropriate. For continuous variables, Student’s t test or Mann-Whitney U test were used. Categorical variables were analysed using chi-square test or Fisher’s exact test as appropriate, and to test differences between people in the seven categories, Kruskal-Wallis test was used.

In the statistical analysis of SECI responses, for each question, answers 1 and 2 (i.e., “never” and “occasionally” for frequency questions, “no problems” and “small problems” for magnitude questions and “not at all” and “a little” for impact questions, respectively) were amalgamated into one response category. In the same way, responses 4 and 5 for each question (i.e., “often” and “very often” for frequency questions, “great problems” and “very great problems” for magnitude questions and “much” and “very much” for impact questions, respectively), were amalgamated into one response category. Thus, the five-point scale originally used in SECI was reduced to a three-point scale.

Adherence was defined both as machine usage time above or below 4 fours per night, and machine usage above 85% of the self-rated mean total sleep time. In addition, average machine usage time was used as a continuous variable.

Results

Study population
After one reminder, 247 subjects answered the questionnaires. The response rate was thus 70.6%. The non-responders did not differ from the responders with regard to age or duration on CPAP. All patients had fixed pressure devices, and 11% had humidifiers. The time on CPAP treatment did not differ significantly between type D and non-type D patients (mean 57 month, range 6-144
months among type D patients as compared to a mean duration of 39 months ranging from 6 to 182 months among non-type D patients. Excessive daytime sleepiness, as measured by the ESS, did not differ between groups prior to treatment initiation. Co-morbidities were similar in both groups, with hypertension and diabetes being the most common.

**Type D personality and side effects**
Type D personality was present in approximately one third of the total sample, with no significant difference between genders. 28% of the men and 39% of the women fulfilled the criteria. The mean (SD) total score for DS14 was 19.5(8.2), and for the individual subscales, the scores were 8.2(5.7) and 11.2(3.4), for the NA and SI scales, respectively.

Regarding side effects, the most common side effects (i.e., the side effects that a highest percentage of both type D and non-type D patients scored as occurring often or very often) were dry throat, uncomfortable pressure from the mask, mask leaks, feeling uncomfortable because of wearing the CPAP in front of others and blocked up nose). The least frequent side effects, defined as the side effects that had the largest percentage of "never" or "seldom" responses, were anxiety during treatment, nose bleed, problems exhaling, cold air and transient deafness. Frequency and magnitude for side effects were correlated among both type D and non-type D patients. For all side effects, except for cold air, problems exhaling and anxiety during treatment, patients with type D personality scored significantly higher than those without.

**Type D personality and adherence**
Adherence was measured in several ways. Data about subjective adherence were taken from the SECI questionnaires. For nine of the side effects, type D patients indicated significantly higher degrees of negative impact on adherence than non-type D patients. This was the case for all side effects except transient deafness, feeling uncomfortable because of wearing the CPAP in front of others, cold air, disturbing noise, problems exhaling and anxiety during treatment.

Regarding objective use, type D patients were less adherent according to all three employed ways of defining adherence (i.e., machine use as a continuous variable, machine use below or above four hours per night and machine use below or above 85% of self-reported total sleep time). The mean (SD) usage time among non-type D patients was 378.2 (116.6) minutes/night, as compared to 292.1 (38.4) minutes/night among non-type D patients (p<0.001). 62% of the type D patients, compared to 30% of the non-type D patients, used the CPAP less than 85% of their estimated
total sleep time. Using a four-hour cutoff, 51% of type D patients vs. 16% of non-type D patients were adherent.
Paper III: Differential item functioning in the Epworth Sleepiness Scale

Rationale for paper III

ESS is very frequently used in sleep medicine and sleep research, and the original description of it has been cited over 5000 times as of 2013. It is used in CPAP research to measure daytime symptoms prior to treatment and improvement from treatment. Since its initial description, it has been the subject of a lot of criticism, mainly related to its psychometric properties. As pre-CPAP sleepiness and improvement on treatment might be related to adherence, it is important to examine the methods used to assess sleepiness in OSAS patients. There is a lack of knowledge as to whether ESS has similar psychometric properties in different populations, although it is reasonable to believe that some of the items might behave differently depending on what kinds of situations the respondents regularly experience.

Methods

Data collection

No data were collected specifically for this study. The study is based on analyses performed on 1168 subjects that had completed the ESS in five other studies that have been published elsewhere (Broström et al., 2004; Broström et al., 2007; Johansson et al., 2009; Broström et al., 2010; Broström et al., 2012). Broström et al., (2007) and Broström et al., (2010b) contributed with 240 and 171 respondents, respectively. They are included in this thesis as papers I and II. Johansson et al., (2009) contributed with 331 respondents. It is a sample consisting of home-dwelling elderly (aged 65-82 years) subjects living in the municipality of Kinda outside Linköping, Sweden (the CoroKind study). The CoroKind study was actually larger, but only data for the subsample undergoing night-time polygraphy (Johansson et al., 2009) was used. All home-dwelling elderly in the age group living in Kinda were invited to take part in the CoroKind study, which was a general population-based cohort study. 876 of 1,130 subjects initially agreed to participate in the cohort. Of those, 346 agreed to take part in a home polygraphy, and in conjunction with that they also completed the ESS. 15 patients were subsequently excluded due to poor technical quality of their polygraphic recordings, and ESS data for those were not available for the differential item functioning study (i.e., the present study). Two other studies contributed with 216 subjects each. One was the Hypersleep study, which is an ongoing prospective, longitudinal study of hypertensive patients in Jönköping, Sweden. All patients between the ages of 18 and 65 years with a diagnosis of hypertension at four primary
care centres in Jönköping, Sweden were eligible. The Hypersleep sample is further described in Broström et al. (2012).

The final study consisted of heart failure patients (Broström et al., 2004). Subjects were ≥18 years and NYHA class II-IV. Exclusion criteria were unstable heart failure, severe psychiatric disease, suffering from another life-threatening disease, severe chronic pulmonary disease, communication problems or inability to read and speak Swedish. Patients were recruited from a medical ward at a university hospital, two heart failure clinics (one university hospital and one county hospital) and five primary health care centres in southern Sweden.

Statistical analysis

Statistics were performed in Stata, version 10 (StataCorp 2007, College Station, Texas, USA) and RUMM2020 (RUMM Labs Pty Ltd, Australia). Baseline statistics were performed using chi-square test and Student’s t test. Two approaches to differential item functioning were used. An ordinal regression, based on the method described by Zumbo (1999) was used, as well as a polytomous Rasch model.

For the ordinal regression, a hierarchical ordinal regression model was developed for each item. This was done in a multi-step process, where item score was predicted from total ESS score in the first model. Then, age was added to the model. DIF was considered to be present when the grouping variable (i.e., age or gender) was significantly associated to item score after adjusting for the total ESS score. The change of McFadden pseudo-R2 change was used to assess the magnitude of DIF, when present. Interaction terms between ESS total score and age and gender, respectively, were used to assess non-uniform DIF.

The Rasch model parameters were estimated using Joint Maximum Likelihood estimation (Hambleton et al., 1991), an iterative process where person and item parameters are estimated jointly. The sample was grouped into eight groups depending on their subjective daytime sleepiness. Global fit and individual item fit were assessed by comparing fit residuals for person and item parameters to expected values, and by item-trait interaction. Visual inspection of item characteristic curves was also used to examine potential misfit.

Person and item parameters were compared to assess targeting. Differential item functioning were examined by dividing each of the eight groups that had been formed by dividing the sample according to their abilities (i.e., daytime sleepiness) by age (i.e., below or above 65 years) or gender, and then perform ANOVAs. Age and gender were tested as main affects for uniform DIF, and interaction terms between daytime sleepiness group and age and gender respectively were used to examine non-uniform DIF. The resulting p values were adjusted due to the number
of ANOVAs performed (i.e., one for each item, two main effects and one interaction effect), meaning that the level of significance was set at \( p<0.0021 \).

**Results**

**Study population**

The initial sample consisted of 1175 subjects. Eight subjects were excluded due to missing data on individual ESS items, leaving 1168 subjects available for further analysis. 25 subjects were excluded as they scored 0 on the ESS, and thus did not contribute any information to the item parameter estimation process. For a further 45 subjects, there were no data on age, and they were thus excluded from the DIF analyses for age. These subjects were, however, included in the DIF analyses for gender. The total sample, after exclusion of subjects on the grounds listed above, consisted of 715 men and 453 women, with a mean (SD) age of 67.8 years (12.2 years) and a mean (SD) ESS score of 7.7 (4.5). Females were significantly older than males (70.4 vs 66.1; \( p<0.05 \)). There were also significantly more females in the old (i.e., 65 years or older) age group than in the young (i.e., below 65 years) (\( p<0.001 \)).

**General psychometric properties of the ESS**

Cronbach’s alpha was 0.80, and persons and items were distributed along the same portion of the difficulty axis, i.e., the items measured the same degree of sleepiness as the respondents reported. When fixing the mean trait location at 0 on the logit scale, the mean (SD) trait location was -1.093 (1.186). The mean (SD) item fit residual was -0.6733 (2.716) and the mean (SD) person fit residual was -0.309 (0.785). There was a global misfit in item-trait interaction, which, by inspecting individual item characteristic curves, was deemed to be largest in item 5 (“Lying down to rest in the afternoon, when circumstances permit”; the ICC is presented in the paper). There were no reversed response alternatives. Item difficulties ranged from -2.087 to 1.98. The lowest difficulty was found for item 5, and the highest difficulty was found for item 8 (“In a car, that has stopped for a few moments in traffic”).
**Differential item functioning**

The Rasch model demonstrated DIF for age in items 3 ("Sitting inactive in a public place, e.g., a theater or a meeting"), 4 ("As a passenger in a car for an hour without a break") and 8 ("In a car, that has stopped for a few minutes in traffic") and for gender in item 3. The findings regarding age were reproduced in the ordinal regression model, however, there was no demonstrated gender-related DIF in the ordinal regression model. Generally, the magnitudes of DIF were small.
Paper IV: CPAP side effects – evolution over time and association to adherence

Rationale
A significant proportion of patients report various side effects of CPAP treatment. While patients often refer to side effects as a reason for poor adherence, studies where reported side effects are related to adherence have yielded conflicting results. As many side effects are potentially treatable, it is important to examine associations between side effects and adherence in more detail.

Method
Data collection
Data were collected from patients with OSAS, defined as AHI≥10/h and ESS≥10, where a decision to initiate CPAP treatment had been made on clinical grounds. The centres were the ENT department at the County hospital of Jönköping, the department of clinical neurophysiology at the University hospital of Linköping, Sweden and the private clinic Aleris FysiologLab in Stockholm, Sweden. 186 patients were consecutively recruited to the study. Exclusion criteria were acute CPAP initiation, severe co-morbidity with expected short survival, malignancy, psychiatric disorders and problems communicating in Swedish. The diagnosis of OSAS was based on PG recordings (Embletta, ResMed), and all recordings were scored manually. Humidifiers were given to all patients at Aleris FysiologLab when treatment was initiated. At the other centres, it was given to patients who complained of dry mouth or blocked up nose. Patients had scheduled routine follow-up visits after 1-2 weeks, 3-6 months and 9-12 months, respectively. Clinical data, as well as CPAP objective machine usage data were collected by CPAP nurses at these visits. In addition, demographic data (i.e., education, marital status, co-morbidities) were collected at the first visit. In conjunction with the visits, patients were asked to complete SECI and ESS. Patients were followed for one year.

Statistical analysis
Statistics were performed in R version 2.14 (The R Foundation for Statistical Computing, Vienna, Austria). The SECI responses were recorded as follows: for each side effect, if the respondent had answered 4 or 5 to any of the three subscale questions (i.e., regarding frequency, magnitude and impact on adherence), the side effect in question was considered to be
significant”. Treatment adherence was measured as treatment dropout (i.e., patients returning their machine) as well as objective machine time as a continuous variable. Adherence data were taken from medical records. To test for differences in background variables between patients treated at the different centres, chi-square test or Fisher’s exact test were used for categorical variables and ANOVA was used for continuous variables. Comparisons between patients who dropped out during the first year and those who did not were performed using Chi-square or Fisher’s exact test for categorical data and Kolmogorov-Smirnov’s test for continuous data. To examine how side effects varied over time, McNemar’s test was used to examine whether the existence of a side effect at one point in time was significantly related to the existence of that side effect at another point in time. Cohen’s κ was calculated to assess the correlation between a side effect at two points in time. Side effects were measured at three points (i.e., after 1-2 weeks, 3-6 months and 9-12 months), and comparisons were made between all pairs of points (i.e., side effects after 1-2 weeks vs. 3-6 months, side effects after 1-2 weeks vs 9-12 months and side effects after 3-6 months vs 9-12 months). Thus, three comparisons were made. Associations between side effects and adherence were examined for the side effects that were reported at the first point in time, i.e., after 1-2 weeks. These side effects were compared to dropout using both relative risks and Mantel-Haenszel ORs with adjustment for treatment centre. Linear regression was used to assess associations between early side effects and machine usage time after six months. Treatment centre, mask type and pre-treatment AHI were added to account for potential differences in initiation routines and disease severity.

Results

Study population

186 subjects were included. Of these, 78 % were men, and their age ranged from 20 to 76 years. Patients at Aleris FysiologLab had lower BMI, and patients from the county hospital of Jönköping had larger neck circumference than those at the other centres. Drop-outs occured continuously throughout the first year. After 1-2 weeks, 17 patients had dropped out. After six months, 39 additional patients had dropped out, and after one year, 30 additional patients had dropped out. At the end of the first year, 100 patients remained on CPAP. There were no difference with regard to any of the background variables between those who dropped out and those who did not. There was no difference in dropout rate between treatment centres.
Prevalence of side effects

After 1-2 weeks, the five most frequent side effects were dry mouth (38%), blocked up nose (32%), mask pressure (26%), increased number of awakenings (22%), and mask leakage (21%). The side effects that most patients thought were of significant magnitude were mask pressure (19%), blocked up nose (16%), mask leakage (14%), dry mouth (13%) and increased number of awakenings (13%). The side effects that were considered to have a significant negative impact on adherence by the largest proportions of patients were mask pressure (17%), dry mouth (15%), increased number of awakenings (15%), and mask leakage, blocked up nose and problems exhaling at 13% each.

After 3-6 months, the most frequent side effects were dry mouth (33%), increased number of awakenings (20%), mask pressure (19%), blocked up nose (14%), and mask leakage and noise at 13% each. The side effects that most patients thought were of significant magnitude were increased number of awakenings (14%), dry mouth (11%), mask pressure (10%), noise (9%) and blocked up nose (9%). The side effects that were considered to have a significant negative impact on adherence by the largest proportions of patients were blocked up nose (9%), mask leakage (7%), noise (6%), increased number of awakenings (6%), and dry mouth (5%).

After 9-12 months, the most frequent side effects were dry mouth (39%), blocked up nose and mask leakage, at 26% each, mask pressure (23%), and irritated eyes (17%). The side effects that most patients thought were of significant magnitude were dry mouth (19%), blocked up nose and mask leakage at 14% each, mask pressure (10%) and noise (9%). The side effects that were considered to have a significant negative impact on adherence by the largest proportions of patients were mask pressure (15%), blocked up nose (13%), runny nose (9%), and cold air and noise at 8% each.

Evolution of side effects over time

Evolution of side effects were studied within subjects. Side effects could both resolve and emerge within subjects. Among the patients who did not suffer from dry mouth, mask leakage and blocked up nose at the first assessment after 1-2 weeks, 32, 28 and 27%, respectively, experienced these side effects as significant problems after one year. At the same time, cold air, problems exhaling and feeling uncomfortable using the CPAP in front of others were resolved in a large proportion of patients. Dry mouth, blocked up nose, mask pressure and mask leaks were among the most common and significant side effects at all points of time. Increased number of awakenings was a common side effect except for at the last assessment after 9-12 months.
Association between side effects and adherence

When dropout during the first year on CPAP was used as the definition of adherence, there was an increased risk of non-adherence for some, but not all, of the side effects reported after 1-2 weeks. These side effects were dry mouth (RR 1.65, 95% CI 1.11-2.45), transient deafness (RR 2.14, 95% CI 1.32-3.47), increased number of awakenings (RR 1.90, 95% CI 1.31-2.76), problems exhaling (RR 2.00, 95% CI 1.38-2.90) and anxiety during treatment (RR 1.77, 1.13-2.78). As patients were treated at three different centres, and as there might be subtle differences in treatment initiation procedures, as well as some differences regarding background variables (i.e., BMI being somewhat lower in one centre and neck circumference being somewhat greater in one), the sample was stratified for treatment centre and re-analyzed using Mantel-Haenszel OR. In this analysis dry mouth (MH-OR 95% CI 1.14-4.40), feeling uncomfortable about using the CPAP in front of others (MH-OR 95% CI 1.48-6.94), increased number of awakenings (1.42-6.27) and problems exhaling (MH-OR 95% CI 1.68-12.61) after 1-2 weeks were significantly related to an increased risk of dropping out during the first year.

When adherence was defined as machine usage time after six months (a continuous variable), there was a significantly worse adherence in patients experiencing significant problems after 1-2 weeks with blocked up nose, dry mouth and increased number of awakenings. Somewhat paradoxically, there was an inverse relationship between experiencing cold air as a significant side effect after 1-2 weeks and machine usage after 6 months (i.e., patients who complained about cold air after 1-2 weeks used the CPAP more after 6 months than those who did not). The analysis is presented in Table 4. AHI, Centre, BMI and neck circumference were adjusted for in the presented table (BMI and neck circumference have been added, and are not included in the model presented in manuscript IV).
Table 4: Side effects after two weeks and adherence after six months. Coefficients are beta coefficients for machine usage time in hours. Negative coefficients indicate that patients experiencing a side effect after 1-2 weeks use the CPAP less after 6 months than those who did not experience the side effect in question after 1-2 weeks. Side effects that are significantly related to adherence are boldfaced.

<table>
<thead>
<tr>
<th>Side effect</th>
<th>Coefficient</th>
<th>Standard Error</th>
<th>Adjusted R2</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blocked up nose</strong></td>
<td>-0.89</td>
<td>0.37</td>
<td>0.06</td>
<td>0.0196</td>
</tr>
<tr>
<td>Runny nose</td>
<td>-0.94</td>
<td>0.55</td>
<td>0.04</td>
<td>0.0911</td>
</tr>
<tr>
<td>Nose bleed</td>
<td>0.73</td>
<td>0.74</td>
<td>0.02</td>
<td>0.3281</td>
</tr>
<tr>
<td><strong>Dry throat</strong></td>
<td>-0.84</td>
<td>0.38</td>
<td>0.05</td>
<td>0.0276</td>
</tr>
<tr>
<td>Irritated eyes</td>
<td>0.08</td>
<td>0.63</td>
<td>0.01</td>
<td>0.9005</td>
</tr>
<tr>
<td>Irritated bowl</td>
<td>-1.24</td>
<td>0.75</td>
<td>0.03</td>
<td>0.0992</td>
</tr>
<tr>
<td>Transient deafness</td>
<td>-2.25</td>
<td>1.16</td>
<td>0.04</td>
<td>0.0552</td>
</tr>
<tr>
<td>Feeling uncomfortable about using the CPAP in front of others</td>
<td>-0.85</td>
<td>0.79</td>
<td>0.03</td>
<td>0.2800</td>
</tr>
<tr>
<td><strong>Increased number of awakenings</strong></td>
<td>-1.17</td>
<td>0.42</td>
<td>0.08</td>
<td>0.0062</td>
</tr>
<tr>
<td>Mask pressure</td>
<td>-0.45</td>
<td>0.41</td>
<td>0.02</td>
<td>0.2801</td>
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<td>Mask leaks</td>
<td>-0.57</td>
<td>0.45</td>
<td>0.03</td>
<td>0.2113</td>
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<tr>
<td><strong>Cold air</strong></td>
<td>1.67</td>
<td>0.72</td>
<td>0.06</td>
<td>0.0215</td>
</tr>
<tr>
<td>Disturbing noise</td>
<td>0.02</td>
<td>0.53</td>
<td>0.01</td>
<td>0.9663</td>
</tr>
<tr>
<td>Problems exhaling</td>
<td>-1.11</td>
<td>0.58</td>
<td>0.04</td>
<td>0.0601</td>
</tr>
<tr>
<td>Anxiety during treatment</td>
<td>-0.34</td>
<td>0.73</td>
<td>0.01</td>
<td>0.6431</td>
</tr>
</tbody>
</table>
ETHICAL CONSIDERATIONS

Several aspects of the studies can be discussed from an ethical perspective. For the development of SECI, interviews were performed in order to find side effects to include. Study III used pooled data from other studies, and did not contain a data collection phase. Data regarding CPAP usage time was taken from the CPAP devices, as they record adherence data on a night-by-night basis. All studies were approved by the Ethical Review Board in Linköping apart from paper III, for which no ethical approval was needed (contact was taken with the Ethical Review Board prior to the study) as no data could be associated to specific individuals. All studies from which data were taken were approved by the regional Ethics committee.

Four general ethical principles are often referred to in healthcare and medical research (SBU, 2013; Beauchamp & Childress, 2009). These are the principles of autonomy, justice, nonmaleficence and beneficence.

Regarding justice, nonmaleficence and beneficence, all studies were observational, and thus did not include any situations where patients were not given care they would have been given if not participants in the studies, nor were they exposed to any treatment-related risks other than those which arise from standard care. Regarding autonomy, especially informed consent, this was collected when informing patients about the study. No data from medical records etc. were available to researchers prior to obtaining written consent.

Regarding interviews, they were not performed by the healthcare personnel involved in treating the patients, as to minimize the risk of patients not being able to share potential barriers related to CPAP treatment due to a desire to maintain a positive relationship to the care provider.

Regarding autonomy in study III, about DIF in the ESS, data were taken from different previous studies, all of which had obtained informed consent for their respective purpose. However, no new informed consent was obtained for the present study, as no identifiable data that could be traced to a specific individual was analyzed. The data file used for the analysis only contains age, gender, ESS responses and what original study the subject participated in, but as the study has over 1,000 participants, it is impossible to identify individual subjects from this information. This is why no results with regard to any other background variables other than age, gender and ESS are given in that study. Obtaining informed consent would not be feasible, especially as not all subjects were alive, some data was collected several years prior to the analysis of Differential Item Functioning was performed. This was discussed with the Regional Ethics Board, who approved of this approach.
Data regarding CPAP adherence was taken from the CPAP machines, as they record data of 
machine usage and delivered pressure on a night-to-night basis. It could be seen as potentially 
intruding the patients’ autonomy. This, however, was not done for the study but is done regularly 
in CPAP care and is the basis for feedback to the patients.
DISCUSSION

The aims of this thesis are all related to development and validation of questionnaires in OSA. Three of the papers have used SECI, which is the first validated questionnaire for CPAP related side effects. We have shown that CPAP side effects can be measured and that they are related to treatment adherence as well as personality constructs (i.e., type D personality). We have also shown that ESS exhibits DIF, at least with regard to age.

Defining side effects

Previous research regarding side effects and adherence have provided various, and sometimes conflicting, results. It is common among patients to cite side effects as a reason for poor adherence (Nino-Murcia et al., 1989; Engleman et al., 1994; Broström et al., 2010), but studies have yielded less clear results (Engleman et al., 1996b; Jansson et al., 1999; Olsen et al., 2008). One reason might be that there is no generally agreed-upon definition of what CPAP side effects are, or how they should be measured. Several studies which have examined side effects have done so without explicitly stating how they developed the instruments they used. Previous research has also defined side effects in different ways, and asked about them in different ways.

We found, for example, an increased number of awakenings to be associated to poorer adherence. Engleman et al. (1996b), did ask about frequent awakenings, but did not define this as a side effect from CPAP treatment. Rather, they defined this as one of several "nuisance problems", and while they did not found a relationship between side effects and adherence, they did find it between nuisance problems and adherence. Pépin et al. (1995) did list a number of potential side effects that they asked patients about (i.e., adverse effects of the nasal mask, such as allergy over the face, discomfort to the ridge of the nose, pain in the teeth or gums, and air leaks near the eyes or over the face, dryness of nose or mouth in the mornings, sinusitis, sneezing, nasal drip, nasal congestion, nose bleeding, and air swallowing). However, they did not report how answers were given. Meurice et al. (1994) reported side effects among compliant and non-compliant users, but they did not report how these data were obtained. In summary, previous studies have had different approaches to side effects as well as to adherence.
Measuring side effects

In the three papers using SECI presented here, SECI scores are calculated in different ways. Responses in all studies have been given on five-point Likert type scales regarding frequency, magnitude and perceived impact on adherence. However, in two of the studies (i.e., papers II and IV), different forms of rescoring criteria were employed. In paper II, responses were reduced to three response alternatives by amalgamating scores 1 and 2 and 4 and 5, respectively, on each item. This was done to obtain more responses in each category, thereby increasing group sizes. The three subscales, i.e., regarding frequency, magnitude and impact on adherence, were, however, analyzed separately. We could still see meaningful correlations between reported side effects and personality. In the fourth manuscript, a further simplification was done, by combining the scores from all three subscales into one score, and by reducing the number of groups by combining those who scored 1 or 2 with those who scored 3. The idea is to simplify SECI, by reducing the number of items and thus make it easier to complete and score. This is especially important in studies comprising several questionnaires, as there is a risk that respondents become overwhelmed by the number of items. It might also make it easier to score in clinical situations. If item scores are summed, as was done in the original study, reporting ten infrequent side effects is equal to reporting one severe side effect, although it might be supposed that they affect side effects differently. At present, it is too early to decide which approach to scoring is preferable in SECI. Reducing the number of response alternatives might reduce the information obtained from the responses, as small changes with regard to frequency, severity or impact from a given side effect on adherence might be less easy to spot. Future research should examine these issues further, for example by comparing the amount of variance in CPAP adherence explained by SECI when different scoring criteria are used. This could possibly have been done in a study with a design similar to paper IV, but given the relatively large dropout in this study, a future study will be examining this instead.

It is also interesting to note, that while some side effects were related to CPAP adherence, others were not, and it might thus make sense to treat side effects as separate entities rather than to sum them. Kwiatkowska et al., (2008) asked CPAP patients about severity and frequency of 11 side effects (nasal congestion, rhinorrhea, rhinosinusitis, epistaxis (nose bleeding), skin abrasion from mask, conjunctivitis from air leaks, aerophagy (air swallowing), sinus discomfort, sleep fragmentation, anxiety and claustrophobia) that were rated regarding frequency and severity on Likert-type scales ranging from 0 to 4. These two responses were then multiplied, and the products were added. While this approach would be possible to perform in SECI as well, as each
side effect is rated on several subscales, and has some interesting features, e.g., by allowing for a change in the frequency of a side effect to be more or less important depending on the perceived severity of the side effects, it also has problems.

If an answer to a question in a questionnaire is conceptualized as depending on a true score and an error component, i.e.,

\[ S_o = S_t + S_e \]

Where \( S_o \) is the observed score, \( S_t \) is the true score and \( S_e \) is the error score, then the product of two observed scores \( S_1 \) and \( S_2 \), each consisting of a true score and an error, will be

\[ S_o = (S_{1t} + S_{1e}) (S_{2t} + S_{2e}) = S_{1t} S_{2t} + S_{1t} S_{2e} + S_{1e} S_{2t} + S_{1e} S_{2e} \]

Of special concern are the two terms \( S_{1t} S_{2e} \) and \( S_{1e} S_{2t} \), as they represent a heteroscedastic error, i.e., there is a relationship between the obtained score and the size of the error. This might affect the validity of statistical analyses, especially those based on a homoscedasticity assumption e.g., regression and ANOVA (Bobko 2001). This is why SECI scores are not multiplied. Besides, we found that the frequency scale in SECI had lower reliability than the other scales, and it might be removed in further versions of the SECI. Another possible approach that would not suffer from the potential homoscedasticity problem described above would be to sum the scores for each side effect rather than summing the scores for all frequency questions, magnitude questions and impact questions separately.

**Defining adherence**

CPAP adherence has been defined in different ways in different studies. One problem is that it is not known how much CPAP is needed in order to have effect, but there seems to be a dose-response relationship, with a threshold effect, i.e., a level (threshold) of CPAP use above which further increases in use are not likely to improve outcome (Weaver et al., 2007). It is, however, not certain that the dose-response relationship is similar for all treatment effects. For example, Weaver et al. (2007) found, that there were different dose-response relationships between CPAP use and ESS, MSLT and FOSQ (Functional Outcomes of Sleepiness Questionnaire; Weaver et al., 1997). Antic et al. (2011) found a dose-response relationship for ESS, the vitality subscale of
SF-36 (Ware, 1993) and FOSQ, but not for MWT. Nor did they find any dose-response relationships for verbal memory and executive function, although they both improved in CPAP treated patients. Interestingly, although they found an improvement in ESS, approximately 20% of those who used the CPAP 7 hours per night or more still had pathologic ESS scores after three months on treatment. Zimmerman et al. (2006), however, found that normalization of visual memory performance in CPAP users were eight times more likely in those who used CPAP more than six hours per night than in those who used it less than two hours per night, among memory-impaired new CPAP users after three months on CPAP as compared to prior to CPAP initiation.

A problem with studying CPAP dose-response effects experimentally is that there seems to be a "carry over" effect after CPAP use, at least according to some studies. In chronic sleep restriction, the correlation between subjective sleepiness and sleep restriction, as well as cognitive performance, may be less clear than in acute sleep restriction, but a modest sleep restriction occurring chronically can have a cumulative effect (Van Dongen et al., 2003). It is also known from studies of sleep deprivation and sleep need that people differ in their sensitivity to sleep loss and the effects from sleep loss (Van Dongen et al., 2004). It might therefore be questioned whether it is appropriate with an adherence definition basically stating that a patient is adherent if he or she uses the CPAP more than a fixed number of hours per night.

Regarding the consequences of OSAS, there are at least two general pathophysiological mechanisms that can be responsible. One mechanism might be that OSAS leads to chronic sleep deprivation through sleep fragmentation. Sleep fragmentation might cause similar effects as sleep restriction (reviewed in Bonnet & Arand, 2003). Another mechanism might be oxygen deficits, which might lead to generation of free oxygen radicals (Christou et al., 2003), sympathetic activation (Hedner et al., 1988) and inflammation (Shamsuzzaman et al., 2002). UARS might be another clue to the various pathogenetic mechanisms linking sleep-disordered breathing to symptoms and long-term adverse health consequences. In UARS, patients have few if any desaturations, yet they might still have arousals, and they still become sleepy (Black et al., 2002). Inflammatory factors might also contribute to sleepiness, as there is an increase in sleep-promoting inflammatory cytokines in obstructive sleep apnea, as compared to normal controls (Vgontzas et al., 1997). Similarly, sleep fragmentation, without oxygen desaturations, might contribute to the cardiovascular aspects of OSAS (Lofaso et al., 1996). Our understanding of these pathogenetic processes influence how we should look at CPAP adherence. If the main problem with OSAS is sleep fragmentation and the resulting sleep deprivation, then it would be reasonable to use either machine usage time or a cutoff time to define which patients are adherent or not. The existence of thresholds for CPAP effects (Weaver et al., 2007) might indicate that a
cutoff time might be reasonable; however, it would be different for different outcome measures and probably also for different subjects (Van Dongen et al., 2004). If the main problem with OSAS is desaturations, then the main objective with CPAP treatment is to reduce sleep without CPAP. In that case, simply measuring the time a subject uses his or her CPAP is inadequate, as we would also want to know the exposure to desaturations, which is related to sleep time without CPAP. In that case, a percentage of the total sleep time spent with CPAP would probably be a more accurate measure of adherence. Most likely, however, both mechanisms (i.e., desaturations and sleep fragmentation) combine to cause adverse short and long-term effects, and thus both need to be reflected in a definition of CPAP adherence. In one of the studies (i.e., study II), one of the definitions of adherence was using the CPAP at least 85 % of self-rated sleep time. While 85 % is a arbitrary cut point, the definition has two advantages: it takes interindividual differences in sleep need into account, and it limits the amount of sleep without CPAP that is allowed, thereby limiting the adverse affects of oxygen desaturations. It was, however, not possible to use this definition in paper IV, as data about subjective sleep time was not available. The effects of type D personality on adherence were similar regardless of the definition of adherence. Dropout, as was used in paper IV, represents the ultimate failure of treatment; as long as the patient retains the machine, there is a hope that future interventions might have an effect.

**Measuring adherence**

Traditionally, CPAP adherence has been defined either as treatment dropout, as subjectively reported CPAP use or as objectively measured machine usage time. CPAP devices automatically measure the amount of time they are used with an effective pressure (Kribbs et al., 1993), and can report this as a night-by-night measure. Regarding treatment dropout, the main problem is the risk that dropouts are unrecognized, as patients may keep the machine without ever using it. If follow-up only occurs in the beginning of treatment, and patients are thereafter responsible for contacting the CPAP provider whenever they need, but without scheduled follow-up, this might be an issue. It can be assumed that the probability of patients retaining the device without ever intending to use it is decreased if the health care provider requires a monthly fee for the device as is done in some, but not all, parts of Sweden (Swedvox, 2011). This is less of a problem in studies, however, where follow-up is more controlled. Approximately 8 to 15 % of patients refuse CPAP initially, i.e., they never start treatment or return the device after the first night (Smith et al., 2009). Rates of refusal or poor long-term use range from 20 to 83 % in the literature (Smith et al., 2009), partly depending on different definitions of adherence.
Subjective data regarding CPAP use tend to produce higher results than objective data. For example, Engleman et al., (1996b) found that patients systematically over-estimated their CPAP use as compared to internal meter readings. The objectively measured mean use was 5.1±2.5 h/night, but subjective mean use per night according to self-report data was 6.0±1.9 h/night (p=0.0003). Their subjective and objective adherence were, however, correlated (r=0.68). It is also known that patients might exhibit non-adherence by not using the CPAP at all certain nights. Regarding objective machine usage time, it is sometimes used as a continuous variable. This is becoming more common, as CPAP devices record it and as it allows for statistical methods that are used on interval data rather than categorical data.

We employed several approaches to adherence, and obtained similar results with them.

**Side effects and adherence: Why would they be related?**

The side effects that have been reported are based on subjective experiences. For some side effects, e.g., anxiety during treatment, this is the only possible approach, while other side effects could, at least in theory, be assessed objectively (e.g., increased number of awakenings). The idea behind examining side effects as a potential reason for non-adherence is that side effects might increase the perceived cost of treatment. Some sort of ”cost of treatment” is involved in several theoretical models of patient adherence. The Health Belief Model, for example, lists four variables that will affect the likelihood of a subject engaging in health-related behaviours (Carpenter, 2010):

1) Perceived susceptibility of a negative outcome (e.g., experienced sleepiness, perceived susceptibility of cardiovascular events etc.).
2) Perceived severity of the negative outcome (e.g., death in the case of cardiovascular events; anything from impaired daily functioning to car crashes in the case of daytime sleepiness).
3) Belief in the efficacy of the health-related behaviour in question (in this case, using the CPAP).
4) Perceived barriers related to the health-related behaviour. This is where side effects come in.

The Trans-theoretical model, which has been used to explain CPAP adherence by Stepnowsky et al., (e.g., Stepnowsky et al., 2006), is based on motivational readiness to adopt or cease a certain
behaviour. This motivational readiness is perceived as a continuous scale, and the patient’s position along this scale might change over time depending on a cognitive 'balance sheet' where advantages and disadvantages are weighted against each other (Stepnowsky et al., 2002). Side effects would then count as a potential disadvantage, thereby making patients less likely to be adherent CPAP users.

Side effects can also be understood from the MET (Motivation to Engage in Treatment) model of Drieschner (Drieschner, 2004). Based upon Social cognitive theory as well as the transtheoretical model, he lists six determinants of treatment motivation is listed:

1) Level of suffering, e.g., symptoms from OSAS.
2) Outcome expectancy, e.g., a belief that daytime sleepiness will disappear.
3) External pressure, e.g., from a partner.
4) Perceived suitability of treatment, e.g., attitudes to CPAP (Broström et al., 2011).
5) Problem recognition, e.g., realising that one has SDB (Broström et al., 2010).
6) Perceived cost of treatment, to which side effects can be thought to belong.

No matter what model one chooses, side effects do not occur in isolation. They might be affected by social support, e.g., from a spouse (Broström et al., 2010), by technical factors related to treatment (e.g., humidification and heating of air); and they might also be affected by personality factors, such as type D personality.

Type D personality

Definition and prevalence
Type D personality was initially studied in cardiovascular research, where it was associated to all-cause mortality in patients with coronary artery disease (Dennolet et al., 1996). In this paper, Denollet et al. hypothesized that poor adherence might be one possible cause for this association, but a lot of the later work trying to discern the relationship between type D personality and mortality tended to focus on various biomedical stress-related risk factors and how these differed in people exhibiting a type D personality (e.g., Habra et al., 2003). Our study regarding type D personality as a factor affecting treatment adherence has later been confirmed in studies concerning adherence to medication in myocardial infarction patients (Williams et al., 2011).
We found a fairly high prevalence of type D personality in our study. 30% of the total sample fulfilled the criteria when using the cutoff values provided by Denollet (2005). These cutoff values were chosen based on a median split of his validation sample. He motivated this by a cluster analysis performed in patients with coronary heart disease, as well as median splits having been used to delineate personality types in previous research (as discussed in Denollet et al., 1996). The reported prevalence of type D personality in the original validation paper for DS14 ranged from approximately 20% in normal controls to approximately 50% in hypertensive subjects, implying that our prevalence figures are in line with what has been reported previously. Besides, the use of median splits by Denollet when deciding on the cutoff levels for defining type D personality means that, by definition, 50% of his subjects would have been high-NA (negative affectivity) and 50% would have been high-SI (social inhibition) subjects. If the constructs are independent, a prevalence of 25% would be expected.

**Relationship to other personality constructs**
Several other personality constructs might be related to type D personality. The BIS/BAS model of personality, for example, states that there are two basic motivational systems underlying personality: the goal of the behavioural inhibition system (BIS) is to avoid negative consequences (i.e., punishment), while the goal of the behavioural activating system (BAS) is to seek reward (Carver & White, 1994). BIS is related to negative affectivity and anxiety, and high levels of BIS is related to worse CPAP adherence (Moran et al., 2011). Both negative affectivity and social inhibition are correlated to neuroticism (De Fruyt & Denollet, 2002), but they are not identical constructs (Denollet 2000). While Moran et al., (2011) found a univariate correlation between neuroticism and adherence, it did not retain statistical significance in their final model.

The DS14 has been examined using various psychometrical approaches. The original development was based on classical test theory, but this has been combined with item response theory in a more recent study (Emons et al., 2007), indicating that there is a high reliability in the range around the cutoff. They did find some evidence of differential item functioning for hypertension, but none that was considered practically significant.
Putative mechanisms linking type D personality to adherence

There are several potential mechanisms that might link type D personality to poor adherence. It has been reported elsewhere that negative affectivity is associated to a higher degree of symptom awareness. For example, Watson and Pennebaker (1989) found clear and consistent associations between negative affectivity and health-related complaints by using a battery of different symptom reporting scales. The tendency to experience more symptoms, including CPAP side effect, could be understood in terms of an increased perceived cost of treatment in light of Drieschner’s model (presented above). Besides, social inhibition might decrease the likelihood of patients discussing their experienced side effects with the CPAP provider. Pelle et al., (2009) found that cardiac failure patients with type D personality were almost two times as likely as non-type D patients (OR 1.80 after adjusting for sociodemographic factors, etiology of heart failure and disease severity) to fail to contact their care provider in case of worsened heart failure symptoms. As there are potentially efficient countermeasures that can be applied for most CPAP side effects, the combination of a higher tendency to experience side effects with failure to report side effects might act together to worsen adherence.

It would be tempting to use SECI to screen for side effects, in order to counteract the potentially lower tendency to report troublesome side effects in type D patients. After all, they did report more side effects in the questionnaire. However, in the present study, SECI as well as the DS14 were mailed to the participants, and the authors were not directly involved in providing the care. If patients are supposed to hand in the questionnaire to the nurse responsible for providing CPAP treatment, there is a greater risk that type D patients will underreport side effects as compared to when they get to answer SECI as part of a study.

Our study regarding the association between type D personality and adherence was cross-sectional. One can expect that subjects suffering from daytime symptoms of a sleep-related breathing disorder might be more prone to endorse the kind of questions that are asked in DS14, due to their daytime sleepiness and fatigue (e.g., ”I am often irritated”, ”I am often in a bad mood” and ”I am often down in the dumps”). Symptoms of sleep-disordered breathing might be more prevalent among non-adherent users, and it might thus be possible that at least parts of the expressed negative affectivity might be related to poor adherence rather than causing poor adherence. It would be difficult to design a study that can answer this question definitely, but one step toward further understanding of the relationship between the constructs of type D
personality and CPAP adherence would be a prospective study, where DS14 would be used at several points of time, both prior to CPAP initiation and at various stages of treatment. A study like that would also be able to include patients that are new to CPAP. In the present study on type D personality patients had had CPAP for at least six months. As we have shown that side effects vary over time, it would be interesting to examine whether the association between type D personality and side effects vary over time as well, and if it is different for different side effects. Denollet showed, however, that mood did not affect DS14 scores (Denollet 2005).

**Temporal evolution of side effects**

Regarding side effects, as has been mentioned, one important factor that has often been overlooked in previous research has been whether side effects are stable over time or not. Based on theoretical considerations, it can be argued that they are most likely not, especially in a clinical sample. If a subject experiences a side effect that bothers him or her, s/he will likely either ask for help or become less adherent. Many side effects can be dealt with effectively, e.g., by changing mask, adding a humidifier etc. Conversely, if patients stop using their CPAP, they will stop experiencing side effects. In the light of existing countermeasures for many side effects, studying their natural course without intervening would not be ethical. The study of side effects over time allowed for patients to contact the provider to get help.

There are thus at least two possible ways that side effects might diminish over time in a clinical sample. Patients might learn to cope with side effects (e.g., by interventions from the provider or by applying other coping strategies), or patients experiencing a side effect might be more likely to stop using the device. In that case, the absolute frequency of a given side effect would decrease over time.

We found that the evolution of side effects over time is somewhat complicated. First of all, side effects are not stable over time. They do resolve in some patients. Whether this is due to interventions or not cannot be determined from the present study, as it was not designed to examine causes for variations in side effects over time. It is likely that mask changes etc. might affect side effect profiles. In some subjects, side effects also evolved over time. The evolution of side effects over time was studied within subjects. In other words, in order to be included in the analyses, subjects had to have been using the CPAP long enough to complete SECI at at the points in time that were compared. Two statistical approaches were used to analyse side effects, Cohens κ and McNemar’s test. Cohen’s κ was used to assess to which degree the existence of a
side effect at one point in time correlated with the existence of the same side effect at a different point in time, as compared to what would have been expected if side effects occurred randomly. A $\kappa$ of 0 would indicate that the variation in side effects over time within a subject is no more or less than what could be expected from chance. In other words, the existence of a side effect at one point of time has nothing to do with the existence of the same side effect, within the same individual, at a later point of time. A $\kappa$ of 1 would indicate that the side effect in question, measured at different points of time, is perfectly correlated and thus stationary, i.e., it does not emerge in those who do not suffer from it and it does not resolve in those who do. A $\kappa$ of -1 would indicate that the side effect is perfectly inversely correlated to itself at a different point in time, i.e., it resolves over time in all patients who suffered from the side effect at the beginning and emerges in all patients who did not. This, of course, is highly unlikely, and the observed $\kappa$ values range from -0.07 to 0.42, indicating that most relationships are positive but not very strong. One reason for this could be that side effects resolve with time, e.g., due to the reasons given above. McNemar’s test was used to test whether side effects differed in their frequency over time. A significant p-value indicates that there is a difference in the prevalence of a side effect between the two different measurements that are compared.

However, side effects do not only resolve. They also emerge. This is harder to explain, but there might be reasons for this phenomenon as well. As sleep improves due to unobstructed breathing during sleep, it is possible that side effects that were less likely to be perceived as disruptive to sleep are noticed to a higher extent and thus reported to a higher extent. It might also be that people lose weight or change their drinking habits as a result of having been diagnosed with a disorder that is affected by BMI and alcohol consumption, and that their disease severity and the pressure needed to alleviate the most severe daytime symptoms is reduced, thereby causing a higher-than-needed pressure to be delivered. As some side effects are likely to be related to CPAP pressure, this might lead to emergence of new side effects.

One of the main daytime symptoms that have been studied is sleepiness. If side effects can be perceived as costs of treatment, daytime sleepiness might be perceived as contributing to the level of suffering caused by the disorder. Measurement of sleepiness has attracted a lot of attention, as it is a common concern with potentially great impact on traffic accidents (reviewed in De Mello et al., 2013).
**Defining and measuring sleepiness**

A significant problem with measuring sleepiness is how to define it (Shen et al., 2006). It is sometimes defined as the tendency of falling asleep, sometimes termed sleep propensity. This is what the MSLT aims to measure (Carskadon et al., 1986). MSLT infers the propensity to fall asleep from the time it takes for this to happen during specified circumstances. This is not the same as sleep need. In insomnia, sleepiness as measured by the MSLT is not increased despite poor nocturnal sleep, which is different from what is seen in experimentally sleep-deprived good sleepers (Bonnet & Arand, 1997). It is also interesting to note, that while MSLT and MWT are correlated, the correlation is only moderate. For example, Sangal et al. (1992), found a correlation coefficient of 0.41 in 258 patients evaluated for sleep apnea or daytime sleepiness, with a factor analysis indicating that two factors could explain 91% of the variance. It might be argued that readiness to fall asleep is not the same as inability to stay awake. In light of the ESS, this might raise concerns as to whether item 5 (“Lying down to rest in the afternoon when circumstances permit”) measures the same construct as the others, as a subject lying down to rest in the afternoon is not necessarily trying to stay awake, which is implied in most of the other items. However, factor analysis of the ESS has not indicated that this item loads on a different factor than others measuring sleep in more active situations (Johns, 1992).

It might furthermore be reasonable to differentiate between sleep propensity and drowsiness, as there are patients who report drowsiness without being obviously sleepy when sleepiness is measured objectively. Åkerstedt (1998) describes sleepiness as an active attempt by the nervous system to go to sleep, from which it follows that a person who is not fighting sleep would not experience sleepiness (Åkerstedt, 1998; Cluydts et al., 2002). Accident risk is related to subjective sleepiness, but with large interindividual differences (Ingre et al., 2006). While there is a relationship between subjective sleepiness and performance, it might thus be suspected that they are not simply the same construct.

**Epworth Sleepiness Scale**

ESS is based on the concept of soporificity, which is ”the extent to which any particular activity or situation facilitates dozing in most subjects” (Johns, 1994) and a four-process model of sleepiness consisting of antagonistic sleep- and wake-promoting processes (Johns, 1998). The items were chosen to represent different degrees of soporificity, based, mostly it seems, on theoretical considerations (the item generation process is not described in detail). The assumption that the described situations are indeed different regarding their soporificity is corroborated by the
Rasch analysis by us as well as by others (Hagell & Broman, 2007; Violani et al., 2003). Comparing these three studies show similar results.

Table 5: Item hierarchy in different studies of the Epworth Sleepiness Scale

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Lying down in afternoon</td>
<td>Lying down in afternoon</td>
<td>Lying down in afternoon</td>
</tr>
<tr>
<td>Watching TV</td>
<td>Watching TV</td>
<td>Watching TV</td>
</tr>
<tr>
<td>Sitting and reading</td>
<td>Sitting and reading</td>
<td>Sitting and reading</td>
</tr>
<tr>
<td>Passenger in a car 1h</td>
<td>Passenger in a car 1h</td>
<td>Sitting quietly after lunch</td>
</tr>
<tr>
<td>Sitting quietly after lunch</td>
<td>Sitting quietly after lunch</td>
<td>Passenger in a car 1h</td>
</tr>
<tr>
<td>Inactive in public place</td>
<td>Inactive in public place</td>
<td>Inactive in public place</td>
</tr>
<tr>
<td><strong>Talking to someone</strong></td>
<td><strong>In a car that has stopped</strong></td>
<td><strong>In a car that has stopped</strong></td>
</tr>
<tr>
<td><strong>In a car that has stopped</strong></td>
<td>Talking to someone</td>
<td>Talking to someone</td>
</tr>
</tbody>
</table>

Most items are arranged in similar order, except for items 4 and 7 that are reversed in the study by Violani et al. (2003), and items 6 and 8 that are reversed in our study. Those are boldfaced in the table. Another finding that has been reproduced is the gap in item difficulty between items 6 and 8 and the other items. This might explain the results from factor analyses of ESS, as a confirmatory factor analysis indicated that a two-factor solution with items 6 and 8 loading on a second factor provided a better fit (Smith et al., 2008). A consequence of this could be that relationships between ESS and other measurements of daytime sleepiness are not linear, as an increase in one point on ESS has different meanings depending on which item the increase affects. Interestingly, Sangal et al., (1999) found that a cubic model is best at explaining the association between ESS and MWT (ESS was the dependent variable). While a cubic model has more freedom to ”wiggle” and thus might provide better fit for purely mathematical reasons, it is noteworthy that they found a downward slope at very low MWT values (to approximately 2.5 mins) followed by a plateau at ESS=18 (i.e., the score that one would get by indicating a high chance of dozing in all situations except for two), and then again a downward slope as MWT reached 12.5 minutes.

We used two ways to assess DIF in the ESS: ordinal regression and Rasch analysis. They both gave similar results. The findings were most clear for age, which was a cause of DIF in items 3, 4 and 8. Older people tended to score lower on items 3 and 4, and higher on item 8. In this study
’old’ was defined as being older than 65 years. This cutoff was chosen as it would most likely represent retirement age. It was assumed that lifestyle changes occurring due to retirement would cause differences in how the situations described in the ESS are handled. Items 3 and 4 ("Sitting inactive in a public place, e.g., a theater or a meeting” and ”As a passenger in a car for an hour without a break”) might represent situations that sleepy elderly people stop exposing themselves to as a result of being sleepy. Regarding item 8, it is noteworthy that it does not specify whether the respondent is a passenger or a driver. It is possible, although it has not been studied explicitly, that people who regularly drive answer the question from that perspective, while elderly people, as a result of driving less, answer the question from the perspective of a passenger. No doubt, being a passenger is more soporific than being a driver, and this might affect the psychometric properties of the item. This also raises the question whether having a drivers’ license might be a cause of DIF in item 8. This has not been studied.

Regarding the gender DIF, it was only found in the Rasch analysis, and the women were significantly older than the men. This raises some doubts as to whether this represents true DIF, or whether it is a spurious finding.

Both models had some issues with misfit. This might be due to sample size. Both models, however, produced similar results, i.e., DIF in the same items with regard to age. There are reasonable reasons as to whether these items would show DIF. Another study that performed a Rasch analysis showed DIF for age in items 1, 2, 4 and 8 when a cutoff at 40 years was used (Martinez et al., 2011). A visual inspection of the item characteristic curves indicate that model fit is reasonable.

The DIF presented is fairly small, meaning that it is probably not affecting the judgement of individual ESS scores or smaller studies. It might be a reason for concern in larger studies, however.

**Future research**
The studies presented in this thesis only elucidate a small part of the vast field that is CPAP adherence in OSAS. Further research is warranted, and ongoing.

Regarding CPAP side effects, further research will continue to develop and validate SECI with regard to scoring procedure and the development of side effects over time. Most models of
adherence in some way assume that whether a patient engages in treatment or not is a consequence of a rational choice, where the advantages and disadvantages of different behaviours are weighed against each other. While there might be an ongoing rational process in patients deciding to adopt a behaviour or not, it is likely not the whole truth. A lot of behaviours, when repeated over time in a specific context, develop into habits. Central to the concept of habits is automaticity, i.e., that the behaviour is performed more or less without thinking (Aarts et al., 1998). Automaticity is not included in any of the models reviewed here, but might be important to understand health-related behaviours (Nilsen et al., 2013). It is possible that formation of habits might affect the association between side effects and adherence. It will also be important to look further into how various interventions affect the perception of side effects in CPAP patients.

Regarding personality and adherence, prospective longitudinal studies are important to further elucidate what effects personality might have on adherence and how personality factors can be taken into account in clinical CPAP care. It is also possible that habit-forming might be related to personality traits, and thus that personality might affect the ability to make CPAP use into a habit.

Regarding the ESS, several questions remain unanswered. One is related to the association between ESS and other measurements of sleepiness. While there is a correlation, it is modest at best. One reason might be that various tests actually measure different aspects or dimensions of sleepiness. Another might be that the items of the ESS are not evenly distributed with regard to difficulty, and thus that changes in ESS scores are dependent on where they occur. It is possible that this could be used to improve the correlation between ESS and objective measurements of daytime sleepiness, but it has not been studied. Knowledge about item difficulty distribution and hierarchy might also be employed in studying what ESS score changes are clinically significant.
CONCLUSIONS

**Aim 1:** To describe the development and initial testing of a new instrument, the side effects to CPAP inventory (SECI).

**Conclusion:** SECI is a reliable and valid instrument to assess side effects of CPAP treatment in patients with OSA. SECI scores are, as would be expected, higher among non-adherent users than among adherent users.

**Aim 2:** To measure the frequency and magnitude of CPAP side effects, as well as their impact on CPAP use.

**Conclusion:** Both study I and IV show that side effects might have an impact on CPAP use. The most frequently occurring side effects in study I were dry throat and mask-related problems. In study IV, the most severe and frequently occurring side effects were dry mouth, blocked up nose, increased number of awakenings and mask-related problems at all points of time.

**Aim 3:** To describe the prevalence of type D personality in OSAS patients with CPAP treatment longer than 6 months and the association with self-reported side effects and adherence.

**Conclusion:** Approximately 30% of the patients fulfilled the criteria for type D personality. These patients experienced more side effects and had lower adherence to treatment.

**Aim 4:** To examine whether any of the items in the ESS exhibits DIF with regard to age or gender, and if so, to which degree.

**Conclusion:** Items 3, 4 and 8 exhibited DIF for age both in a Rasch analysis and when ordinal regression was used. In the Rasch analysis, but not the ordinal regression, item 3 also exhibited DIF for gender. The DIF for gender might, however, be a spurious finding related to an age difference between men and women in the sample. Generally, the DIF were small, and are probably not clinically relevant in individual patients, although they might be relevant in large studies.

**Aim 5:** To examine the evolution of CPAP side effects over time.

**Conclusion:** Side effects can both resolve and emerge over time. While patients reporting anxiety during treatment after 1-2 weeks on CPAP either dropped out or stopped experiencing it, other side effects, such as upset bowel, became more common after a 9-12 months than after 1-2 weeks. More research is needed to explore these changes over time.
**Aim 6:** To prospectively assess correlations between early CPAP side effects and treatment adherence.

**Conclusion:** Patients reporting dry mouth or increased number of awakenings after 1-2 weeks had significantly lower adherence. Transient deafness, difficulties exhaling and anxiety during treatment were related to poor adherence measured as drop-out rate during the first year, as were dry mouth, feeling uncomfortable about using the CPAP in front of others, increased number of awakenings and problems exhaling as significant problems after 1-2 weeks when stratifying for treatment centre. No associations were found for other side effects. The conflicting results that have been reported previously are probably related to different definitions of side effects and adherence.
kriterierna för typ D-personlighet (det avgörs via ett frågeformulär). Dessa personer upplevde fler biverkningar av sin CPAP-behandling och använde CPAP-maskinerna i mindre utsträckning än övriga.

I ett av delarbetena fokuserade vi på ett frågeformulär, Epworth Sleepiness Scale (ESS), som ofta används inom sjukvård och forskning för att mäta dagsömnighet. Patienten får ange risken att han/hon skulle somna i åtta olika situationer på en fyragradig skala från 0 till 3, där höga siffror motsvarar en stor upplevd sannolikhet att somna. Dessa siffror summeras sedan och ger en poäng mellan 0 och 24. ESS har fått väldigt stor spridning sedan det utvecklades i början av 1990-talet, eftersom det är enkelt och billig. Det har dock kritiserats på flera grunder, bland annat för urvalet och formuleringen av de situationer i vilka man ska skatta risken att somna. En del av dessa situationer kan man tänka sig påverka äldre och yngre, eller män och kvinnor, olika. Med olika statistiska metoder har vi undersökt om så är fallet. Data bestod av 1,175 personer som fått fylla i frågeformuläret i tidigare studier. Vi fann att personer över 65 svarade annorlunda på tre av frågorna än personer under 65 år. Det är inte det samma som att personer över 65 är mer sömniga, utan även om man tar hänsyn till individuella skillnader i sömnighet kvarstår en tendens att en person över 65 år svarar annorlunda än en lika sömnig person under 65 år. En möjlighet är att pensionärer hanterar dagsömnighet annorlunda än yngre, kanske i högre utsträckning genom att undvika vissa situationer. Skillnaderna i hur man svarar på frågeformuläret är för små för att ha betydelse på individnivå, men kan ha betydelse för hur man tolkar resultat av stora studier där många personer ingår.
ACKNOWLEDGEMENTS

No thesis is the result of the work of a single person. Too many people have supported me throughout these years for it to be possible to mention every single one of them. There are, however, a few that I would like to take this opportunity to thank especially.

First of all professor Eva Svanborg, my main supervisor, clinical tutor and head of clinic, for waking up my interest in sleep medicine and sleep research, for providing me with generous research opportunities that few clinically active physicians have. Thank you for all your support throughout these years, for your hospitality and kindness, and for sharing your immense knowledge in sleep and related areas.

I would also like to thank professor Anders Broström, my co-supervisor and research colleague for all your enthusiasm, creativity and deep and broad methodological knowledge, spanning from phenomenography to structural equation modeling, but also for your encouragement and support with everything from discussing research ideas to taking me to concerts and movies that I would certainly not have seen otherwise.

David Lorr, for being a constant source of inspiration and new ideas, as well as for your hospitality.

Kristofer Årestedt, my research colleague and statistical discussion partner, for helpful comments and fruitful cooperations in more papers than are included in the thesis, and more to come. Furthermore, I would like to thank Peter Johansson at the dept of Cardiology and Per Nilsen at the department of Social medicine for introducing me to new fields of research and new concepts. I look forward to a future fruitful collaboration.

Anna Strömberg, Jan Mårtensson, Malin Svensson Johansson and Amanda Ekegren Ewaldh for fruitful research collaboration, and Lena Harder for fruitful research collaboration and for introducing me to polygraphy.

All patients who have been involved in the research. It would not be possible without you.

My future and previous research colleagues in Jönköping, including Ola Sunnergren at the ENT department, and colleagues at the ENT and Pulmonology departments.

My colleagues and friends at the Department of Clinical Neurophysiology at the University Hospital in Linköping including the CPAP unit.

My international colleagues and hopefully future research partners, especially Harald Hrubos Strom, Oslo, for valuable and stimulating discussions and hospitality.

My friends, especially Emma Colnerud Nilsson, Per Hellman and Hans Petersson, who have given me well needed opportunities to relax from research and clinical work.

And last, but definitely not least, my dear and beloved family, my parents Bengt and Ulrike, my sisters Nina, Veronica and Jenny and your respective families; Peter, Rich, Fredrik, Simon, Joel, Alexander, Harry and Märta. Words are not enough to express my love for you.
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