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Obesity, Sleep and Sleep-disordered Breathing

ANDREAS PALM

Dissertation presented at Uppsala University to be publicly examined in Brömssalen, Gävle sjukhus, Lasarettsvägen 1, Gävle, Friday, 9 November 2018 at 13:00 for the degree of Doctor of Philosophy (Faculty of Medicine). The examination will be conducted in Swedish. Faculty examiner: Professor Ludger Grote (Centre for Sleep and Wake Disorders, Sahlgrenska Academy, Gothenburg University, Gothenburg, Sweden.).

Abstract
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Background: Sleep problems are associated with impaired quality of life and daytime sleepiness. Obstructive sleep apnoea (OSA) and obesity hypoventilation syndrome (OHS), are associated with metabolic changes and an increased cardiovascular morbidity and mortality. The most preferred treatment of OSA and OHS is positive airway pressure (PAP) therapy. Diagnostic delay and non-adherence to PAP therapy are major clinical problems.

Aims and methods: Paper I: A longitudinal population-based cohort study aimed to investigate the role of obesity and weight gain in the development of sleep problems in 1,896 men and 5,116 women who responded to questionnaires at baseline and followed up after 10–13 years.

Paper II: A national registry-based cohort study aimed to analyse gender differences in patients with OHS starting long term mechanical ventilation (LTMV) and to study how the prescription of LTMV due to OHS has changed over time with data on 1,527 patients derived from the Swedish quality registry Swedevox between 1996 and 2014.

Paper III: A longitudinal observational cohort study aimed to investigate the impact of adherence to continuous positive airway pressure (CPAP) treatment on IGF-1 concentration in 69 patients with OSA followed up after 4.8 ± 2.5 months.

Paper IV: A national registry-based cohort study aimed to identify protective and risk factors against the discontinuation of CPAP treatment in patients with OSA and to estimate the mortality risk in those who were non-adherent to CPAP therapy on 16,425 patients derived from the Swedish quality registry Swedevox between July 2010 and March 2017.

Results and conclusions: Weight gain is a risk factor for developing several sleep problems and daytime sleepiness. Women with OHS are older with a more advanced clinical picture at initiation of LTMV and start LTMV more frequently in a non-elective situation than men. CPAP usage ≥ 4 h/night is associated with increased IGF-1 concentration in patients with OSA. Use of humidifier, increasing age, more severe OSA and BMI up to 35 are associated with greater adherence to CPAP treatment. Female gender and coexisting hypertension are risk factors for the discontinuation of CPAP. Failure to adhere to CPAP is associated with increased mortality.

Keywords: Sleep, Obesity, Obstructive Sleep Apnea, Obesity Hypoventilation syndrome

Andreas Palm, Department of Medical Sciences, Lung- allergy- and sleep research, Akademiska sjukhuset, Uppsala University, SE-75185 Uppsala, Sweden. Centre for Research and Development, Uppsala University/Region Gävleborg, SE-80188 Gävle, Sweden.

To my family

Humans have always appreciated a good night´s sleep. In his tragedy Julius Caesar, William Shakespeare associated good sleep with obesity (1), an association that has been revised since then.

Julius Caesar speaks to Mark Anthony:
'Let me have men about me that are fat,
Sleek-headed men and such as sleep a-nights.
Yond Cassius has a lean and hungry look.
He thinks too much. Such men are dangerous.'

"The fat boy Joe", a character in Charles Dickens "The *Posthumous Papers of the Pickwick Club*" *(2),* suffered from obesity with hypersomnolence, a clinical picture nowadays more relevant than ever.

'Now, Joe, the fowls. Damn that boy; he's gone to sleep again. Joe! Joe!' (Sundry taps on the head with a stick, and the fat boy, with some difficulty, roused from his lethargy.) 'Come, hand in the eatables.'

List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

I   Palm A, Janson C, Lindberg E. The impact of obesity and weight gain on development of sleep problems in a population-based sample. *Sleep medicine.* 2015;16(5):593–7.

II   Palm A, Midgren B, Janson C, Lindberg E. Gender differences in patients starting long–term home mechanical ventilation due to obesity hypoventilation syndrome. *Respiratory medicine.* 2016;110:73–8.

III   Palm A, Berne C, Igelström H, Åsenlöf P, Janson C, Lindberg E. The Impact of Continuous Positive Airway Pressure on Circulating IGF–1 in Patients with Obstructive Sleep Apnea. *Journal of clinical sleep medicine:* 2018;14(3):385–391.

IV   Palm A, Midgren B, Theorell-Haglöw J, Ekström M, Ljunggren M, Janson C, Lindberg E. Factors influencing adherence to continuous positive airway pressure treatment in obstructive sleep apnea and mortality associated with treatment failure – a national registry-based cohort study. *Sleep medicine.* 2018; 51:85–91.

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Contents

Abbreviations

AHI = Apnea-Hypopnoea Index
AHRF = Acute Hypercapnic Respiratory Failure
ALS = Amyotrophic Lateral Sclerosis
BE = Base Excess
BMI = Body Mass Index
CI = Confidence Interval
CVF = Cardiovascular Failure
COPD = Chronic Obstructive Pulmonary Disease
CSAS = Central Sleep Apnoea Syndrome
CPAP = Continuous Positive Airway Pressure
DIS = Difficulties Initiating Sleep
DMS = Difficulties Maintaining Sleep
EDS = Excessive Daytime Sleepiness
EPAP = Expiratory Positive Airway Pressure
ERV = Expiratory Reserve Volume
ESS = Epworth Sleepiness Scale
FEV_1 = Forced Expiratory Volume in 1 second
FU = Follow-up
FVC = Forced Vital Capacity
FRC = Functional Residual Capacity
GERD = Gastro Oesophageal Reflux Disease
GH = Growth Hormone
IGF-1 = Insulin-Like Growth Factor-1
IPAP = Inspiratory Positive Airway Pressure
LTMV = Long-Term Mechanical Ventilation
LTOT = Long-term Oxygen Therapy
NIV = Non-Invasive Ventilation
ODI = Oxygen Desaturation Index
OSA = Obstructive Sleep Apnoea
OSAS = Obstructive Sleep Apnoea Syndrome
OHS = Obesity Hypoventilation Syndrome
$PaCO_2$ = Arterial carbon dioxide tension
PaO_2 = Arterial oxygen dioxide tension

PAP = Positive Airway Pressure
PS = Pressure Support
RCT = Randomised Controlled Trial
REM = Rapid Eye Movement
QoL = Quality of Life
SDB = Sleep-disordered Breathing
VC = Vital Capacity

Introduction

Obesity – epidemiology and health risks

In parallel with the on-going obesity pandemic, diseases linked to obesity such as the metabolic syndrome, cardiovascular diseases (3) and obstructive sleep apnoea syndrome (OSAS) are increasing (4).

The concept body mass index (BMI) indicates nutritional status and is regarded to be a good proxy for adiposity and problems related to overweight and obesity. BMI is calculated by dividing a person´s weight in kilograms by the square of the person´s height in meters (kg/m^2). The WHO has recently redefined the BMI categories (**Table 1**) (5).

Table 1. *The WHO definition of BMI categories.*

BMI	Nutritional status
Below 18.5	Underweight
18.5–24.9	Normal weight
25.0–29.9	Pre-obesity
30.0–34.9	Obesity class I
35.0–39.9	Obesity class II
Above 40	Obesity class III

Global age-standardised mean body mass index (BMI) in men increased from 21.7 kg/m^2 in 1975 to 24.2 kg/m^2 in 2014, and in women from 22.1 kg/m^2 in 1975 to 24.4 kg/m^2 in 2014 and the worldwide prevalence of obesity increased from 2.3% in 1975 to 10.8% in 2014 in men and from 6.8% to 14.9% in women (6). In Sweden, the prevalence of obesity (BMI>30 kg/m^2) among adults doubled to a level of 10% between 1980 and 2005 (7). The proportion of men and women with obesity in Sweden has further increased to 14% 2015. However, the proportion of adults with pre-obesity (BMI 25–29.9 kg/m^2) did not increase between 2004 and 2015 and accounts now for 42% of men and 29% of women (8). The increase rate of BMI has slowed down since 2000 in high-income countries (6). Even though the proportion of overweight and obese people is increasing worldwide and that overweight is an independent risk factor for diabetes and cardiovascular diseases, the mortality from cardiovascular diseases has decreased for decades in high-income countries. This is probably due to improved primary and secondary prevention of risk factors

for cardiovascular morbidity, decreased smoking and improvement of medical care (9, 10). A recent study shows that in the last three decades the BMI associated with the lowest all-cause mortality has increased from 24.2 to 27.2 in Denmark (11). That implies that the definitions of overweight and obesity might have to be revised again.

In the developed world overweight and obesity peak in men around age 55, when two of three men are overweight and one in four are obese. In women obesity peaks around age 65, when one in three are obese (12). Obesity is associated with an increased morbidity and mortality and a reduced life expectancy (3, 13, 14). At BMI 30–35 kg/m^2, median survival is reduced by 2–4 years; at BMI 40–45 kg/m^2, it is reduced by 8–10 years (14). The nadir of all-cause mortality is age-dependent and BMI 22 kg/m^2 for baseline age 35–49 years, BMI 23 kg/m^2 for baseline age 50–69 years, and BMI 24 kg/m^2 for baseline age 70–89 years are associated with best survival (15). Two meta-analyses conducted on critically ill patients at intensive care units (ICU) have not shown increased mortality but prolonged duration of stay associated with obesity (16, 17).

Obesity, sleep and breathing

Obese people have, especially in supine position, raised gastric and oesophageal pressure and an associated reduction in functional residual capacity (FRC) and expiratory reserve volume (ERV) that is exponential with increasing BMI (18-20). Patients with obesity are breathing near their residual volume. At a BMI of 30 kg/m^2, FRC and ERV is only 75% and 47%, respectively, of the values for a lean person with a BMI of 20 kg/m^2 (21). Increasing BMI correlates with decreasing PaO2 and increasing PaCO2 (18). The reduction of PaO2 in obese patients is due to micro-atelectasis and ventilation-perfusion mismatch in the lung bases (22). Especially abdominal obesity is associated with a reduction of both forced expiratory volume at 1 second (FEV_1) and forced vital capacity (FVC) (23). Increased body mass produces more carbon dioxide and consumes more oxygen and demands increased respiratory effort, so the respiratory rate and minute ventilation is higher in obese subjects (24). The mobility of the diaphragm is reduced in supine position, especially in the presence of abdominal obesity, leading to a further reduction of lung function (19). Reversal of obesity leads to normalisation of pulmonary function (25, 26).

When falling asleep there is a reduction in alveolar ventilation by up to 20–25% due to decreased muscular tonus and altered chemosensitivity, particularly during rapid-eye-movement sleep (REM sleep) (27-29). The intercostal muscles contribute less to ventilation during REM-sleep with a decrease from 44 to 19% of total respiratory effort (30). Ventilation becomes more dependent on the diaphragm muscle.

Sleep problems

Insomnia is a common sleep problem that is marked by the difficulty in initiating sleep (DIS) and/or difficulty in maintaining sleep (DMS) and/or problems with early morning awakenings (EMA). In addition, the sleep that is obtained is non-refreshing or of poor quality with excessive daytime sleepiness (EDS) as a consequence. The sleep disturbance should cause clinically significant distress or impairment in social, occupational, educational, academic, behavioural, or other important areas of functioning, and it should be lasting and occur despite adequate opportunity for sleep (31).

In the general population, approximately 6–10% experience insomnia and 30–39% experience sleep problems, and these prevalence rates are increasing (32-34). Cross-sectional (35-41) studies reveal that sleep problems and daytime sleepiness are associated with obesity and that the association is independent of the coexistence of obstructive sleep apnoea (OSA) (39, 42). Sleep problems are more prevalent in women than in men (33, 40, 43). Short and long sleep time (44, 45) and insomnia and sleep problems are risk factors for weight gain (46-48) and obesity (44, 45, 49). Although weight gain is a well-known risk factor for the development of snoring (50) and sleep apnoea (51), the impact of weight gain on other sleep problems is still relatively unknown.

Epworth Sleepiness Scale

Epworth Sleepiness Scale (ESS) is a self-administrated questionnaire with 8 questions, each with a 4-point scale (0-3), used to assess daytime sleepiness (52). The questions are based on how likely the patients are to doze off or fall asleep during common activities that differ widely in their somnificity: sitting and reading, watching TV, sitting inactive in a public place, as a passenger in car for an hour without break, lying down to rest in the afternoon when circumstances permit, sitting and talking to someone, sitting quietly after lunch without alcohol and sitting in a car, while stopped for a few minutes in the traffic. The ESS score can range from 0 to 24. The higher the ESS score, the higher the daytime sleepiness. The commonly used cut-off for determining excessive daytime sleepiness is an ESS score of > 10.

Sleep-disordered breathing

Sleep-disordered breathing (SDB) or sleep-related breathing disorders is a term describing respiratory disturbances that occur during sleep. Sleep-disordered breathing is usually grouped into three categories: 1) Obstructive sleep apnea (OSA), 2) central sleep apnoea syndrome (CSAS) and 3) sleep related alveolar hypoventilation. A subgroup of the latter is obesity hypoventilation syndrome (OHS) (53).

OSA

OSA is a condition with recurrent episodes of partial or complete airway obstructions during sleep with repetitive apneas and hypopneas and episodes of hypoxia as a result. OSA is defined as the presence of at least five obstructive respiratory events (apneas, hypopneas or respiratory effort-related arousals)per hour of sleep in combination with sleep related symptoms or the presence of 15 or more obstructive respiratory events per hour of sleep in the absence of sleep-related symptoms (53). Despite poor correlation between AHI, daytime sleepiness and clinical symptoms (54, 55), the severity of OSA is still gradated by the apnoea-hypopnoea index (AHI), the mean number of apneas and hypopneas per hour of sleep. OSA with AHI between 5 – < 15 is categorised as a mild OSA, AHI between 15 – < 30 as moderate OSA and AHI ≥30 as severe OSA (56, 57). The disease was previously termed obstructive sleep apnoea syndrome (OSAS) and referred to the combination of OSA and daytime impairment (58). Nowadays only the term OSA is used but the sleep related symptoms are still considered and influence the treatment options (56). There is need for a new definition of OSA not only based on AHI but also on other clinical and pathophysiological traits (59).

Obesity hypoventilation syndrome (OHS)

OHS is a severe, often life-threatening condition that is defined as a combination of obesity (BMI >30 kg/m^2), chronic daytime hypercapnia, (PaCO2 >6.0 kPa) and sleep-disordered breathing, mainly OSA in the absence of any other cause of hypoventilation (60, 61).

Epidemiology of SDB

SDB is highly prevalent. In a recent review based on 11 epidemiological studies between 1993 and 2013 22% of men (range 9–37%) and 17% of women (range 4–50%) had AHI ≥5. OSA with excessive daytime sleepiness is present in 6% (range, 3–18%) in men and in 4% (range, 1–17%) in women (4). In a Swiss population-based study, where 2,121 patients underwent full polysomnography, the median AHI was 6.9 in women and 14.9 in men (62). There was an independent association between the quartile with an AHI exceeding 21 and the presence of hypertension, diabetes, metabolic syndrome and depression. In 400 women aged 20–70 years from a population-based cohort, OSA with AHI ≥5 occurred in 50%: 20% had moderate and 6% had severe OSA. OSA was found in 80% of women with hypertension and in 84% of obese females with a BMI above 30 kg/m^2 (63).

The prevalence and gender distribution of OHS in the general population is unknown since no community-based cohort studies on patients with OHS have been conducted. The prevalence varies in different studied populations.

In selected cohorts from sleep clinics with a high probability of SDB, the prevalence range from 2 to 22% and the prevalence of OHS in those already diagnosed with OSA ranges from 6 to 37% (64-75).

In 150 hospitalised patients at medical wards 27% of those with BMI 35–39 kg/m^2 and 48% of those with BMI exceeding 50 had OHS (76). In a recent French screening study, 1,004 unselected patients with BMI $\geq$ 30 frequenting to a hospital chemical laboratory for any reason, bicarbonate was measured and 1.10% of the patients could be diagnosed with OHS after further investigation (77). A commonly used estimate of the prevalence rate of OHS in the general population in the United States is 0.2–0.4%. This is based on the following assumptions: in the United States 3,7% of the adult population suffer from obesity class III (BMI$\geq$40 kg/m^2) (78) and half of patients with severe obesity have OSA (6), and the assumption that 9–20% of obese patients with OSA have OHS (60). In a cohort of premenstrual obese women evaluated for bariatric surgery 8% had OHS (79). In a recent Spanish study 72% of patients with OHS had severe OSA (AHI $\geq$ 30 events/hour) (80).

The prevalence of OSA is twice as high in men (4, 81-84) and approximately 90% of patients with OHS have coexisting OSA (66). Studies on patients with OHS stratified by gender are sparse and many previous studies of OHS have been performed at sleep clinics on subjects with OSA, where men are generally over-represented . Despite the close link between OSA and OHS and the male predominance among patients with OSA, women appear to proportionally more affected by OHS in cohorts from sleep clinics (64-69, 71, 73-75) but statistical analyses have only exceptionally been performed to confirm this (**Table 2**) (64, 68). In 937 patients from 8 different cohorts of patients with OHS from respiratory wards and outpatient clinics, the proportion women was 52% (80, 85-92). In a cohort from hospitalised patients at internal medical services the proportion women was 49% (76) and in two cohorts from ICU the proportion women whit OHS was 77% (93, 94) (**Table 3**).

Table 2. *Proportion of women (%) with and without daytime hypercapnia in consecutive patients with SDB in sleep clinic cohorts.*

Study	Region	Cohort	Women with OSA without daytime hypercapnia. (%)	Women with SDB and daytime hypercapnia (%)
Leech (64) 1987	United States	n=152, AHI>10*	24	44**
Resta (65) 2000	Italy	n=96, FEV1% ≥ 70	59	37
Kessler (66) 2001	France	n=254, FEV1%≥60, without restrictive lung disease	10	27
Laaban (67) 2005	France	n=1141 (patients from the ANTADIR registry), FEV1% ≥ 70 and FEV1 ≥ 80, without respiratory restrictive disease	17	23
Kawata (68) 2007	Japan	n=1407, AHI≥5 + clinical symptoms of SDB, *	12	7**
Mokhlesi (69) 2007	United States	n=410, FEV1% ≥ 70	41	34
Alzaabi (71)2013	United Arab Emirates	n=212, AHI≥5*	17	39
Basoglu (73) 2014	Turkey	n=1079, AHI≥5 with symptoms of SDB/AHI≥15, without COPD	36	47
Harada (74)2014	Japan	n=981. AHI≥5. Those with other hypercapnic diseases excluded	35	45
BaHammam (75) 2015	Saudi Arabia	n=1973, AHI≥5 + symptoms of SDB. Those with heart failure, chronic lung/restrictive/neurologic disease excluded	34	67

ANTADIR = A French national database for patients with chronic respiratory insufficiency with home treatment (Association Nationale pour le Traitement a` Domicile de l'Insuffisance Respiratoire Chronique). BMI = Body mass index; COPD = Chronic obstructive pulmonary disease; OSA = Obstructive sleep apnea. * = Patients with impaired lung function are not excluded from analysis; ** = Statistically significant difference in prevalence of OHS between men and women.

Table 3. *Proportion of patients diagnosed with OHS in an acute setting and gender distribution in cohorts ≥50 patients from respiratory wards and outpatient clinics and hospitalised patients from internal medicine services and ICU.*

Study	Country	Cohort	Diagnosed in acute setting (%)	Women (%)
Cohorts from respiratory wards and outpatient clinics				
Perez de Llano (85) 2005	Spain	Retrospective cohort of 54 patients discharged with NIV from a respiratory ward	37	33
Budweiser (86) 2007	Germany	Retrospective cohort of 126 patients with OHS discharged with NIV from respiratory ward.	Not presented	44
Priou (87) 2010	France	Retrospective cohort of 130 patients with OHS discharged with NIV from a university hospital.	29	43
Murphy (88) 2012	UK	Cohort of 50 consecutive patients with OHS from a university hospital.	34	54
Borel (89) 2013	France	Retrospective cohort of all 107 patients with OHS on NIV from 5 centres.	36	56
Castro-Añón (90) 2015	Spain	Retrospective cohort study of 110 patients with OHS on PAP therapy from a university hospital.	70	44
Masa 2015 (80), 2016 (91)	Spain	Cohort of 300 consecutive patients with OHS, with stable hypercapnic respiratory failure, referred for pulmonary consultations at 16 tertiary hospitals.	0	63
Howard (92) 2017	Australia	Cohort of 60 consecutive patients with OHS from two respiratory failure clinics.	42	47
Hospitalised cohorts				
Nowbar (76) 2004	United States	150 consecutive patients with OHS at internal medicine services		49
Carrillo (93) 2012	Spain	173 consecutive patients with AHRF and OHS at ICU		77
Marik (94) 2014	United States	61 consecutive patients with OHS and BMI ≥40 at ICU		77

AHRF = Acute hypercapnic respiratory failure; AHI = Apnea-hypopnoea index; BMI = Body mass index; ICU = Intensive care unit; NIV = Non-invasive ventilation; OHS = Obesity hyperventilation syndrome; PAP = Positive airway pressure

Pathophysiology of SDB

Muscular tonus in the upper airways is altered during sleep with increased risk of airway collapse as a consequence. This risk is aggravated in coexisting obesity when fat deposition makes the upper airway lumen narrower and increases the risk of airway collapse (95, 96). Obesity also leads to reduction of ERV and FRC and alters the traction of the upper airway, which also contribute to the airway collapse. (96). There is a pathological reflex activation of muscles in the upper airways in patients with OSA compared to healthy subjects (97, 98). Anatomical factors, e.g. tonsillar hypertrophy, retrognathia, macroglossia and acromegaly as well as alcohol and sedatives also increase the risk of airway collapse (95, 99).

The presence and severity of OSA is dependent on weight (**Figure 1**) (100). A 10% weight gain leads to a 32% increase in AHI independently of baseline BMI and a six-fold increase in odds of developing moderate-to-severe OSA (101). The odds ratio for developing OSA with AHI>5 events/hour is 1.14 per increased BMI unit (102). Conversely, weight loss leads to a reduction of AHI (101, 103). The aggravation of OSA by weight gain has been shown to be greater than the improvement by weight loss (51). In Sweden, the mean BMI at initiation of continuous positive airway pressure (CPAP) treatment is 32 kg/m^2 (104).

The biochemical links between sleep, obesity and SDB are not fully understood. Leptin is a peptide hormone secreted from adipose tissue and is a key regulator of energy balance, and it acts on receptors in the hypothalamus to suppress appetite and increase metabolism (105). Leptin also stimulates ventilation (106). Plasma leptin levels are positively correlated to BMI (107) but the effect of leptin on appetite and on respiratory stimulation is decreased by central resistance to leptin in obese patients (108). Plasma leptin levels are higher in OSAS and OHS compared with weight-matched control subjects without sleep-disordered breathing (109, 110) and higher leptin concentrations are associated with a reduced respiratory drive and to a reduced response to hypercapnia in obese patients (111). Leptin resistance has been linked to hypoventilation and to the development of OHS (109, 112).

Leptin increases sympathetic outflow (113, 114). Subjects with insomnia have increased levels of circulating catecholamines (115, 116). Hence, weight gain may lead to sleep problems partly via the leptin and sympathetic pathways. Markers of systemic inflammation, such as Interleukin-6 and C-reactive protein, are increased in obesity (117). These markers have been proposed as mediators of sleepiness associated with obesity (118, 119).

The prevalence of OHS increases with increasing BMI (65, 67, 69, 72, 76) but there is no correlation between BMI and daytime hypercapnia (65). In fact, leptin levels are a better predictor of hypercapnia than degree of obesity (109). The pathophysiology behind OHS and the development of daytime hypercapnia is a complex interaction involving respiratory mechanics, upper airway resistance, down regulation of chemoreceptors, leptin resistance and bicarbonate compensation (120). Physiologic variation is gradually transformed into a disease.
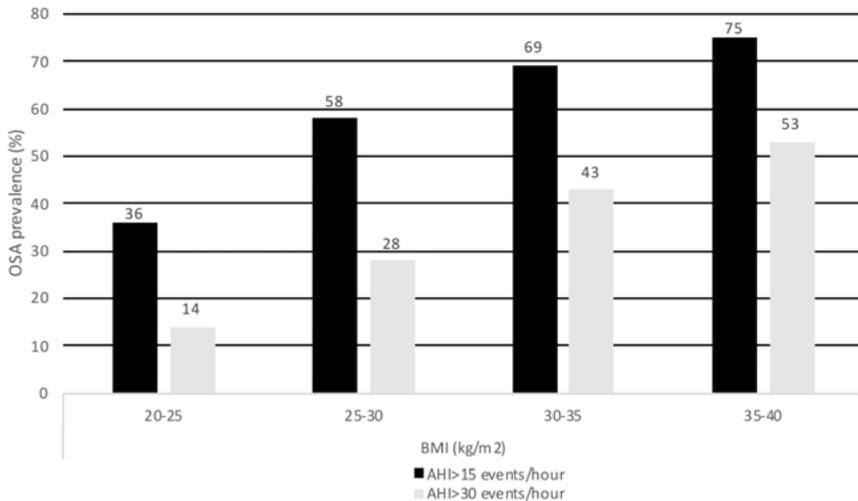
AHI = Apnea-hypopnoea Index; BMI = Body mass index; OSA = Obstructive sleep apnea

Figure 1. Modified from Ling, Sleep 2012 (100). OSA prevalence by BMI.

Diagnosis of SDB

The gold standard method for diagnosing sleep-disordered breathing is video supervised polysomnography (PSG). This is a complex and hence time- and resource-consuming investigation to measure sleep architecture and cardiorespiratory functions during sleep. It consists of electroencephalogram, echocardiogram, activity measurement in m. tibilalis anterior, oximetry, monitoring of snoring sounds, respiratory movements of thorax and abdomen, oronasal airflow and body position (53). It may also include continuous monitoring of $PaCO_2$ and oesophageal pressure.

Since SDB is very prevalent in the general population, sleep studies have had to be rationalised and simplified. To gain quantity without giving up better-than-acceptable quality, the routine examination in Sweden for diagnosing OSA is an over-night sleep recording performed in the patient´s home. It most often consists of at least registration of oro-nasal airflow, body position, pulseoximetry and respiratory movements of thorax and abdomen (121).

Total sleep time is estimated by use of the subject´s diary in conjunction with visual assessment of the overnight tracing. Obstructive apneas are defined as cessation of airflow in nasal pressure for at least 10 seconds with continuing abdominal and thoracic movements while hypopneas are defined as ≥50 % reduction in baseline airflow for at least 10 seconds in combination with oxygen desaturation of ≥3 %. AHI is calculated as the number of apneas and hypopneas per hour of sleep. Oxygen desaturation index (ODI) is calculated as the number of desaturations of ≥3 % per hour of sleep (58).

The definition of OHS includes raised daytime $PaCO_2$. Obese patients without raised daytime $PaCO_2$ but with raised base excess (BE) have an altered ventilatory response and lowered oxygenation nightly resembling patients with OHS (122) suggesting that several pathophysiological mechanisms have arisen before a manifest OHS with daytime hypercapnia has developed. A standard bicarbonate ≥27 mmol/l has a sensitivity of 88% for predicting OHS in obese patients with OSA (73). It has recently been suggested that an arterial BE >3 mmol/l or a standard bicarbonate >27 mmol/l (in the absence of another cause for a metabolic alkalosis) should be included in the definition of OHS (123) and not merely be used as a screening toll to identify patients with hypoventilation.

The severity of disease varies and several approaches to classify the severity of OHS have been proposed. The classification can be based on multiple variables such as $PaCO_2$, PaO_2, BMI, AHI, and presence of comorbidities (124) or by just using $PaCO_2$ categories (125). It has recently been proposed to divide hypoventilation in obesity into five stages: stage 0 (pure OSA), stages I/II (obesity-related sleep hypoventilation) and III/IV (awake hypoventilation, OHS) (126).

Misdiagnosing and diagnostic delay of OHS

OSA and OHS is often diagnosed late and when diagnosed, the patient has often suffered from significant metabolic and cardiovascular co-morbidities for several years and the burden of co-morbidities is even higher in patients with OHS than in those with OSA (127). Patients with OHS are much more likely to be hospitalised than equally obese controls in five years prior to the diagnosis and treatment of OHS. The consumption of hospital care is reduced when the patients receive treatment with LTMV (128). In cohorts of patients with OHS and $PaCO_2$ ≥6.0 kPa diagnosed at pulmonary wards and outpatient clinics, 29–42% are diagnosed in an acute instead of in a stable condition indicating that OHS is under-diagnosed (87-89, 92). In one cohort OHS patients with $PaCO_2$-values ≥6.7 kPa the proportion of patients starting PAP treatment non-electively was 70% (**Table 3**) (90).

Analysis of patients with full-blown OHS admitted to ICU units with acute hypercapnic respiratory failure underscores the high rate of misdiagnosing and

diagnostic delay of OHS. Of 173 consecutive patients with OHS, 65% had a previous ICU admission, only 9% had domestic PAP-therapy (93). The patients in a cohort of 61 patients with OHS had been hospitalised on average 6 times the previous two years and a majority had been misdiagnosed and managed as COPD or cardiovascular failure (CVF) when hospitalised. All of them had type-II diabetes. Only three patients were diagnosed with OHS before admission to hospital (94). In another series of 78 consecutive patients admitted to an ICU, an assessment with pulmonary function tests, echocardiography and polysomnography after 3 months showed COPD in 67% of the cases, but those without COPD were primary obese and 81% of them proved to have severe OSA. In those with COPD, 51% had severe OSA. Twenty-three of 78 (29%) patients had a known history of OSA, but only 7 of 23 (30%) were treated by continuous positive airway pressure or NIV at study inclusion (129).

Consequences of OSA

OSA is an independent risk factor for morbidity and mortality in cardiovascular disease (130-132). In cross sectional data, even after adjusting for severity of OSA, a higher prevalence of hypertension has been observed in those with OSA combined with daytime sleepiness compared to those without (133).

The development of cardiovascular disease is mediated via several mechanisms: direct effects of hypoxia, increased sympathetic activation, endothelial dysfunction, impaired glucose and triglyceride metabolism and increased systemic inflammation (134). OSA leads to micro-arousals and sleep fragmentation and as a consequence increased daytime sleepiness, impaired quality of life and an increase in sleepiness-related accidents (135).

Hormonal and metabolic changes in SDB

Obesity is the major determinant of insulin resistance (136) but there is also an independent association between OSA, insulin resistance and the development of diabetes (136, 137). In non-diabetic patients, there is a dose-response relationship between the severity of OSA and HbA1c-levels (138), insulin sensitivity (139) and presence of metabolic syndrome (140).

CPAP improves insulin sensitivity and the effect is rapid and can be detected after 2 nights of CPAP treatment (141). Weight loss is the most effective way to improve insulin resistance but CPAP in patients with OSA provides an incremental reduction (142). Still, large population-based studies on the effect of CPAP treatment on diabetes and pre-diabetes is missing.

Consequences of OHS

Since there is a continuum between OSA and OHS the pathophysiological mechanisms between OSA/OHS and cardiovascular diseases are partially the same (143). Patients with OHS have by definition worse blood gas values with hypercapnia and often also more hypoxia than patients with eucapnic OSA and they also have more pulmonary hypertension (66). Obesity combined with untreated OSA is associated with a worsened mortality rate compared with those with simple obesity (131, 132) and the morbidity and mortality as well as QoL are even worse among patients with OHS (66, 73, 76, 90). In an observational study, patients with OHS diagnosed at medical wards, had a mortality of 23% at 18 months compared to 9% in those with simple obesity (76). Cardiovascular co-morbidities are highly prevalent in patients with OHS and are the main factor predicting mortality in patients with OHS even under LTMV treatment (89). Subjects with OHS have more visits to physicians than those with simple obesity (128). Although there is an association between the severity of OSA and cardiovascular morbidity, a recent analysis of a Spanish cohort of 302 patients with OHS divided into tertiles by their ODI found the highest prevalence of cardiovascular disease in the group with the lowest ODI (144). A possible explanation of this unexpected finding was that those in the tertile with the highest ODI were younger than those in the other tertiles (57 ± 13 vs 64 ± 11 years).

Insulin-like growth factor-1 (IGF-1)

IGF-1 is a polypeptide mainly of hepatic origin and the secretion is dependent on growth hormone (GH) production from the pituitary gland and portal insulin exposure (145, 146). The release of GH is stimulated by growth hormone releasing hormone (GHRH) predominantly during slow-wave sleep (147). IGF-1 is an important mediator of the effects of GH and also has insulin-like effects with stimulation of protein synthesis and lowering of blood glucose. Serum IGF-1 concentration is low in obese subjects (148) and in patients with OSA (149) and is even lower in patients with OHS (150). It is furthermore associated with metabolic syndrome, insulin resistance (151, 152) and cardiovascular disease (153, 154). Increase in IGF-1 after CPAP treatment has been reported in some (155-161) studies while others have failed to identify such a relationship (162). However, the compliance to CPAP has only been considered in a minority of the previous studies (158).

Treatment of SDB

The rationale behind treatment of SDB is to prevent cardiovascular and metabolic complications and to decrease daytime impairment related to the-night time sleep difficulty. Since the etiology of SDB is multifactorial, the therapeutic options are also divergent.

Positive airway pressure (PAP) treatment in SDB

By applying room air under positive pressure via a nasal or an oro-nasal mask a pneumatic splint is provided, keeping the upper airways open (163). PAP is predominantly administrated via a nasal or an oro-nasal mask. The airway pressure can either be constant throughout the respiratory cycle, CPAP, or variating, bi-level PAP, with higher inspiratory positive airway pressure (IPAP) than the expiratory positive airway pressure (EPAP). PAP can also be delivered in a fixed or an auto-titrating mode. The difference between IPAP and EPAP is termed pressure support (PS) and correlates with the tidal volume, the ventilation increases with increasing PS. Non-invasive ventilation (NIV) refers to ventilation via a usually nasal or oro-nasal mask in contrast to invasive ventilation, which is applied via an endotracheal tube or via tracheostomy. NIV can be of many different modes, pressure support, pressure control, volume control or a combination of these (164). Long-term mechanical ventilation (LTMV) is a generic term including both invasive ventilation via tracheostomy and NIV.

OSA and PAP treatment

Treatment with CPAP is nowadays the most commonly used treatment for OSA and is regarded as the most effective treatment of especially moderate-to-severe OSA (56, 165, 166). Treatment with CPAP has an impact on respiratory, functional and sleep outcome by reducing airway obstructions and thereby preventing episodes of hypoxia. As a consequence, metabolic and cardiovascular effects of OSAS are reduced. Randomised controlled trials have shown effects of CPAP on surrogate endpoints such as hypertension (167, 168), endothelial function (169) and insulin resistance (170). Observational studies have shown effects of CPAP on cardiovascular diseases and on cardiovascular death (130, 171). However, CPAP therapy however has limited impact on cardiovascular risk in randomised controlled trials. CPAP has not shown any effect on cardiovascular outcome on the group level (172-176). When performing post-hoc analyses, those with CPAP-adherence ≥4 hours nightly displayed lower incidence of cardiovascular outcomes (173-175) but post-hoc analyses should always be interpreted with caution.

Treatment of obesity

A majority of patients with OSA would significantly reduce their AHI if they could lose weight (101, 103). Lasting weight reduction is difficult to obtain as it requires lifelong behavioural changes such as dietary modification and increased physical activity. Orlistat, a triglyceride lipase inhibitor is the only approved drug for weight reduction in Europe. It adds a modest effect on weight loss to the life style modification (177, 178). Bariatric surgery has proven to be the most effective way to treat morbid obesity, providing long-lasting reduction in mortality (179), reduction in development of obesity-related co-morbidities (180) and reduction in health care consumption (181).

Other treatment modalities of OSA

Avoidance of supine sleeping position can decrease sleep apneas in those with positional-dependent OSA (182). Use of alcohol (183) and tobacco smoking (184) aggravate OSA, and the consumption should be minimised. Treatment with mandibular advancement devices is an alternative to CPAP and is effective in patients with mild-to-moderate OSA and especially in women (185). Results from studies on surgical treatment of OSA including maxillomandibular advancement, pharyngeal surgery such as uvulopharyngopalatoplasty, laser-assisted uvulopalatoplasty and radiofrequency ablation are inconsistent and adverse events are commonly reported (186). Surgery is nowadays an infrequently used treatment option for patients with OSA. A novel treatment modality for OSA is electrostimulation of the hypoglossal nerve. Small studies suggest that those with OSA who are unable to tolerate CPAP can be successfully treated with upper airway stimulation (187, 188).

OHS and PAP treatment

Based on results from observational studies, Bi-Level PAP has been considered to be an efficient treatment to reduce morbidity and mortality and to improve daytime sleepiness and QoL in patients with OHS (85-87, 89, 189). The effect of positive pressure ventilation on $PaCO_2$-levels in patients with OHS has been shown to become significant after 4.5 hours use and its benefit plateaus between 5 and 7 hours of therapy (190). There are no randomised controlled studies focusing on mortality. In a small study the mortality rate in an average follow-up period of 50 months among patients with OHS who refused treatment with LTMV was 46% compared with 5.6% among those who tolerated NIV (85). This dramatic improvement of survival further underscores the importance of diagnosing and treating patients with OHS correctly.

Randomised controlled studies dealing with OHS are sparse and have short follow-up periods of 1–3 months (80, 88, 91, 92, 191, 192). Bi-level PAP has proven to be superior to lifestyle modification in improving daytime PaCO2

and daytime sleepiness (80, 91, 191). The majority of patients with OHS have coexisting OSA and the chronic hypercapnia is in varying degree a consequence of upper-airway obstruction. Hence, many patients with OHS can be successfully treated with CPAP. In two randomised controlled trials with a sample size of 36 and 60 patients respectively (92, 192), there was no difference in the treatment effect after 3 months while a recent Spanish RCT cohort consisting of 221 patients with OSA and AHI exceeding 30 events/hour and a follow-up time of two months showed that bi-level PAP was more effective in improving daytime $PaCO_2$ than CPAP (80). Another study from the same cohort showed decreased pulmonary artery systolic pressure, reduced left ventricular hypertrophy and improved 6-minutes walking distance in the Bi-level group but not in the CPAP group (193). An RCT in a cohort of 50 subjects with OHS and obesity class III showed no difference in outcome between treatment with volume-targeted NIV (AVAPS) and NIV with fixed pressure support after two months (88). A recent study with a small sample size gives support to the possibility of switching from NIV to CPAP after two months in patients with OHS with moderate to severe concomitant OSA (194).

NIV can be effectively used in patients with OHS and acute hypercapnic respiratory failure (AHRF) (93).

Adherence to PAP treatment

Adherence to PAP treatment in OSA is crucial. As many as 46–83% of patients with CPAP due to OSA have been reported to be non-adherent with a nightly use of CPAP of less than 4 hours (195). Early CPAP adherence (196, 197) and certain psychological traits such as self-efficacy (198-200) are strong predictors of long-term adherence. Socio-economic factors are also of importance (201, 202). The severity of OSA with more pronounced desaturations during sleep and more severe daytime sleepiness is associated with improved adherence to CPAP therapy (199, 200), but data relating to the impact of humidification (203-210), gender, age and BMI (171, 196, 211-222) on adherence are more conflicting (**Table 4**).

Table 4. *Impact of patient characteristics on adherence to CPAP therapy in patients with OSA.*

	Study population	Gender (Women)	Age	BMI	AHI (ODI)	ESS (baseline)	Hypertension
McArcle 1999 (211)	n=1211, FU 22 months	n.s.	n.s.	n.s.	+	+	
Janson 2000 (212)	n=103, FU 1.5–10 year	ns	-	ns	ODI +		ns
Pelletier-Fleury 2001 (213)	n=163, FU 887 days	-	n.s.	+	+	+	
Sin 2002 (214)	n=296, FU 6 months	+	+	n.s.	n.s.	delta-ESS +	
Budhiraja 2007 (196)	n=100, FU 30 days	n.s.	+	n.s.	n.s.	n.s.	
Kohler 2010 (215)	n=639, FU 3.9 year	n.s.	n.s.	n.s.	ODI +	n.s.	
Galetke 2011 (216)	n=303, FU 13 months	n.s.	n.s.	n.s.	+	+	
Gagnadoux 2011 (217)	n=1141, FU 504 days	n.s.	n.s.	+	+	n.s.	(CVD n.s.)
Campos-Rodriguez 2013 (171)	n=706 (females), FU 6.2 year		-	n.s.	n.s.	n.s.	n.s.
Schoch 2014 (218)	n=1756, FU 26 months	n.s.	n.s.	+	+	+	
Campos-Rodriguez 2016 (219)	n=357, FU 4 year	n.s.	n.s.	n.s.	+		+
Budhiraja 2016 (220)	n=558, FU 5–6 months	n.s.	+	n.s.	n.s.	n.s.	(CVD n.s.)
Eysteinsdottir 2017 (221)	n=796, FU 6.7 year	n.s.	n.s.	+	n.s.	+	
Nadal 2018 (222)	n=91 (PC)	+	n.s.	n.s.	n.s.	+	
	n=100 (SU) FU 6 months	n.s.	n.s.	+	n.s.	+	

CVD = Cardiovascular disease; FU = Follow-up; n.s.= non-significant; PC = Primary are setting; SU = Sleep unit setting

Impact of humidifier on adherence

Upper-airway symptoms, such as nasal congestion, rhinorrhoea and mouth dryness are common in patients with OSA on CPAP and are associated with CPAP failure (212, 223, 224). Several studies have shown that humidifiers causes a reduction in upper-airway symptoms in patients with OSA on CPAP (203-210) but only two of the listed studies have shown any improvement of adherence to CPAP treatment following use of humidifiers (**Table 5**) (203, 204). Despite lack of unambiguous evidence more and more OSA centres in Sweden nowadays have as a clinical routine to use an integrated humidifier as a part of the standard CPAP equipment (104).

Table 5. *Impact of humidifier on adherence to CPAP treatment.*

	Study population	Study design	Result adherence
Massie 1999 (203)	n=38, FU 8 weeks	Randomised crosso-ver design	Positive
Neill 2003 (204)	n=42, FU 3 weeks	Randomised crosso-ver design	Positive
Mador 2005 (205)	n=98, FU 1,3,12 months	RCT	n.s. but less nasal symptoms
Ryan 2009 (206)	n=125, FU 4 weeks	RCT	n.s. but less nasal symptoms
Worsnop 2011 (207)	n=54, FU 12 weeks	RCT	n.s. but less nasal symptoms
Ruhle 2011 (208)	n=44, FU 4 weeks	Randomised crosso-ver design	n.s. but less nasal symptoms
Kreivi 2016 (209)	n=561, FU 1 year	Those with nasal symptoms got humid-ifier (n=417)	n.s. but less nasal symptoms
Soudorn 2016 (210)	n=20, FU 4 weeks	Randomised crosso-ver design	n.s. but less nasal symptoms

FU = Follow-up; n.s. = Non-significant; RCT = Randomised controlled trial

National health care registries in Sweden

In Sweden, there is a long tradition of registering people. Since 1686, it be-came mandatory for the Swedish Church to keep parish registers, but the first documented regulation of a Swedish local population register administrated by the Church is from Västerås in the 1620s (225). This made it possible for the Swedish state to keep a population census and to conscript soldiers into the army. In 1749, "Tabellverket", was founded with the mission of compiling local parish registers, thereby enabling Sweden to start the world´s oldest still still-ongoing population statistics. In 1858, this mission was transferred to a new, still existing authority, Statistics Sweden (Statistiska centralbyrån) (226). In 1947, Sweden´s system of personal identity numbers started (227). In 1964, the National Board of Health and Welfare (Socialstyrelsen) started to collect information regarding in-patients at public hospitals, the National Patient Register (NPR), and registration became mandatory in 1987 (228). The National Board of Health and Welfare nowadays also has registries about e.g. cancer (since 1958), causes of death (since 1961), dental health (since 2008) and pharmaceuticals (since 2005). In 1975, the first national quality registry, the Swedish Knee Arthroplasty Register, started and currently there are 107 quali-ty registries in Sweden (229, 230). All this provides a prerequisite to perform-ing world-unique high-quality registry-based research.

Swedevox

Swedevox is a Swedish national quality registry (about 10 million inhabitants 2018) with four branches, with inclusion of patients with long-term oxygen therapy (LTOT), LTMV and CPAP due to OSA and children ≤ 18 years with respiratory insufficiency and need for support with either LTOT, LTMV, CPAP, tracheostomy and phrenic stimulation (104). The registry is administrated by the Swedish Society of Respiratory Medicine with financial support from the authorities.

Patients with LTOT and LTMV have prospectively been included in the registry since 1997 and 1 January 1996, respectively, with 100% geographical coverage and a population-based coverage of approximately 85–90% (230-232). The number of centres across Sweden reporting to the LTOT branch is 48 and the number reporting to the LTMV branch is 40. Patients treated with bilevel PAP to mobilise mucus and patients with OSA treated with bilevel PAP due to adherence reasons are not reported to the LTMV branch.

An increasing number of centres have prospectively included patients with OSA on CPAP into the registry´s CPAP branch since inclusion started in 1 July 2010. The geographical coverage is estimated at 90% and the number of reporting centres across Sweden is 37 in 2018.

Since 2015, children in need of respiratory support are reported into a separate branch of the registry. The number of centres reporting patients to the registry is 11. The number of prospectively registered patients is 25,754 for LTOT, 7,692 for LTMV, 65,407 for CPAP due to OSA and 105 children as of 5 March 2018.

Procedures for reporting patients with LTMV to Swedevox

At the start of treatment with LTMV, a physician or a delegated nurse from every centre prescribing LTMV fills in a standardized computerized form for every patient, with information including starting date of LTMV, gender, age, height, weight, arterial blood gas tensions when breathing air, spirometer values, score on the Epworth Sleepiness Scale (ESS) (52), primary diagnosis causing ventilatory failure and, when applicable, even secondary diagnosis, usage of concomitant oxygen therapy and type of ventilator interface. It is also recorded whether the LTMV is started under elective (planned visit for starting the treatment) or acute ("cannot wait until the next day") conditions. Vital capacity has been reported to the registry since 1996 but FEV1 was not included before 2004. Lung function values are expressed as a percentage of predicted (233). The registry contains no further details about how LTMV is performed or about AHI.

The primary and secondary diagnoses are grouped into the following clusters: "Hypoventilation due to obesity and/or OSA", "Restrictive thoracic disease", "Pulmonary disease", "Neurological disease", "Amyotrophic lateral

sclerosis (ALS)" and "Other". The "Restrictive thoracic disease" cluster is a merger of the three eligible diagnoses "Post-polio", "Scoliosis" and "Post-tuberculosis", while the "Pulmonary disease" cluster is a merger of the two eligible diagnoses "Chronic obstructive pulmonary disease (COPD)" and "Other pulmonary disease".

After one and three years, a follow-up form, including information about arterial blood gas tensions when breathing air, spirometer values, weight and whether or not LTMV treatment has been discontinued, is filled in. Possible reasons for discontinuation are non-compliance, no further need of LTMV, change to another form of treatment and death. A separate form for discontinuation can be filled in at any time after the one- and three-year forms.

Procedures for reporting patients with CPAP to Swedevox

When a patient starts CPAP treatment, information about gender, age, height and weight, AHI, oxygen desaturation index (ODI), Epworth Sleepiness Scale (ESS) score (52), the presence of hypertension and information about the use of a humidifier is registered. Body mass index (BMI) is calculated as the weight divided by the square of height (kg/m^2). At the scheduled one-year follow up, information on weight and actual ESS score is again reported to the registry. Adherence to CPAP treatment is documented as Yes/No and the mean time of CPAP use (hours/night) is registered. Patients discontinuing CPAP treatment are categorized as "CPAP no longer wanted", as "CPAP no longer needed" or as "Deceased".

Rationale for thesis

Pulmonary medicine is a medical discipline in flux. Worldwide obesity rates are increasing rapidly (6) as are the prevalence rates of morbidities associated with obesity. More and more patients with obesity-related respiratory disorders are taken care of by pulmonologists. Benign sleep disorders, insomnia symptoms such as difficulties initiating and maintaining sleep as well as having non-restorative sleep and early morning awakenings are associated with obesity (47), along with more severe sleep disorders, OSA and OHS (76, 100). Insomnia symptoms in general are associated with impaired QoL and daytime impairment and sleepiness (234). It is not clear to what extent the development of sleep problems is due to obesity and weight gain or to what extent other confounding factors are of importance.

OSA and OHS are associated with an increased cardiovascular morbidity and mortality (130-132) and high health care costs, especially when undiagnosed and untreated (235). The most preferred treatment of OSA and OHS is PAP therapy. It is previously known that more benign sleep problems are more prevalent in women whereas OSA is more prevalent in men. It is important to diagnose SDB and to initiate adequate therapy without unnecessary delay. However, diagnostic delay (94, 128) and suboptimal adherence to PAP therapy (195) are major clinical problems with potential devastating consequences and these issues need to be highlighted.

Aims of thesis

Paper I
To investigate the role of obesity and weight gain in the development of sleep problems in a population-based cohort.

Paper II
To investigate gender differences in patient characteristics and treatment effect in patients with obesity hypoventilations syndrome (OHS) on long-term mechanical ventilation (LTMV) and to study how the prescription of LTMV due to OHS has changed over time in a national registry-based cohort.

Paper III
To investigate the impact of adherence to CPAP treatment on IGF-1 concentration in patients with OSA in a clinical cohort.

Paper IV
To identify factors influencing adherence to CPAP treatment in patients with OSA and to estimate the mortality risk associated with the discontinuation of CPAP in a national registry-based cohort.

Statistical methods

Statistical analyses were performed using Stata 12.1 (paper I and II) and Stata 13.1 (paper III and IV) (StataCorp, College Station, TX, USA).
A p-value of <0.05 was considered statistically significant.

Continuous data were expressed as mean ± SD and frequency variables were presented as percentage.

For categorical variables, the differences between groups were compared with the χ^2- test (papers I–IV).

For continuous variables, the differences between two groups were compared with the Student´s t-test (papers II–IV) and the differences between more than two groups were compared with one-way analysis of variance (ANOVA) in combination with post hoc analysis with Bonferroni corrections (papers I and IV).

For dichotomous dependent variables, multiple logistic regression analysis presented as odds ratios (OR) with corresponding 95% confidence intervals (95% CI), was used to examine the statistical dependence between the outcome and suggested explanatory variables (paper I). In case of more than two possible discrete outcomes multinomial logistic regression analysis, presented as adjusted relative risk ratios (aRRR) with corresponding 95% CI, was used (paper IV).

Unadjusted (papers II and III) and multiple linear regression analysis (paper III) was used to examine the association between dependent continuous variables and independent or explanatory variables.

Risk of death and impact of explanatory variables was calculated using a multiple Cox's proportional hazard regression analysis (papers II and IV) presented as hazard ratio (HR) with corresponding 95% CI.

Kaplan-Meier curves were used to estimate survival function and a significance test for differences in survival function between groups was performed using a log-rank test (papers II and IV).

Ethics

Paper 1 and paper III were approved by The Regional Ethical Review Board in Uppsala and paper II and paper IV were approved by The Regional Ethical Review Board in Lund.

Material and methods

Paper I

A prospective, population-based cohort study.

Study population

Two cohorts in the municipality of Uppsala, Sweden, were assessed. Sleep and Health is an on-going cohort study focusing on the impact of sleeping habits and sleep disorders on health. The male cohort was first investigated in 1984 when 4021 men aged 30–69 years were randomly selected from the population registry for the Municipality of Uppsala, Sweden. All responders still alive 1994 (n=3201) were sent a postal questionnaire, with a response rate of 89.7% (n=2668): this constituted the baseline investigation in the present study. All responders still alive in 2007 (n= 2231) were sent a follow-up questionnaire with a response rate of 91.4% (n=2040).

The female cohort was first investigated in 2000 when a baseline postal questionnaire was sent to a random sample of women aged ≥20 years and living in the same area. Of the 7051 women who responded and who were still alive (n=6590) were sent a follow-up questionnaire in 2010 with a response rate of 80.5 % (n=5193). All men and women who had participated both at baseline and follow-up and who provided information about their height and weight on both occasions were included in the present study (n=7012).

Defining sleep problems

The participants were asked to grade, on a five-grade scale, how much trouble they had falling asleep at night, with wakening up during the night and with sleepiness at daytime. The response options were "none", "small", "moderate", "severe" and "very severe". If the subjects answered "severe" or "very severe", they were considered positive for difficulties in initiating sleep (DIS), difficulties in maintaining sleep (DMS), and excessive daytime sleepiness (EDS). The variable "insomnia" was defined here as either, or both, DIS and DMS in combination with EDS. In the subsequent analyses, subjects who developed DIS, DMS, EDS and insomnia were identified among those who did not report the respective sleep problem at baseline.

Paper II

A national registry-based cohort study.

Study population

Patients reported to the Swedevox registry with the primary diagnosis of "Hypoventilation due to obesity and/or OSA" with a BMI exceeding 30 kg/m^2 and with full information about weight and height were analysed further. Those who were reported to the registry as "Hypoventilation due to obesity and/or OSA" with a BMI 30 kg/m^2 (n=136) were regarded as non-OHS. Patients reported to the registry as "Hypoventilation due to obesity and/or OSA" without full information about weight and height were excluded from subsequent analysis (n=445). In the present study, we have analysed registry data from the time when LTMV was started and from the one-year follow-up (**figure 2**). The dates of death were obtained from the Swedish Population Registry. Dates of death up to 15 January 2015 were available. Gender differences in baseline characteristics, treatment effect and survival as well as over-all trends in prescription of LTMV to patients with OHS were then analysed.
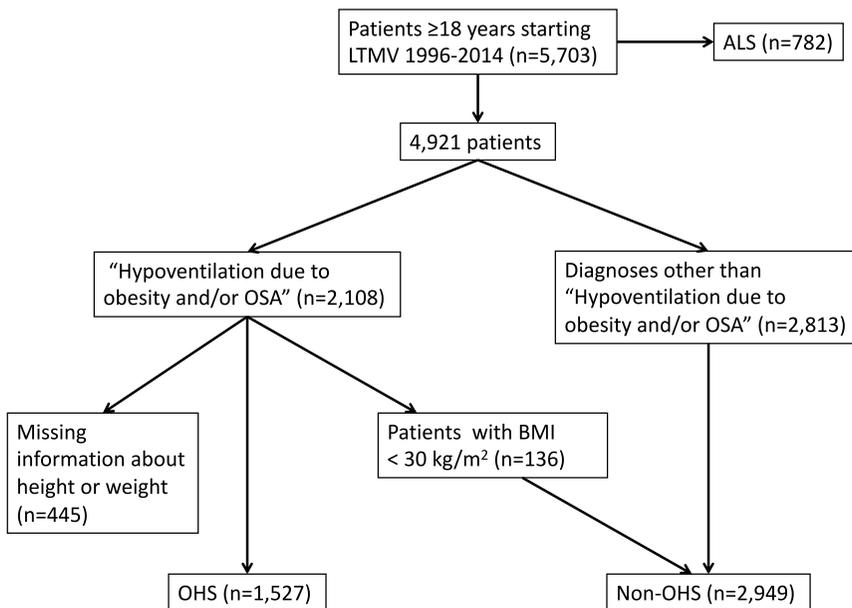
OHS=Obesity hypoventilation syndrome; LTMV=Long-term mechanical ventilation; BMI=Body mass index; ALS= Amyotrophic lateral sclerosis

Figure 2. Definition of study population.

Paper III

A longitudinal observational cohort study.

Study population

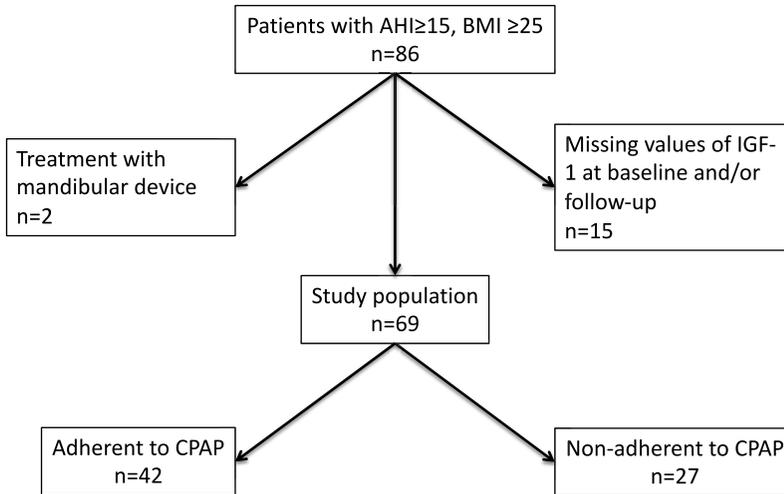In 86 patients diagnosed with moderate to severe OSA (AHI≥15 events/hour) at the sleep clinic of Uppsala University Hospital, serum IGF-1 concentrations were intended to be measured at initiation of CPAP treatment and at follow-up after 4.8±2.5 months. Data were collected from March 2010 to March 2012. Patients without information about IGF-1 at baseline and/or at follow-up (n=15) and patients with OSA treated with mandibular device because of inability to use CPAP (n=2) were excluded from subsequent analysis. The patients had been included consecutively into a study with the main purpose to evaluate the effects on OSA of a tailored behavioural medicine intervention program targeting physical activity and eating behaviour (236). Inclusion criteria were BMI≥25 kg/m^2 and a sedentary life-style with a self-reported leisure-time physical activity less than 30 minutes, 5 days a week. Exclusion criteria were symptomatic heart disease despite medication and participation in a current weight-reduction program. Approximately one month after initiation of CPAP treatment, there was a clinical check-up. If the patients had problems with their CPAP treatment, CPAP settings or CPAP interface were adjusted in order to optimize treatment comfort and compliance.

Compliance to CPAP treatment at follow-up was assessed based on self-reported information on mean number of nights/week and mean number of hours/night of CPAP usage. CPAP usage was categorised into following groups: "Non-adherent" defined as an average CPAP usage <4h/nightly and "Adherent" defined as an average CPAP usage ≥4 hours nightly" (195).

Information about CPAP usage was missing in 14 patients at the 6-month follow-up visit. Patients were considered adherent to CPAP if they were adherent at the first clinical visit to the CPAP nurse after 1 month and also at the long-term follow-up after the study completion at 28±7 months according to the medical records.

Weight and height were measured and BMI was calculated. The patients were asked about smoking habits. A structured interview was performed by the research nurse and the presence of former thromboembolic disease, diabetes types I and II, atrial fibrillation, hypertension, coronary disease, CVF, lung disease or stroke was recorded.

In total, 42 patients (61%) were categorised as adherent and 27 patients (39%) as non-adherent to CPAP treatment. Two of the non-adherent patients started to use CPAP immediately after the follow-up control and achieved at that time a compliance of ≥4 h/night. The overall CPAP compliance ratio in the whole group was hence 44/69 (64%) (**Figure 3**).

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                    ┌─────────────────────────┐
                    │ Patients with AHI≥15, BMI ≥25 │
                    │          n=86           │
                    └─────────────────────────┘
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Patients with AHI≥15, BMI ≥25
n=86

Treatment with
mandibular device
n=2

Missing values of IGF-1 at baseline and/or follow-up
n=15

Study population
n=69

Adherent to CPAP
n=42

Non-adherent to CPAP
n=27

AHI = Apnoea-hypopnoea index; CPAP = Continuous positive airway pressure; IGF-1 = Insulin-like growth factor-1

Figure 3. Definition of study population.

OSA was diagnosed by a single night's sleep recording using the Embletta™ type 3 portable monitor (Embla, Reykjavik, Iceland) or Breas SC 20™ (Breas Medical AB, Mölnlycke, Sweden). EDS was diagnosed using the ESS.

Chemical analysis

A fasting venous blood sample was taken for determination of total serum IGF-1 concentrations and Haemoglobin A1c (HbA1c). IGF-1was determined by using a commercial immunochemiluminescent assay, Liasion® (DiaSorin S.p.A, Saluggia Italy), which uses two monoclonal antibodies prepared against two different antigenic sites of IGF-1 molecule (237). HbA1c was analysed immunologically on a Cobas 6000 instrument with Tina-quant Hemoglobin A1c reagents (Roche Diagnostics, Mannheim, Germany).
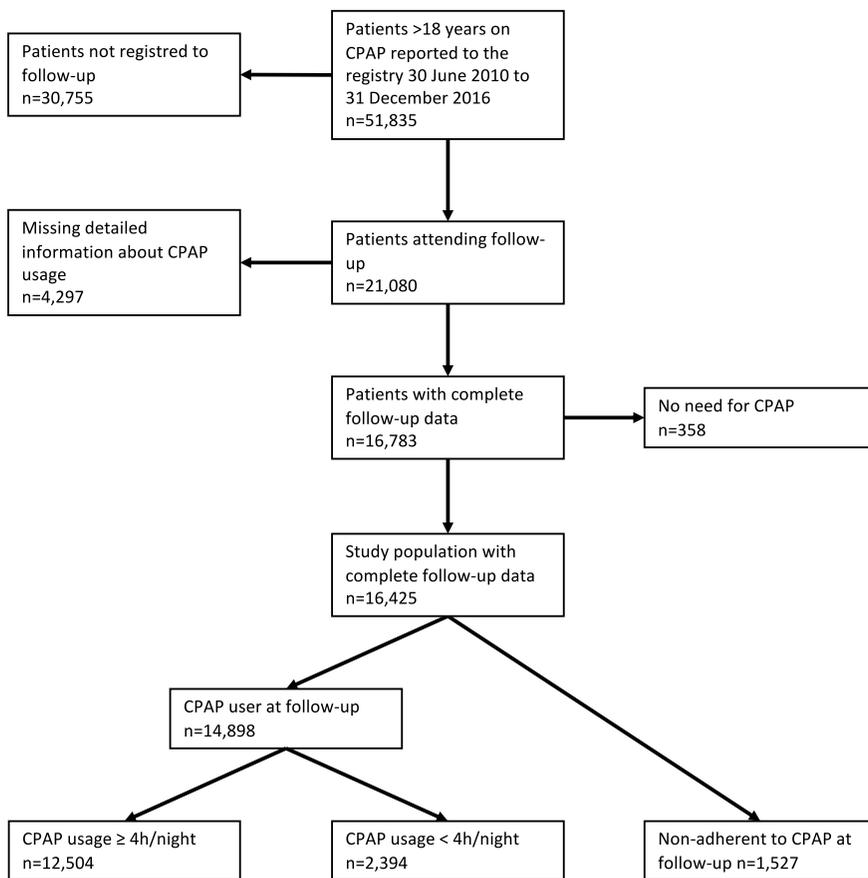
Paper IV

A prospective, population-based cohort study.

Study population

Those with complete information about CPAP use at the scheduled one-year follow-up visit were included. Baseline data from 1 July 2010 until 31 December 2016 and follow-up data until 10 March 2017 were analysed. Survival was assessed using the National Population Registry. No patient was lost to follow-up of survival. Those who had discontinued their CPAP treatment because of no further need for CPAP were excluded from subsequent analysis. The patients were divided into three categories based on their CPAP use, fully adherent with use ≥4 hours/night (200), partially adherent with use <4h/night and non-adherent.

Information on 51,835 patients was registered and 21,080 of them attended the follow-up visit after 1.2±0.8 year. Detailed information on CPAP use was missing in 4,297 patients and a further 358 were excluded from subsequent analysis since they had reported no further need for CPAP at the follow-up visit. Of the remaining patients, 12,504 were categorised as fully adherent (mean use 6.4±1.3 hours/night), 2,395 as partially adherent (mean use 2.5±1.1 hours/night) and 1,527 as non-adherent (**Figure 4**). A vast majority, 93.7% of the patients were treated with an auto-titrating CPAP, 5.1 % got a CPAP with fixed pressure levels, 1.0% got a bilevel PAP and 0.2% got adaptive servo-ventilation therapy.

Patients not registred to follow-up n=30,755

Patients >18 years on CPAP reported to the registry 30 June 2010 to 31 December 2016 n=51,835

Missing detailed information about CPAP usage n=4,297

Patients attending follow-up n=21,080

Patients with complete follow-up data n=16,783

No need for CPAP n=358

Study population with complete follow-up data n=16,425

CPAP user at follow-up n=14,898

CPAP usage ≥ 4h/night n=12,504

CPAP usage < 4h/night n=2,394

Non-adherent to CPAP at follow-up n=1,527

CPAP = Continuous positive airway pressure

Figure 4. Flowchart of study population.

Results

Paper I

The prevalence of DMS at baseline increased with increasing weight whereas the prevalence of DIS, EDS and insomnia were highest both among those who were underweight and those with obesity (**Table 6**).

Table 6. *Prevalence of sleep problems by BMI at baseline.*

	All	<20	20.1–25	25.1–30	≥30	p-value
DIS (n=6963)	7.3	8.6	6.8	7.1	10.2	0.020
DMS (n=6943)	13.5	12.0	12.4	14.8	17.6	0.001
EDS (n=6932)	11.7	16.0	11.1	11.1	13.4	0.003
Insomnia (n=6932)	3.6	4.7	3.3	3.6	4.5	0.249

DIS = Difficulties inducing sleep; DMS = Difficulties maintaining sleep; EDS = Excessive daytime sleepiness

The prevalence of all measured sleep problems and daytime sleepiness at baseline was higher among women than among men (**Figure 5**).
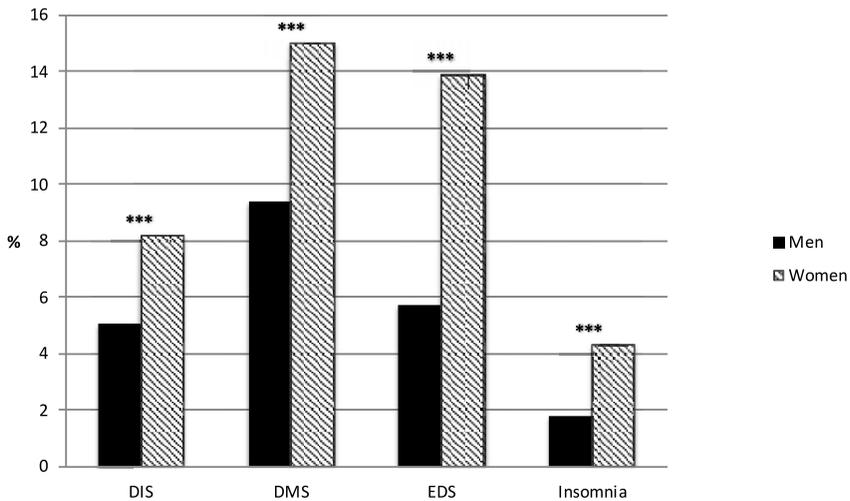
DIS = Difficulties inducing sleep; DMS = Difficulties maintaining sleep; EDS = Excessive daytime sleepiness

Figure 5. Prevalence of sleep problems at baseline by gender. *** n= p<0.001

There were U-shaped associations between weight gain and development of DIS, DMS, EDS and insomnia (**Figure 6**). The incidence of sleep problems and EDS was high within the group of participants who lost weight, but not as prominent as within the group who gained the most weight.
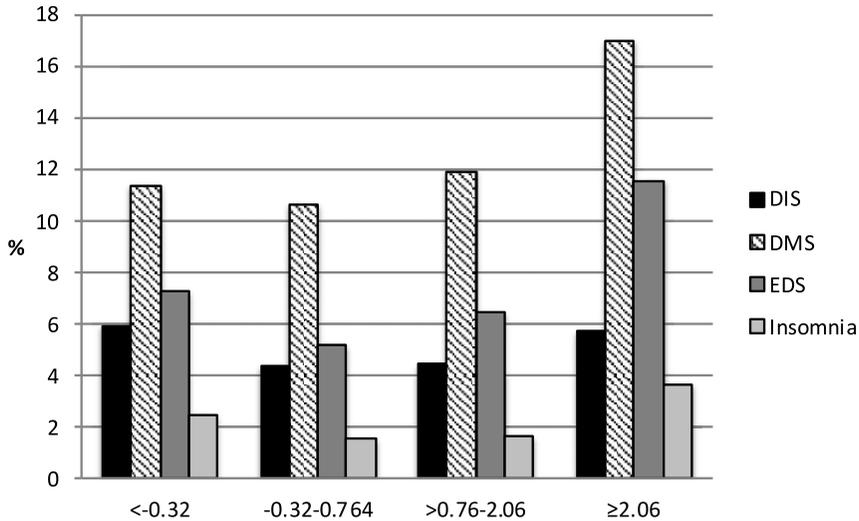
DIS = Difficulties inducing sleep; DMS = Difficulties maintaining sleep; EDS = Excessive daytime sleepiness

Figure 6. Incidence of new sleep problems by change in BMI. The participants are divided into quartiles: quartile 1 with Δ-BMI <-0.32, quartile 2 with Δ-BMI ≥-0.32 – <0.76, quartile 3 with Δ-BMI ≥0.76 –<2.06 and quartile 4 with Δ-BMI≥2.06.

In order to identify risk factors for development of sleep problems, a multiple logistic regression analysis was performed, adjusting for gender, BMI at baseline, age, physical activity, smoking, alcohol use, somatic disease and snoring (**Table 7**). There was an increased risk of developing DMS, EDS and insomnia among the subjects in the quartile with the highest rise in BMI. In contrast, there was no association between BMI at baseline and the risk of developing sleep problems. Ageing increased the risk of developing DIS, but reduced the risk of developing DMS, EDS and insomnia. Female gender was an independent risk factor for developing DMS. Gastro-oesophageal reflux disease (GERD) at baseline was a risk factor for development of all sleep problems, even after adjusting for confounders.

Table 7. *Odds Ratios (95% confidence interval (CI)) for developing sleep problems during the follow-up period after adjusting for gender, BMI-category at baseline, age, physical activity, smoking habits, alcohol dependence, comorbidities and snoring.*

Δ-BMI Quartiles	Incident DIS n=328	Incident DMS n=756	Incident EDS n=457	Incident insomnia n=328
<-0.32	1.28 (0.90–1.81)	1.08 (0.84–1.39)	1.47 (1.06–2.04)	1.71 (0.97–3.02)
-0.32–<0.76	1	1	1	1
0.76–<2.06	1.12 (0.78–1.61)	1.20 (0.94–1.53)	1.34 (0.97–1.86)	1.09 (0.59–2.00)
≥2.06	1.27 (0.89–1.81)	1.57 (1.24–1.98)	2.23 (1.64–3.02)	2.51 (1.48–4.27)

DIS = Difficulties inducing sleep; DMS = Difficulties maintaining sleep; EDS = Excessive daytime sleepiness

Paper II

Of the non-ALS patients who started LTMV treatment in Sweden between 1 January 1996 and 31 December 2014, 1,527 patients (47.4 % women) met the inclusion criteria for OHS (**Figure 2** and **Table 8**).

At the time of starting LTMV, women were generally older, more obese, more hypoxic, had more hypercapnia and higher base excess compared with men. Women had slightly higher vital capacity (VC) as a percentage of predicted but there were no gender differences in FEV1 of predicted or FEV1/VC values or ESS score at initiation. Women were also more frequently reported to have pulmonary disease as a secondary diagnosis and they had a higher frequency of concomitant oxygen therapy. In addition, the initiation of LTMV was more often non-elective in women (Table 6).

Table 8. Gender differences and baseline characteristics of OHS patients (BMI > 30 kg/m^2 and age ≥18 years) at initiation of LTMV between 1996 and 2014 in Sweden.

	Men (n=804)	Women (n=723)	p-value
Age (years)	60.1±12.1	64.4±11.2	<0.001
Body Mass Index (kg/m^2)	41.5±7.9	43.0±8.2	<0.0003
PaO$_2$ (kPa)	7.9±1.6	7.6±1.5	0.0001
PaCO$_2$ (kPa)	6.9±1.3	7.2±1.3	0.0004
Base Excess (mmol/l)	5.8±4.7	6.9±4.1	<0.001
VC (% of predicted)	64.3±19.9	67.3±21.0	0.0232
FEV$_1$ (% of predicted)	57.0±20.4	57.6±21.1	0.6517
FEV$_1$/VC (%)	70.0±16.1	71.6±18.7	0.1885
Epworth Sleepiness Scale (ESS)	10.4±5.4	11.2±5.8	0.0925
Pulmonary disease; COPD included (%)	168 (20.9)	201 (27.8)	0.002
Concomitant oxygen therapy (%)	83 (10.8)	129 (19.0)	<0.001
Non-elective initiation of LTMV (%)	287 (37.5)	298 (43.2)	0.026

OHS = Obesity Hypoventilation Syndrome; LTMV = Long-term mechanical ventilation; PaO$_2$ and PaCO$_2$ = Arterial oxygen and carbon dioxide tensions; VC = Vital capacity; FEV1 = Forced expiratory volume in one second; COPD = Chronic obstructive pulmonary disease

When analysing only the elective cases (n=871), women had a lower PaO$_2$ (7.8±1.4 vs. 8.2±1.6kPa, p= 0.002 and a higher PaCO$_2$ (6.8±1.1 vs. 6.6±1.2 kPa, p=0.0116) than men. In the non-elective cases (n=585), the absolute gender difference in PaO$_2$ (7.3 ±1.5 in women vs. 7.5±1.5 in men, P=0.109) and PaCO$_2$ (7.6±1.5 in women vs. 7.4 ±1.5 in men, P=0.215) persisted but it no longer reached statistical significance.

All arterial blood gas parameters improved on LTMV and the improvement in absolute figures showed no gender difference.

The overall five-year survival after the initiation of LTMV was 68.2% (95% CI, 63.6–72.3%) in men vs. 59.3% (95% CI, 54.2–64.0%) in women (**Figure 7**). After adjusting for age at the initiation of LTMV, we found no increased mortality in women, hazard ratio 1.07 (95% CI, 0.88–1.30).
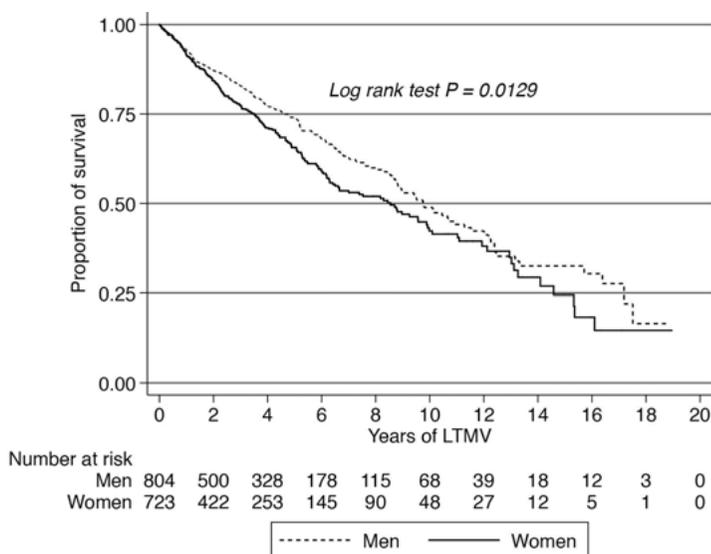
LTMV = Long-term mechanical ventilation

Figure 7. Kaplan-Meier survival curve for men and women with OHS on LTMV in Sweden 1996–2014

The prevalence of LTMV due to OHS increased steadily (p<0.001) and as of 2001 OHS is the major indication for LTMV in Sweden. The registry comprised 873 obese patients, 409 women and 464 men, with OHS at the end of 2014 (**Figure 8**). During the period, 387 of those with OHS who were on LTMV died and another 267 discontinued the treatment (due to unwillingness to continue treatment, n=156, no further need for treatment, n=88, change to some other form of treatment, n=17, or unknown reason, n=6). During the study period, the age of patients at the initiation of LTMV rose by 1.9 years/decade (P=0.048) in men and 3.4 years/decade (P=0.001) in women, but there were no significant changes in gender distribution (P=0.18) or BMI (P=0.425).
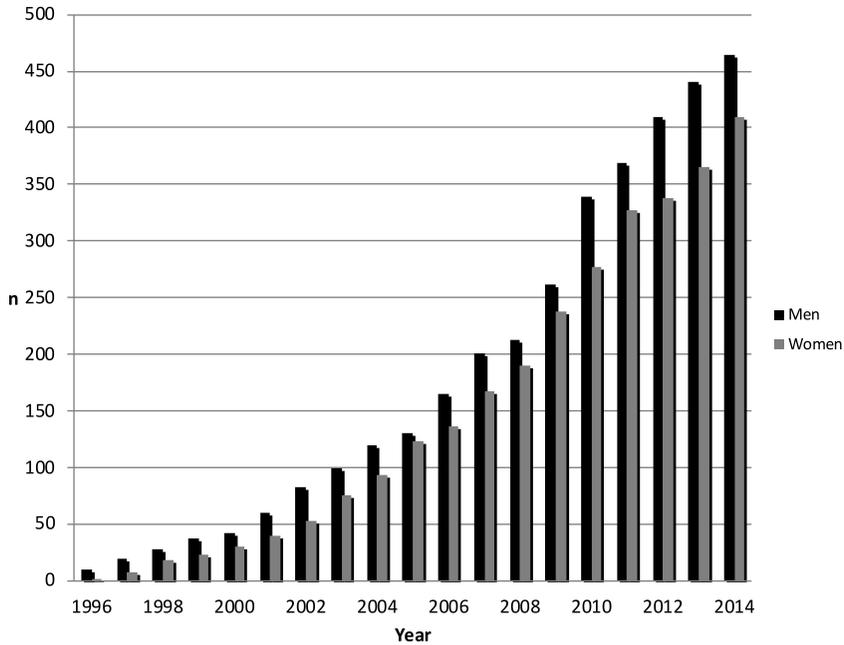
LTMV = Long-term mechanical ventilation

Figure 8. Men and women with on-going LTMV due to OHS in 1996–2014 in Sweden (464 men and 409 women in 31 Dec 2014).

Paper III

Complete data were obtained from 69 patients (men 86%, mean age 56±12 (range 29–79) years, mean AHI 43±21 (range 17–92), mean BMI 34.2±5.0 (range 26–48 kg/m^2)) (**Figure 3** and **Table 9**). There were no significant differences between CPAP-adherent and non-adherent patients in gender distribution, age, AHI, BMI, IGF-1 concentration, HbA1c concentration, ESS, smoking habits or comorbidities.

Table 9. *Baseline characteristics.*

	All n=69	Non-adherent to CPAP n=27	Adherent to CPAP N=42	p-value
Men	59(85.5)	24(88.9)	35(83.3)	0.4093
Age (years)	55.5±11.7	57.8±10.4	54.0±12.3	0.1869
AHI (events/hour)	42.6±21.3	37.3±21.1	46.0±20.9	0.0963
ODI3 (events/hour)	39.5±20.6	35.5±16.9	42.1±22.5	0.1917
BMI (kg/m^2)	34.2±5.0	33.9±5.3	34.3±4.9	0.7026
25–29.9 (kg/m^2, %)	14 (20.6)	8 (29.6)	6 (14.6)	0.326
30–34.9 (kg/m^2, %)	23 (33.8)	8 (29.6)	15 (36.6)	
≥35 (kg/m^2, %)	31 (45.6)	11 (40.7)	20 (48.8)	
ESS	12.3±4.5	11.6±4.2	12.8±4.6	0.2617
Smoking				
never smoker (%)	31(44.9)	11(40.7)	20(47.6)	0.517
ex-smoker (%)	27(39.1)	10(37.0)	17(40.5)	
smoker (%)	11.1(5.9)	6(22.2)	5(11.9)	
Comorbidities				
thromboembolic disease (%)	3(4.3)	0(0)	3(7.1)	0.156
type 1 diabetes (%)	1(1.45)	0(0)	1(2.4)	0.419
type 2 diabetes (%)	14(20.4)	8(29.6)	6(14.3)	0.122
atrial fibrillation (%)	2(2.9)	0(0)	2(4.8)	0.250
hypertension (%)	42(60.9)	15(55.6)	27(64.3)	0.468
coronary disease or CVF (%)	8 (11.6)	4(14.8)	4(9.5)	0.503
lung disease (%)	7(10.1)	5(18.5)	2(4.8)	0.065
stroke (%)	0(0)	0(0)	0(0)	
IGF-1 (µg/L)	131.7±44.4	129.9±50.0	132.8±41.0	0.7877
HbA1c (mmol/mol)	43.1±10.1	45.1±12.6	41.8±8.0	0.1945

AHI = apnoea hypopnoea index; CVF = Cardiovascular failure; OHI = oxygen desaturation index of 3%; ESS = Epworth sleepiness scale

At baseline, there was a negative association between IGF-1 and BMI and a positive association between IGF-1 concentration and mean saturation during the sleep recording (**Table 10**). No association was found between IGF-1 concentration at baseline and age, AHI, ODI3, HbA1c or ESS.

Table 10. *Univariate linear regression model with IGF-1 at baseline as dependent variable.*

Independent variable	β-coef	(95% CI)	P-value
Gender (man)	-4.9	(-35.4 – 25.6)	0.751
Age (year)	-0.5	(-1.4 – 0.5)	0.326
BMI (kg/m^2)	-2.1	(-4.2 – -0.03)	0.047
AHI (events/hour)	-0.2	(-0.7 – 0.4)	0.546
ODI3 (events/hour)	-0.2	(-0.7 – 0.3)	0.398
Mean saturation (%)	4.4	(0.1 – 8.8)	0.046
ESS	-0.7	(-3.1 – 1.7)	0.537
HbA1c (mmol/mol)	0.04	(-1.7 – 1.8)	0.960

AHI = apnoea-hypopnoea index; OHI3 = oxygen desaturation index of 3%; ESS = Epworth sleepiness scale

The mean time between initiation of CPAP treatment and the follow-up measurement of IGF-1 was 4.8±2.5 months. In the group, adherent to CPAP there was a mean rise in IGF-1 of 21.1 (95% CI: 13.1-29.2) µg/L at the follow-up compared to 4.7 (95% CI: -4.1–13.5) µg/L in the non-adherent group (P=0.008) (**Figure 9** and **Table 11**). At follow-up, the ESS score decreased more in those who were adherent to CPAP compared to those who were non-adherent. In the non-adherent individuals, there was a greater reduction of BMI and also in HbA1c compared to those who were adherent. A linear multivariate model showed an association between change in IGF-1 versus CPAP adherence and inverse associations between change in IGF-1 versus change in BMI and change in HbA1c (**Table 12**). No association was found between change in IGF-1 and gender, age, AHI, ODI3, mean saturation during night recording, BMI or ESS at baseline, change in ESS or participation in the tailored behavioural medicine interventional program.
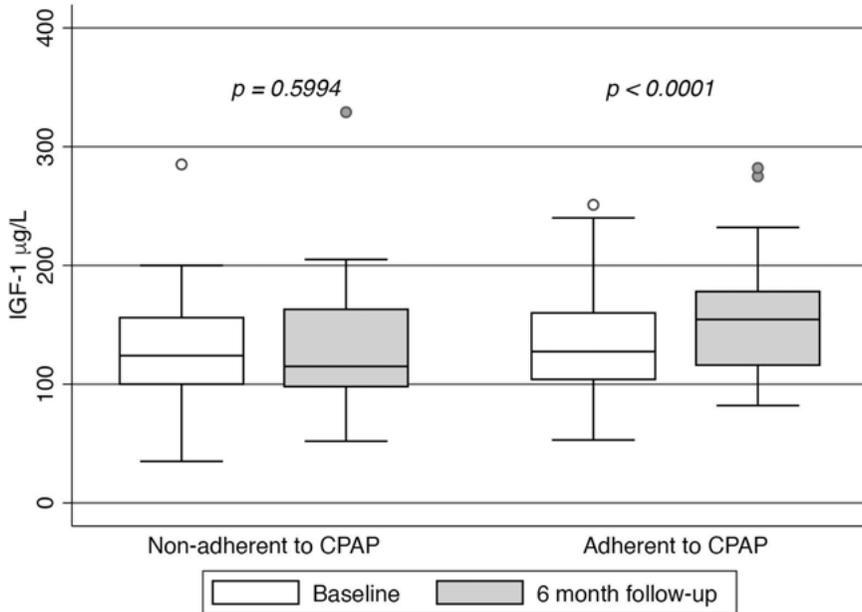
CPAP = Continuous positive airway pressure; IGF-1 = Insulin-like growth factor-1

Figure 9. IGF-1 at baseline and follow-up.

Table 11. *Characteristics at follow-up.*

	All n=69	Non-adherent to CPAP n=27	Adherent to CPAP n=42	p-value
Time to follow-up (months)	4.8±2.5	4.1±2.5	5.2±2.4	0.0728
CPAP usage/night (hours)	4.5±3.1	0.9±1.2	6.7±1.1	<0.0001
Change in IGF-1 (µg/L)	14.7±25.6	4.7±22.3	21.1±25.8	0.0083
Change in HbA1c (mmol/mol)	-0.2±3.5	-1.2±2.2	0.6±4.1	0.0430
Change in ESS	-4.9±4.8	-3.0±4.6	-6.2±4.5	0.0053
Change in BMI (kg/m^2)	-0.4±1.4	-0.8±1.3	-0.1±1.4	0.0252
Interventional program (%)	36 (52.2)	17 (63.0)	19 (45.2)	0.150

BMI = Body mass index; CPAP = Continuous positive airway pressure; ESS = Epworth sleepiness scale; HbA1c = Glycated Hemoglobin; IGF-1 = Insulin-like growth factor-1

In males (n=59), those adherent to CPAP (n=35) had an increase in IGF-1 of 23.3±27.2 µg/L compared to 3.5±22.7 µg/L (p=0.005) in those who were not adherent to CPAP (n=24). In women (n=10), those adherent to CPAP (n=7) had an increase in IGF-1 of 10.6±14.4 µg/L compared to 14.3±19.1 µg/L

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(p=0.74) in those who were not adherent to CPAP (n=3). Among those adherent to CPAP who had an ESS score < 10 (n=10, mean ESS 6.5±2.5), the mean increase in IGF-1 was 26.6±22.7 µg/L compared to 19.4±26.8 µg/L (p=0.4504) in those with ESS-score ≥10 (n=32, mean value 14.5±2.8].

Those adherent to CPAP with age > 50 years (n=26) had an increase in IGF-1 of 21.5±18.9 µg/L compared to 20.5±35.0 µg/L in those with age ≤50 years (n= 16, p=0.90). Those adherent to CPAP with a short period (<3 months) between initiation of CPAP treatment and the follow-up value of IGF-1 (n=5) had an increase of IGF-1 with 23.6±36.9 µg/L compared to 20.8±24.6 µg/L in those with a follow-up period≥3 months (n=37, p=0.824).

Excluding patients with diabetes (n=15) did not significantly change any of the results (data not shown).

Table 12. *Linear regression model with dependent variable "Change in IGF-1"*
* Adjusted for CPAP adherence and change in BMI. Independent variables are added separately

Independent variable	Unadjusted β-coef	(95% CI)	p-value	Adjusted* β-coef
Adherent to CPAP	16.4	(4.4 – 28.5)	0.008	21.8
Change in BMI (kg/m^2)	-5.0	(-9.4 – -0.7)	0.0025	-7.1
Gender	-3.5	(-21.1 – 14.1)	0.691	-6.1
Age (years)	-0.2	(-0.6 – 0.5)	0.945	-0.06
BMI (kg/m^2) at baseline	-0.6	(-1.9 – 0.6)	0.329	-0.6
AHI at baseline (events/hour)	0.1	(-0.2 – 0.4)	0.510	0.1
ODI at baseline (events/hour)	0.1	(-0.2 – 0.4)	0.702	0.1
Average saturation (%)	-1.5	(-4.0 – 1.1)	0.245	-1.4
ESS at baseline	0.07	(-1.3 – 1.5)	0.915	-0.5
Change in ESS	-0.8	(-2.1 – 0.4)	0.201	-0.3
Interventional program	-0.7	(-13.1 – 11.7)	0.914	-1.4
Change in HbA1c (mmol/mol)	-1.3	(-3.0 – 0.4)	0.140	-1.8

AHI = Apnoea-hypopnoea index; OHI = Oxygen desaturation index of 3%; ESS = Epworth sleepiness scale

Paper IV

At baseline, those who were non-adherent to CPAP treatment were more often female, younger, had lower AHI and ODI, had higher ESS score and had more seldom been prescribed a humidifier than those who were partially adherent and fully adherent to CPAP treatment (**Table 13**). In the cohort during the study period, the use of humidification at initiation of CPAP treatment increased linearly from 30% in 2010 to 72% in 2016. When comparing baseline data by gender, women who started CPAP treatment were older (60.6±11.2 vs 57.3±12.3 years, p<0.001), had a higher BMI (32.7±7.1 vs 31.8±5.7 kg/m^2 p<0.001) but a lower AHI (27.7±21.8 vs 33.8±22.4 events/hour, p<0.001) and

a lower ODI (31.6±22.5 vs 35.1±22.0 events/hour, p<0.001) than men. There was no statistically significant gender difference in ESS score (10.5±5.1 in women vs 10.4±4.9 in men, p=0.057) or in the presence of hypertension (54.3% in women vs 53.1% in men, p=0.17). Women were more often prescribed humidifiers (50.0% vs 45.0%, p<0.001). At baseline, those with hypertension were older (61.6±10.3 vs 54.5±12.8 years, p<0.001), had higher BMI (32.8±6.0 vs 31.3±6.2 kg/m^2, p<0.001), higher AHI (38.4±21.8 vs 34.8±22.1 events/hour, p<0.001), higher ODI (36.6±22.0 vs 32.2±22.3 events/hour, p<0.001), a lower ESS score (10.1±4.9 vs 10.8±4.9, p<0.001 and used humidifier more frequently (47.0 vs 44.7%, p=0.004) than those without hypertension.

Table 13. *Baseline characteristics. Results are presented as n (%) or as mean ± SD.*

n=16425	Fully adherent to CPAP (use≥4h/night)	Partially adherent to CPAP (use<4h/night)	Non-adherent to CPAP	p-value
Women	3592 (28.7)	692 (28.9)	505 (33.1)	0.002
CPAP use (hours/night)	6.4±1.3	2.5±1.1	0	
Age (years)	58.6±11.9	56.8±12.0	57.7±13.3	<0.001
BMI (kg/m^2)	32.0±6.0	32.4±6.5	31.8±6.6	0.006
AHI (events/hour)	38.1±22.1	33.6±21.7	29.3±20.3	<0.001
ODI (events/hour)	35.2±22.3	31.8±21.7	28.4±20.7	<0.001
ESS	10.6±4.9	10.0±4.9	9.6±5.0	<0.001
Hypertension	6201 (53.6)	1141 (51.9)	758 (54.3)	0.258
Humidifier	5865 (47.2)	1172 (49.2)	542 (35.8)	<0.001

CPAP = Continuous positive airway pressure; BMI = Body mass index; AHI = Apnea-hypopnea index; ODI: = Oxygen desaturation index; ESS = Epworth sleepiness scale

In a multinomial logistic regression model, female gender and presence of hypertension were associated with increased risk of becoming non-adherent to CPAP treatment while increasing age, more severe OSA with higher AHI and ESS scores and use of a humidifier were associated with lower risk of discontinuing CPAP treatment (**Table 14**).

Table 14. *Adjusted relative risk ratios (aRRR) for being partially adherent or non-adherent to CPAP treatment. Adjusted for all variables in the table.*

	Fully adherent to CPAP (use≥4h /night)	Partially adherent to CPAP (use <4h/night) (95% CI)	p-value	Non-adherent to CPAP (95% CI)	p-value
Female gender	1	0.99 (0.88–1.10)	0.796	1.28 (1.12–1.46)	<0.001
Age per 10 years	1	0.88 (0.84–0.92)	<0.001	0.87 (0.82–0.92)	<0.001
BMI per 5 units (kg/m^2)	1	1.09 (1.04–1.14)	<0.001	1.04 (0.99–1.10)	0.13
AHI per 10 units/hour	1	0.89 (0.87–0.92)	<0.001	0.80 (0.77–0.83)	<0.001
ESS	1	0.97 (0.96–0.98)	<0.001	0.96 (0.95–0.98)	<0.001
Hypertension	1	1.02 (0.92–1.13)	0.749	1.24 (1.09–1.42)	<0.001
Humidifier	1	1.11 (1.01–1.22)	0.032	0.57 (0.50–0.65)	<0.001

CPAP = Continuous positive airway pressure; BMI = Body mass index; AHI = Apnea-hypopnea index; ESS = Epworth sleepiness scale

An ESS score ≥ 11 associated with increased adherence (**Table 15**). BMI as a continuous variable did not independently influence adherence but the association between BMI and the risk of being non-adherent to CPAP treatment was U-shaped. In relation to the reference level of BMI<25 and BMI 25–34.9 was associated with greater adherence, whereas BMI ≥35 was not (**Table 15**). When stratifying for gender and hypertension in the multinomial logistic regression model all the results were consistent, apart from the presence of hypertension no longer being a risk factor for non-adherence in woman (data not shown). There was however no significant interaction between gender and hypertension in relation to the risk of becoming non-adherent to CPAP treatment ($p_{interaction}$=0.092).

Table 15. *Adjusted relative risk ratios (aRRR) of different BMI categories for being partially adherent or non-adherent to CPAP treatment. Adjusted for gender, age, AHI, ESS, presence of hypertension or use of humidifier.*

	Partially adherent to CPAP (use <4h/night) (95% CI)	p-value	Non-adherent to CPAP (95% CI)	p-value
BMI				
<25	1		1	
25–29.99	1.07 (0.88–1.31)	0.477	0.77 (0.62–0.96)	0.018
30–34.99	1.17 (0.96–1.43)	0.116	0.73 (0.58–0.91)	0.005
≥35	1.27 (1.03–1.56)	0.024	0.97 (0.77–1.22)	0.784
ESS				
<8	1		1	
8–10	0.84 (0.74–0.96)	0.012	0.85 (0.72–1.004)	0.056
11-15	0.78 (0.69–0.88)	<0.001	0.69 (0.59–0.80)	<0.001
≥16	0.75 (0.64–0.87)	<0.001	0.64 (0.53–0.79)	<0.001

CPAP = Continuous positive airway pressure; BMI = Body mass index; AHI = Apnea-hypopnea index; ESS: = Epworth sleepiness scale

In contrast to those who were fully adherent to CPAP treatment, those who were non-adherent to CPAP lost weight during the follow-up period. Patients in all groups experienced a decrease in daytime sleepiness and it was most pronounced in the group adherent to CPAP (**Table 16**). In those fully adherent to CPAP, 12 % still had excessive daytime sleepiness with an ESS score ≥ 11.

Table 16. *Change in BMI and ESS at follow-up. Results are presented as mean ± SD*

	Fully adherent to CPAP (use≥4h/night)	Partially adherent to CPAP (use<4h/night)	Non-adherent to CPAP	p-value
Delta BMI	-0.04±2.3	-0.11±2.6	-1.6±4.6	<0.001
Delta ESS	-4.8±4.8	-3.1±4.4	-3.1±4.5	<0.001
ESS ≥11 (%)	1,202 (11.9)	353 (19.0)	40 (19.6)	<0.001

BMI = Body mass index; CPAP = Continuous positive airway pressure; ESS = Epworth sleepiness scale

Between the scheduled follow-up visit and the end of the study period, 378 patients died, and 221 of them (1.8%) were adherent to CPAP, 44 (1.8%) were partially adherent and 113 (7.4%) were non-adherent (p<0.001). The median follow-up time in the mortality analysis was 2.4 years. In the multivariate Cox regression model adjusting for gender, age, BMI, AHI, ESS and the presence of hypertension, being non-adherent to CPAP at the 1-year follow up was associated with increased mortality, HR 1.73 (95% CI 1.30-2.29) compared with

those who were fully adherent. No difference was found between those who were partially adherent and those who were fully adherent (**Table 17** and **Figure 10**).

Table 17. *Hazard ratios (HR) for death after follow-up. Adjusted for all variables in the table.*

	Hazard ratio (95% CI)	p-value
CPAP usage		
Fully adherent (CPAP≥ 4h/night)	1	
Partially adherent (CPAP<4h/night)	1.12 (0.79–1.58)	0.523
Non-adherent	1.73 (1.30–2.29)	<0.001
Female gender	0.71 (0.55–0.92)	0.008
Age per 10 years	2.67 (2.34–3.03)	<0.001
BMI per 5 units (kg/m^2)	1.10 (1.00–1.22)	0.054
AHI per 10 units/hour	1.10 (1.03–1.16)	0.001
ESS	1.02 (0.99–1.04)	0.115
Hypertension	1.06 (0.83–1.36)	0.618

CPAP = Continuous positive airway pressure; BMI = Body mass index; AHI = Apnea-hypopnea index; ESS = Epworth sleepiness scale
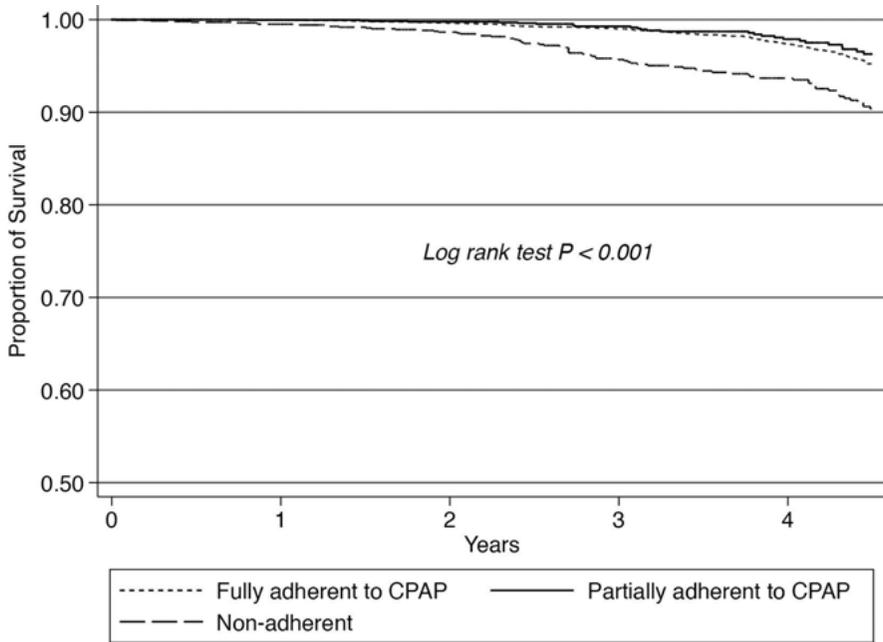
CPAP = Continuous positive airway pressure

Figure 10. Kaplan-Meier survival curve for patients with obstructive sleep apnoea on continuous positive airway pressure stratified by adherence rate; fully adherent with CPAP use ≥4 hours/night, partially adherent with CPAP use <4h/night and non-adherent.

Discussion

The main finding of paper I is that weight gain was an independent risk factor for development of DMS, EDS and insomnia, but not for developing DIS. At baseline, the prevalence of sleep problems increased parallel with BMI and underweight subjects also had a higher prevalence of DIS and EDS. The U-shaped association between body weight and sleep problems was consistent with findings from previous cross-sectional studies (35-40). The overall higher prevalence of sleep problems in women was in accordance with previous studies (33, 40, 43). In contrast to the results of some previous studies (41, 238), no longitudinal association was found between BMI-level at baseline and development of sleep problems. This may be due to sleep problems already being more common among obese subjects.

The relation between development of a new sleep problem and weight gain was U-shaped with the highest incidence among those who gained most weight and among those who lost weight. The association between underweight, weight loss and sleep problems is most likely linked with medical illness and health problems as sleep disorders and weight loss are often comorbid with medical and psychiatric conditions (32, 35, 40, 43, 239). The observed associations between heart disease, asthma, GERD and development of sleep problems further confirmed this.

Weight gain was associated with the development of insomnia. It is also known from previous studies that short and long sleep, insomnia and sleep problems are associated with obesity and weight gain (44-46, 48, 49). We therefore suggest that weight gain and sleep problems create a vicious circle.

The main finding in paper II is that women with OHS are older, more obese, have more deranged blood gases at the time of initiation of LTMV and also start LTMV more frequently in a non-elective situation than men. The prevalence of LTMV due to OHS is steadily increasing and patients who gain access to treatment have become older during the study period.

The finding that women have worse hypercapnia at initiation of PAP treatment is in line with the findings in a recent British study on 245 patients with OHS (53% men) where women had significantly higher $PaCO_2$ at diagnosis, men 6.3 ± 1.1 kPa vs women 6.9 ± 1.1 kPa (240). According to the Swedish Swedevox registry's CPAP branch, there is also a gender difference in patient characteristics in patients with OSA starting treatment with CPAP. Women are older, have higher BMI but have lower AHI (104).

In the present study, there was a slight predominance of men with OHS receiving LTMV. The prevalence of OSA is twice as high in men (4, 81-84) and approximately 90% of patients with OHS have coexisting OSA (66), while 9–22% of patients cohorts evaluated for OSA at sleep clinics have OHS (68-72, 74, 75). Studies on patients with OHS stratified by gender are sparse and many previous studies of OHS have been performed at sleep clinics on subjects with OSA, where men generally are over-represented. Despite the close link between OSA and OHS and the male predominance among patients with OSA, in several previous studies from sleep clinics, women appear to be proportionally more affected by OHS but statistical analysis has not generally been performed to confirm this (64-69, 71, 73-75). Furthermore, in studies performed outside sleep clinics, women appear to be at least equally affected by OHS as men (76, 80, 85-93).

The overall rate of initiation in an acute setting was 40%, which is in line with previous studies with a frequency of non-elective initiation of LTMV in 29–42% of cases (87-89, 92). One novel finding of study II is that women have a higher rate of non-elective initiation of LTMV than men and that they are older and have more severe disease when LTMV is started. This indicates that women with OHS are more often misdiagnosed until they develop full-blown OHS with acute illness. This conclusion is supported by the finding from two studies of consecutive patients with OHS admitted to ICU due to AHRF, where the proportion women were 77% (93, 94).

It is known from previous studies that patients with OHS are generally di-agnosed at a late stage and have often previously been misdiagnosed. In a study in which patients with obesity class II–III at an internal medicine unit were screened for OHS, only 20% of OHS patients had previously been diag-nosed and 40% required intensive care (76). In another study, 61 patients were diagnosed with OHS at an intensive care unit and all the patients had been admitted to hospital in the preceding 24 months an average of 6 ± 7 times, while 42 (68%) had been erroneously diagnosed with chronic obstructive pul-monary disease (COPD) without evidence of obstructive airway disease (94).

The main finding in paper III is that CPAP adherence ≥ 4 hours/night was associated with elevations of serum IGF-1 concentration, at least in males. This supports the result from a previous study of 78 patients (86% men) in which those adherent to CPAP (usage ≥ 4 hours/night) after 7.8 ± 1.3 months had an increase in IGF-1 in contrast to those who were non-adherent (158).

In either of these studies, no change in serum IGF-1 concentration was ob-served in females. However, these two studies with 9 and 11 females respec-tively were not powered to allow further conclusions about gender differences.

We found no association between change in IGF-1 and ESS at baseline or change in ESS. However, the patients were rather homogenous in regard to ESS score with an overwhelming majority with ESS scores >10 (72%) and ESS at baseline of 12.3 ± 4.5. The absence of association between IGF-1 and ESS could possibly be explained by the limited number of patients with low

ESS scores. In a previous study of 35 OSA patients with more pronounced diversity in daytime sleepiness, only those with sleepiness (mean ESS score 16) had a rise in IGF-1 after initiation of CPAP while no effect was seen in controls with similar OSA severity but a mean ESS score 4 (157).

In paper IV, several factors that influence CPAP adherence have been identified. The use of a humidifier at initiation of CPAP treatment was strongly associated with higher adherence to CPAP treatment. Other identified factors associated with CPAP adherence are directly related to patient characteristics and therefore cannot be influenced when starting treatment. Increasing age, more severe OSA with a higher AHI and ESS score, and overweight up to BMI 35 also associated with higher adherence, whereas female gender and coexisting hypertension were risk factors for discontinuation. The importance of treatment adherence is emphasised by the near doubling of the mortality rate in non-adherent patients.

Despite that previous studies have shown that humidifiers decrease upper airway symptoms in patients with OSA on CPAP, they have with few exceptions failed to show a positive effect on adherence (203-210). The size of the cohort in the present study is much larger than the sample sizes in the previous studies and these studies have hence probably been under-powered. The follow up time is also longer in the current study but that is probably of less importance since early adherence to CPAP is a strong predictor of long-term adherence (196, 197).

Studies of CPAP treatment stratified by gender are sparse. In paper IV, women starting CPAP treatment due to OSA were older and had a higher BMI but a lower AHI and ODI than men. These findings are in line with those of previous cohort studies (241, 242) and also with the results from study II, where women with OHS also were older and had a higher BMI at the initiation of LTMV. We also found that women were more frequently prescribed humidifiers. In the present study however, female gender was a risk factor for being non-adherent to CPAP treatment at follow-up. One potential explanation could be that caregivers, in the event of impending CPAP failure, may be more prone to change treatment from CPAP to treatment with mandibular advancement devices in women than in men. Treatment with mandibular advancement devices is an alternative to CPAP and is effective in patients with mild to moderate OSA and especially in women (185). Another possible explanation is that insomnia symptoms are associated with the discontinuation of CPAP treatment (221) and sleep problems are more prevalent in women than in men (43). In most previous studies, no gender difference in CPAP adherence in OSA patients has been detected (196, 211, 212, 215-218, 221) while other studies have found both a positive (214, 222) and a negative (213) association between female gender and adherence to CPAP. In line with our finding, a French study on 130 patients with OHS, female gender was a risk factor for NIV failure (87). In the present study, women were more frequently

prescribed humidifiers, which suggests that women have more problems getting used to their CPAP treatment than men.

Higher age is associated with better adherence to CPAP treatment. This supports what some previous studies (196, 214, 220) have shown although other studies have shown opposite result (171, 212) or no influence of age on CPAP adherence (211, 213, 215-219, 221, 222).

Those who were non-adherent to CPAP at follow-up lost weight, in contrast to those who were fully or partially adherent. A meta-analysis of 3181 OSA patients from 25 randomised studies found that CPAP treatment promotes significant increase in BMI and weight (243). Whether CPAP causes change in basic metabolic rate is under debate (244, 245). In a recent Finnish cohort study consisting of 1023 patients with OSA followed up after 6.6±1.2 years there was no significant weight change in the majority of patients with OSA treated with CPAP (241). One possible explanation of the increase in weight is that those who are adherent to CPAP treatment improve clinically and are then less motivated to modify their lifestyle than those with CPAP failure. The latter group might change their eating and physical activity habits and, as a result, lose weight.

A BMI between 25 and 34.9 was associated with better adherence to CPAP treatment. This U-shaped association has also been observed in a previous study with a smaller sample size (218). In line with previous studies, no association between BMI used as a continuous variable and adherence to CPAP treatment was found (171, 196, 211, 212, 214-216, 219, 220) but it has been observed when using BMI as a categorical variable (213, 217, 221). One plausible explanation of the U-shaped association is that those with marked obesity require higher CPAP pressures which influence the treatment comfort and adherence.

A higher AHI and a higher ESS score were associated with a lower risk of discontinuing CPAP treatment. The finding that more severe forms of OSA are associated with a lower risk of non-adherence is consistent with the findings in many previous studies (211-213, 215, 216, 218, 219, 221, 222). Those with a severe and symptomatic OSA have a greater chance of improving clinically as a result of treatment and are therefore more motivated to continue with CPAP. Nearly 12 % of those who were fully adherent to CPAP treatment experienced a residual excessive daytime sleepiness at follow-up. This is in line with a previous study by Pepin et al. (246).

Hypertension was a risk factor for not adhering to CPAP treatment. One possible explanation is that those with hypertension can be less motivated to undertake treatment. They might have been referred to a sleep clinic on their doctor´s initiative to a greater extent, simply because of the presence of hypertension and other cardiovascular diseases and not because of problems experienced with snoring and daytime sleepiness.

Even though PAP therapies have shown to have limited effect on cardio-vascular disease and cardiovascular mortality in randomised controlled studies (172-176), this study shows an increased mortality risk in those who are not adherent to CPAP. This is in line with previous observational studies which also have shown a reduction in mortality in patients with severe OSA who are adherent to CPAP treatment (130, 247).

Methodological considerations

The strengths of paper I were the longitudinal design, the size of the cohort, the long follow-up time and the high participation rates. BMI and the occurrence of sleep disorders were examined at both baseline and follow-up. However, some limitations should be considered when interpreting the results. The study population was pooled from two different cohorts, one with men aged 40–79 years with a follow-up after 13 years and one with women aged over 20 years with a follow-up after 10 years. All data were self-reported and over reporting of height and underreporting of weight are common (248), thus, associations between obesity and health conditions may be overestimated if self-reported BMI is used (249). However, it could be assumed that an underestimation of weight would influence BMI both at baseline and follow-up in the same direction and Δ-BMI, that is the main variable, would be less sensitive. Another weakness is the definition of insomnia that was based on responses on DIS, DMS and EDS in questionnaires. Although the insomnia variable was similar to the ICD10 definition of nonorganic insomnia, there was not enough information to rule out any known causative organic factor. As definitions of insomnia and sleep problems vary, the findings and prevalence rates are difficult to compare with other studies. In addition, the questionnaires did not include questions about psychiatric or psychosocial problems, which are associated with sleep problems (32, 238, 250) and depression and pharmacotherapy against psychiatric diseases are associated with change of weight (251, 252). Therefore, future studies should consider psychiatric and psychosocial aspects.

The strengths of the registry-based papers II and IV, are the uniquely large size of the cohorts, the length of the follow-up period and the high degree of completeness of data. The LTMV branch of the registry has 100% geographical coverage and the coverage of the CPAP branch of the registry is increasing and is estimated at 90 % at the end of the study period. No patient in papers II and IV was lost to follow-up, since mortality data was obtained from the Swedish national population registry. To the best of our knowledge, neither gender differences in patients with OHS or factors influencing adherence to CPAP therapy have not previously been evaluated in registry studies of this magnitude.

Some limitations should however be considered when interpreting the results. The patients with OHS in the registry might be non-representative of the

entire population of OHS patients since OHS is under-diagnosed and less severe cases of OHS can be treated with CPAP (192). We did not have access to additional data from medical records which makes it impossible to validate the quality of the reported data and to detect misclassification.

The fact that there are a limited number of variables that are reported to the registry is both an advantage and a disadvantage. Information about post-bronchodilatation spirometry values, AHI, presence of cardiovascular diseases and other comorbidities, smoking history, socio-economic data are for instance not reported to the LTMV branch of the registry but would, if information was available, have given paper II another dimension. The presence of hypertension was the only clinical variable, apart from BMI and severity of OSA (AHI, ODI and ESS) and length and weight, which was reported to the CPAP branch of the Swedevox registry at baseline. Paper IV would have been more informative if e.g. data about more cardiovascular co-morbidities were available. On the other hand, when designing a national quality register, a pragmatic approach is crucial when choosing which and how many variables that are to be included. If the registry becomes too extensive, the quality of reported data will be impaired and in addition, fewer patients will be reported in.

The strengths of paper III were the sample size and the fact that the study groups were stratified by CPAP adherence. When interpreting the results of this study, some limitations must be considered. This study was not randomised. It was not population-based with a subsequent risk of selection bias. Information about CPAP adherence was assessed based on self-reported information with a risk of over-estimation of CPAP usage. Non-adherent patients could have been misclassified as adherent CPAP users that would cause an underestimation of the difference in change in IGF between the groups. The results should also be interpreted with caution due to the low number of female participants. Power analyses revealed that at least 10 women in each group would have been needed to discard the hypothesis of a similar difference between adherent and non-adherent CPAP users in women as in men.

General discussion

In paper I, we showed an increased prevalence of sleep problems with increasing weight and that the weight gain itself is an independent risk factor for development of new sleep problems and daytime sleepiness. It is previously known that sleep problems cause weight gain (46-48). A vicious circle is created (**Figure 11**).
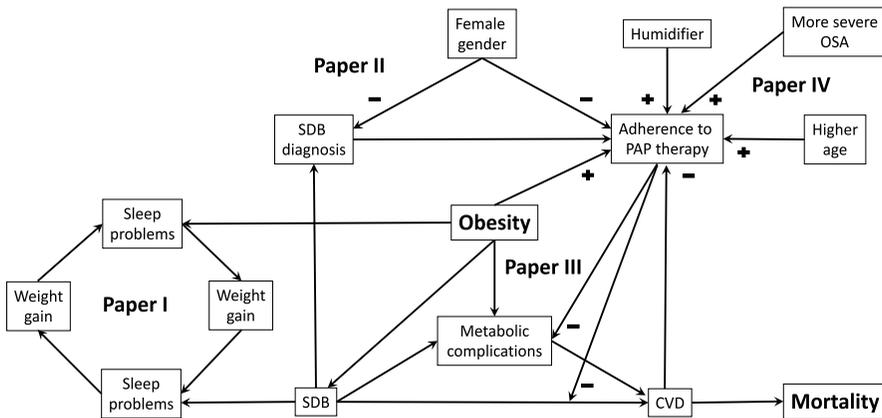
CVD = Cardiovascular disease; OSA = Obstructive sleep apnea; PAP = Positive airway pressure; SDB = Sleep-disordered breathing

Figure 11. Integrated model of the relation between obesity, weight gain, sleep problems, SDB, cardiovascular morbidity and mortality.

Men and women are created equal but papers I, II and IV show that men and women differ when it comes to sleep problems and sleep-disordered breathing. The prevalence of DIS, DMS, EDS and insomnia defined as either, or both, DIS and DMS in combination with EDS, was higher among women than among men and this finding is consistent with earlier studies (47, 253, 254). There was no apparent gender difference in risk of developing new sleep problems. Population-based studies have shown that both snoring (253) and OSA are more prevalent in men than in women (4, 62).

The underdiagnosing of OHS is a major clinical problem (87, 90, 93, 94, 129). In paper II, we showed that OHS is more advanced at diagnosis in

women and that women have higher BMI, are older and more often start treatment in an acute setting. Also, women with OSA are suggested to be underdiagnosed (255). They are older and have higher BMI at initiation of treatment than men (104). There is hence a more pronounced diagnostic delay in SDB in general in women (**Figure 11**). Fortunately, when patients with OHS eventually are diagnosed, there is no gender difference in outcome. A gender difference was also demonstrated in study IV. Female gender was identified as a risk factor for patients with OSA to become non-adherent to CPAP. Analogously, a previous French study on patients with OHS on NIV has shown that women have lower long-term adherence than men (87). This suggests that also the gender difference in adherence demonstrated in study IV can be generalised to all SDB on different modes of PAP therapy (**Figure 11**).

Women are less affected by OSA than men (4) and women with OSA have a lower AHI at initiation of CPAP treatment (104). Also, in women with OHS, the OSA component is less pronounced. In two recent studies from Spain on 307 patients from an OHS cohort, 56% were females in those with a coexisting severe OSA (AHI $\geq$ 30 events/hour) compared with 79% in those with OHS and AHI <30 events/hour (80, 91).

There are hence two different phenotypes of OHS which differ in the way they come to clinical attention. (**Figure 12**). In those with a burden of concomitant severe OSA, men are overrepresented. Those patients present with a clinical picture persisting of classical OSA symptoms such as headache, nycturia, and different daytime symptoms, i.e. sleepiness and attention, concentration or memory impairment and OHS is diagnosed at sleep clinics. The other phenotype lacks a severe OSA component and is dominated by women. They are more often diagnosed after an episode of acute respiratory failure at medical wards or at ICU with a clinical picture of full-blown OHS with hypoxia, fluid retention and right heart failure. Physicians might have a stereotypic picture of OHS patients as an obese, snoring, elderly man. Women may not match this stereotype, leading to no blood gas analysis or sleep recording being performed with a delayed or even worse, a missed diagnosis of OHS as a consequence. Besides the doctor´s delay in the diagnosis of OHS in women, there might also be a more pronounced patient's delay in women than in men.

AHI

Men

Women

Severity of OHS at diagnosis
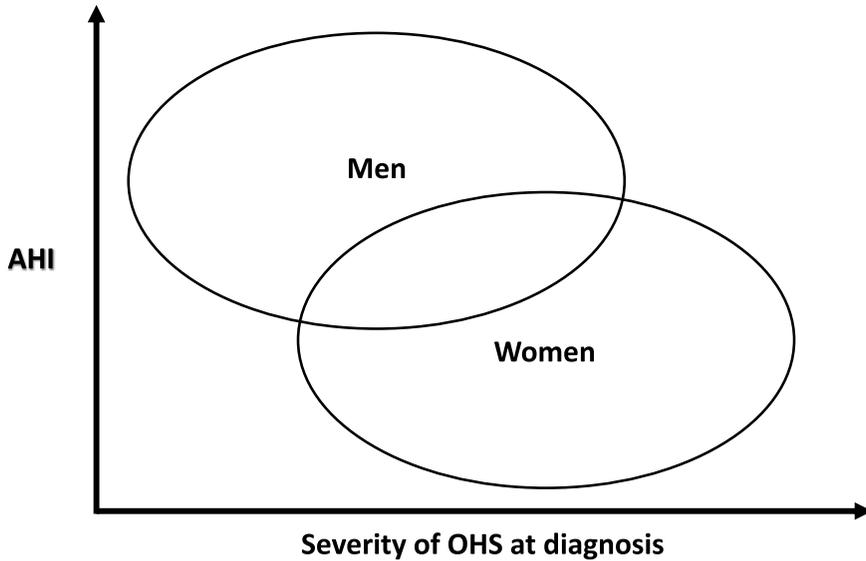
AHI = Apnea-hypopnoea index; OHS = Obesity hypoventilation syndrome

Figure 12. Schematic picture of the gender differences and the different phenotypes of OHS.

The importance of adherence is evident in paper III, where those who were adherent to CPAP treatment had an increase in IGF-1. CPAP reduces airway obstructions and prevents episodes of hypoxia and as a consequence, adverse metabolic and cardiovascular effects of OSA are reduced (**Figure 11**). The sleep quality improves and the amount of slow-wave sleep increase which in turn might explain the increase in IGF-1. IGF-1 can be regarded as a surrogate marker for successful treatment of OSA. On the other hand, decreased IGF-1 is associated with impaired glucose metabolism (151, 152) and with cardio-vascular diseases (153, 154), suggesting that decreased IGF-1 in patients with OSA and OHS not only is a consequence of SDB but also constitutes an im-portant pathway for the increased cardiovascular risk. IGF-1 and the somato-tropin axis have also been suggested to have effects on the ventilatory drive and respiratory muscle function implying that low IGF-1 also may have a pathophysiological role in the development of OHS (150). Our results under-score that adequate adherence to treatment is crucial for a favourable outcome for CPAP treatment. Those with the greatest improvement of IGF-1 after ini-tiation of CPAP may be those who benefit most from CPAP in a metabolic and a cardioprotective perspective. The role of IGF-1 as a biomarker of SDB, as a potential mediator of metabolic and cardiovascular complications of SDB as well as its potential role in the pathogenesis of SDB must be more thor-oughly examined. It is suggested that future longitudinal studies designed to

evaluate the effect of CPAP on cardiovascular morbidity and mortality should include analysis of IGF-1 to clarify this issue. It is also important that future studies in this field ensure a sufficient number of female patients as well as a wide distribution of daytime sleepiness severity.

The importance of adherence is further underscored in paper IV, where those who were non-adherent to CPAP had almost doubled mortality.

The previously demonstrated reduction of CPAP-associated upper-airway symptoms by humidifiers (203-210) and clinical experience made the finding that humidifiers promote adherence to CPAP expected. During the study period, the percentage of patients reported to the Swedevox registry with a humidifier from start of treatment has increased from 30% to 72% (104). The use of a humidifier also varies across hospitals, with a spread from 16% to 100% in 2016. It is possible that low usage of humidifiers at some centres is associated with other factors influencing CPAP adherence negatively, such as infrequent provider follow-up (165). This study makes the clinical routine, in which a majority of patients with CPAP due to OSA should be prescribed an integrated humidifier as a part of the standard CPAP equipment, evidence based. As expected, those with more severe OSA had better adherence to CPAP. BMI up to 35 kg/m^2 was also associated with better adherence. One plausible explanation is that those with obesity class II and above require higher CPAP pressures, which influence the treatment comfort and adherence. Severely obese patients with impending CPAP failure might have better adherence to Bi-level PAP.

Obesity and weight gain are thus risk factors for the development of many sleep problems and especially for the development of SDB. Healthcare and society in general should focus even more on the struggle against the "obesity pandemic". Reflecting the potential presence of gender differences in clinical pictures or in treatment outcome are not limited to sleep problems and SDB but should be considered in every patient interaction and also in future research.

Conclusions

Paper I
Weight gain but not obesity is an independent risk factor for developing several sleep problems and daytime sleepiness.

Paper II
The diagnosis of OHS is more delayed in women and the disease is more advanced when diagnosed. In spite of this, there is no gender difference in survival rate in patients with OHS treated with LTMV. More and older patients with OHS nowadays gain access to LTMV.

Paper III
CPAP usage ≥4 hours/night is associated with increased serum IGF-1 concentration at least in male patients with OSA.

Paper IV
Use of humidifier is associated with greater adherence to CPAP treatment. Other protective factors are increasing age, more severe OSA and overweight up to BMI 35, whereas female gender and coexisting hypertension are risk factors for discontinuation. Failure to adhere to CPAP is associated with increased mortality.

Clinical implications

- The presence of overweight and weight gain should be considered when treating patients with sleep disorders.

- It is important to be aware of gender differences when dealing with patients with sleep problems and SDB

- OHS is underdiagnosed and diagnosed late. It is important to have a high degree of suspicion and to have a low threshold for performing blood gas analysis and sleep recordings when meeting obese patients, especially women.

- All patients with CPAP due to OSA should be prescribed an integrated humidifier as part of standard CPAP equipment.

- Female gender and presence of hypertension are risk factors for CPAP failure in patients with OSA.

Future perspectives

The Swedevox registry is unique in the world and it has a very high geographical coverage and a high degree of completeness. This gives unique possibilities for following these patient groups over time. Paper II and IV were based on data from the Swedevox registry. Despite the uniquely large size of the registry and the high quality of data, the number of studies based on LTMV patients from Swedevox is limited (232, 256-261). Paper IV was the first published study from the registry´s CPAP branch.

To assure a high degree of completeness, the number of requested variables to be reported into the registry has deliberately been minimised. This limits the scientific usefulness of the registry with its uniquely large patient cohorts. The solution is to link the Swedevox registry with other national registries. This is possible in Sweden and in a few other countries due to the system of personal identity numbers allowing identification of individuals in any national registry. Work with this has already begun and a database is under construction by merging the Swedevox registry with the health care registries National Diabetes Registry, the Swedish Intensive Care Registry, the Swedish Palliative Care Registry, The Swedeheart Registry, RiksHIA (Intensive Cardiac Care Registry), RiksStroke (Stroke Registry) and the governmental registries Swedish Cancer Registry, Cause of Death Registry, the Drug registry, the National Patient Register, Statistics Sweden and the Dental Health Registry. A matched population-based control group will also be created.

The aim is to examine the disease course and risk factors for incident disease, impaired QoL, hospitalisation risk and mortality in patients with chronic respiratory insufficiency with LTOT or LTMV and in patients with OSA with CPAP.

Examples of research questions:

What is the impact of drugs, co-morbidities and socio-economic factors?

What is the impact of sleepiness in patients with OSA?

Are there gender differences?

LTMV in patients with COPD is controversial and can be examined.

Summary in Swedish – sammanfattning på svenska

Lungmedicin är en specialitet i förändring. Det pågår en global fetmaepidemi och fler och fler patienter med överviktsrelaterade andningsbesvär tas om hand inom specialiteten. I Sverige har andelen vuxna med fetma med ett BMI ≥30 ökat från 5 % till 14 % mellan 1980 och 2015. Andelen personer som klassificeras som överviktiga med BMI ≥25 var 2015 42% av männen och 29 % av kvinnorna. Parallellt med detta ökar folksjukdomar kopplade till fetma såsom hjärt-kärlsjukdomar och diabetes.

Mera godartade sömnstörningar, som att inte kunna sova utan nattliga uppvaknanden är också kopplade till övervikt och så även allvarliga sömnrelaterade andningsstörningar (SDB), obstruktiva sömnapnéer (OSA) och som namnet antyder, fetmarelaterad underventilation (OHS). Sömnstörningar är associerade med sänkt livskvalitet och dagtrötthet och OSA och OHS även med en ökad förekomst av diabetes och en ökad sjuklighet och dödlighet i hjärt-kärlsjukdom. Insulin-lik tillväxtfaktor-1 (IGF-1) är en viktig mediator av effekten av tillväxthormon och har också blodsockersänkande egenskaper. Nivåerna är låga hos överviktiga personer och hos personer med OSA. Låga nivåer är också associerade med förstadier av diabetes och hjärt-kärlsjukdom. Behandlingen för OSA är företrädesvis övertrycksandning via näsmask (CPAP) medan svårare fall av OHS behandlas med hemrespirator.

Sedan tidigare är det känt att mer godartade sömnstörningar är mer vanliga hos kvinnor medan OSA är vanligare hos män. Det är viktigt att utan onödigt dröjsmål diagnostisera OSA och OHS och sätta in adekvat behandling. Fördröjd diagnostisering av dessa tillstånd och dålig följsamhet till behandling är stora kliniska problem som behöver belysas.

Studie I syftade till att utvärdera vilken roll övervikt och viktuppgång har för utveckling av sömnstörningar. Här svarade 1896 män och 5116 kvinnor på enkäter vid studiens början och vid uppföljning efter 10 till 13 år. Förekomst av sömnstörningar utvärderades genom frågor rörande insomningssvårigheter, nattliga uppvaknanden, tidiga morgonuppvaknanden och dagtrötthet och störfaktorer utvärderades genom frågor rörande alkohol- och tobaksbruk, motionsvanor, andra sjukdomar och snarkning. Studiepersonerna fick också uppge längd och vikt.

Studie II syftade till att kartlägga könsskillnader hos patienter med OHS som påbörjar hemrespiratorbehandling och att studera hur förskrivningen av

hemrespirator vid OHS har förändrats över tid. Data på 1527 patienter som påbörjat behandling med hemrespirator för OHS mellan 1996 och 2014 hämtades från det svenska nationella kvalitetsregistret Swedevox.

Studie III syftade till att undersöka vilken effekt följsamhet till CPAP-behandling har på förändring av serumkoncentrationen av den insulinlika tillväxtfaktorn IGF-1. IGF-1-koncentrationen i serum mättes vid behandlingsstart hos 69 patienter och vid uppföljning efter i genomsnitt 5 månader. De följsamma patienterna (42 stycken) med en CPAP-användning på ≥4 timmar per natt jämfördes med de, som hade en användningstid på mindre än 4 timmar (27 stycken).

Studie IV syftade till att identifiera olika faktorer som påverkar följsamhet till CPAP-behandling hos patienter med OSA och att undersöka om de som inte var följsamma till behandlingen hade en ökad risk att dö i förtid. Data på 16 425 patienter, som påbörjat CPAP-behandling och med en inrapporterad uppföljning efter i genomsnitt 1,2 år, hämtades från Swedevox-registret.

Viktuppgång i sig är en oberoende riskfaktor för utveckling av flera sömnstörningar som nattliga uppvaknanden och tidiga morgonuppvaknanden samt dagtrötthet. En ond cirkel uppstår - sömnstörningar vet man sen tidigare ge viktuppgång och vi har nu visat att viktuppgång leder till nytillkomna sömnstörningar.

Kvinnor med OHS är vid behandlingsstart med hemrespirator äldre och har högre BMI än män. Kvinnor med OHS har också en mer långt gången sjukdom och påbörjar oftare behandlingen under akuta omständigheter istället för att det sker planerat. Sedan tidigare vet man att kvinnor inte har lika mycket sömnapnéer som män. Detta gäller också hos kvinnor med OHS. Kvinnor uppvisar alltså en annan klinisk bild vid diagnostillfället och behandlingsstart vilket delvis kan förklara den senare satta diagnosen. Personal inom vården måste bli mer medvetna om att OHS är en underdiagnostiserad sjukdom, framför allt hos kvinnor, och anstränga sig hårdare för att hitta dessa fall tidigare och inleda behandling. I Studie IV visade vi att kvinnor har en ökad risk att avsluta sin CPAP-behandling mot OSA jämfört män.

I tidigare studier har man sett att kvinnor med OSA är äldre och har högre BMI vid behandlingsstart samt att de kan vara mer underdiagnostiserade än män. I en studie har man också sett att kvinnor med respiratorbehandling mot OHS också oftare avslutar sin behandling än vad män gör. Resultaten från studierna II och IV skulle kunna generaliseras till att gälla patienter med sömnrelaterade andningsrubbningar i stort: Kvinnor med SDB diagnostiseras senare än män och är sjukare vid behandlingsstart och de har dessutom en sämre följsamhet till CPAP och hemrespirator.

Antal patienter som startar behandling med hemrespirator mot OHS ökar för varje år under studietiden och allt fler och allt äldre patienter får tillgång till behandling. Följsamhet till CPAP-behandling leder förutom till att patien-

terna blir mindre dagtrötta till en återställning av de metabola komplikation-
erna till OSA. I studie III ger sig detta i utryck som ökade uppmätta serum-
koncentrationer av IGF-1 i gruppen som var följsam till CPAP.

Användning av en luftfuktare som tillägg vid start av CPAP-behandling vid
OSA är associerad med en kraftigt ökad följsamhet till behandling. Man har
tidigare visat att befuktare vid CPAP-behandling minskar CPAP-orsakade
luftvägsbekymmer, så som nästäppa och snuva, men klara bevis för att tillägg
av befuktare vid behandlingsstart påverkar följsamheten har hittills inte fun-
nits. Trots detta förskrivs befuktare ut till en klar majoritet av CPAP-patienter
idag och denna förskrivning ökar årligen. Med denna studie har denna nya
kliniska rutin blivit vetenskapligt förankrad. Andra faktorer associerade med
en ökad följsamhet är stigande ålder, ett mer avancerat sömnapnésyndrom
med fler andningsuppehåll, mer uttalad dagtröthet samt ett BMI upp till 35.
Att ha högt blodtryck, som tolkas som en markör på manifest hjärt-kärlsjuk-
dom, var associerat med en sämre följsamhet.

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