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SLEEP-DISORDERED BREATHING IN WOMEN

by

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To my children Eemeli and Emma

Ulla Anttalainen

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ABSTRACT

Sleep-disordered breathing (SDB) is underdiagnosed in women, probably due to the different gender-related manifestation. We investigated the differences in presentation, symptoms and co-morbidities of SDB in men and in pre- and postmenopausal women by a clinical, retrospective, cross-sectional study of 601 consecutively referred women and 233 age- and BMI-matched male-female pairs studied with the static-charge-sensitive bed (SCSB) and an oximeter. Data on the use of nasal CPAP were gathered from the Paimio hospital database, and the co-morbidity information was based on reimbursed medication data from the National Agency for Medicines and the Social Insurance institution.

The abnormal breathing episodes at night were more frequent in men than in women, and in postmenopausal women compared to premenopausal ones. Partial upper airway obstruction was the most common type of SDB in both genders but especially in females. BMI and the major symptoms of SDB were similar in pre- and postmenopausal women, and a menopause effect on symptoms was not found. CPAP adherence did not differ between symptomatic patients with partial upper airway obstruction and those presenting with conventional obstructive sleep apnea. Co-morbidities were more frequent in SDB patients than in the general Finnish population. Compared to sleep apnea, partial upper airway obstruction was associated with a three-fold prevalence of asthma and/or COPD in both genders, and with a 60% reduced prevalence of hypertension in females matched for age and BMI.

Our results emphasize that partial upper airway obstruction is not a milder form of SDB but a different entity, the severity of which is underestimated when using the conventional apnea-hypopnea index. It seems clinically relevant to diagnose and treat the co-morbidities and SDB also in patients with partial upper airway obstruction, especially in elderly and symptomatic women.

Keywords: Co-morbidity; gender; menopause; nasal CPAP adherence; partial upper airway obstruction; periodic obstructive breathing; static-charge-sensitive bed; sleep-disordered breathing; sleep apnea; women.

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TIIVISTELMÄ

Unenaikaiset hengityshäiriöt ovat naisilla alidiagnosoituja, koska todennäköisesti unenaikaiset hengityshäiriöt ilmenevät eri sukupuolilla eri tavoin. Tutkimme sukupuolten sekä pre- ja postmenopausaalisten naisten välisiä eroja unenaikaisten hengityshäiriöiden, oireiden ja liitännäissairauksien esiintymisessä. Tutkimus oli kliininen, taaksepäin katsova poikkileikkaustutkimus, jossa oli mukana 601 peräkkäin tutkittua naista ja 233 iän ja painoindeksin (BMI) suhteen kaltaistettua miesparia naisille. Unitutkimus sisälsi SCSB-unipatjan ja yöoksimetriseurannan. Paimion sairaalan tietokannasta kerättiin CPAP-laitteen käyttötiedot. Liitännäissairauksien tiedot saatiin KELA:n erityiskorvattavien lääkkeiden tietokannoista.

Tutkittaessa unenaikaisen poikkeavan hengityksen määrää, unenaikaiset hengityshäiriöt olivat yleisempiä miehillä kuin naisilla, kuin myös postmenopausaalisilla naisilla verrattaessa premenopausaalisiin naisiin. Osittainen ylähengitysteiden ahtauma oli yleisin hengityshäiriön tyyppi molemmilla sukupuolilla, mutta erityisesti naisilla. Painoindeksi ja unenaikaisen hengityshäiriön oireet olivat samanlaisia pre- ja postmenopausaalisilla naisilla. Vaihdevuosien aiheuttamaa vaikutusta oireisiin ei tullut esiin. CPAP-hoitoon sitouminen ei vaihdellut oireisten osittaista ylähengitystieahtaumaa tai obstruktiivista uniapneaa sairastavien välillä. Liitännäissairaudet olivat yleisempiä unenaikaista hengityshäiriötä sairastavilla kuin suomalaisilla yleensä. Sekä miehillä että naisilla, jotka sairastivat osittaista ylähengitysteiden ahtaumaa, oli kolminkertainen astman ja/tai keuhkoahtaumataudin vaara uniapneaa sairastaviin verrattuna. Osittaista ahtaumaa sairastavilla naisilla verenpainetaudin vaara oli 60 % pienempi uniapneaa sairastaviin verrattuna iästä ja BMI:stä riippumatta.

Tulosten perusteella osittainen ylähengitystieahtauma ei ole unenaikaisen hengityshäiriön lievä muoto. Se on oma kokonaisuutensa, jonka vaikeutta aliarvioidaan käytettäessä vain apnea-hypopneaindeksiä. Kliinisesti on tärkeää löytää ja hoitaa unenaikaisten hengityshäiriöiden liitännäissairaudet sekä osittaista ahtaumaa sairastavat, erityisesti vanhemmat ja oireilevat naiset.

Avainsanat: Liitännäissairaudet; sukupuoli; vaihdevuodet; CPAP-hoitoon sitoutuminen; osittainen unenaikainen ylähengitysteiden ahtauma; jaksoittainen obstruktiivinen hengitys; SCSB-unipatja; unenaikaiset hengityshäiriöt; uniapnea; naiset.

CONTENTS

ABBREVIATIONS

AHI = apnea-hypopnea index
AHI_{est} = estimated apnea-hypopnea index
AF = atrial fibrillation
BMI = body mass index (kg/m^2)
BNSQ = Basic Nordic Sleep Questionnaire
CAD = coronary artery disease
CO_2 = carbon dioxide
COPD = chronic obstructive pulmonary disease
CPAP = continuous positive airway pressure
CRP = C-reactive protein
CSA = central sleep apnea
DM = diabetes mellitus
E1 = estrone
E2 = estradiol
ECG = electrocardiogram
EDS = excessive daytime sleepiness
EEG = electroencephalogram
EMG = electromyogram
EOG = electro-oculogram
ESS = Epworth sleepiness scale
FEV_1 = forced expiratory volume in one second (L/min)
FEV1% = FEV_1 as percentage of predicted value
FSH = follicle-stimulating hormone
FVC = forced vital capacity (L/min)
FVC% = FVC as percentage of predicted value
GER = gastroesophageal reflux
HF = heart failure
HT = hormone therapy
IL-6 = interleukin-6
IRR = increased respiratory resistance pattern
LH = luteinizing hormone
MSLT = multiple sleep latency test
ODI_4 = oxygen desaturation events of 4%-unit or more
OP-1 = obstructive periodic breathing pattern 1
OP-2 = obstructive periodic breathing pattern 2
OP-3 = obstructive periodic breathing pattern 3

OSA = obstructive sleep apnea
OSAS = obstructive sleep apnea syndrome
PAH = pulmonary arterial hypertension
P-1 = periodic breathing pattern
P_{crit} = critical value of transmural pressure
PCOS = polycystic ovarian syndrome
PLM = periodic leg movements
PMS = periodic movements in sleep
PSG = polysomnogram
RDI = respiratory disturbance index
REM = rapid eye movement
RERA = respiratory effort-related arousal
RLS = restless leg syndrome
SaO_2 = arterial oxyhemoglobin saturation
SDB = sleep-disordered breathing
SCSB = static-charge-sensitive bed
$TcCO_2$ = transcutaneous carbon dioxide
TNF-α = tumour necrosis factor-α
TIB = time in bed
UARS = upper airway resistance syndrome
UPPP = uvulopalatopharyngoplasty

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original communications, which are referred to in the text by the Roman numerals I-IV. In addition, some unpublished data are presented. The original publications are reproduced with the permission of the copyright owners.

I. Anttalainen U., Saaresranta T., Toivonen J., Kalleinen N., Vahlberg T., Virtanen I., Polo O. Impact of menopause on the manifestation and severity of sleep-disordered breathing. Acta Obstet Gynecol Scand 2006;85:1381-1388

II. Anttalainen U., Saaresranta T., Kalleinen N., Toivonen J., Vahlberg T., Polo O. Gender differences in age and BMI distributions in partial upper airway obstruction during sleep. Respir Physiol Neurobiol 2007;159:219-226

III. Anttalainen U., Saaresranta T., Kalleinen N., Toivonen J., Vahlberg T., Polo O. CPAP adherence and partial upper airway obstruction during sleep. Sleep Breath 2007;11:171-176

IV. Anttalainen U., Saaresranta T., Vahlberg T., Polo O. Reimbursed drugs in patients with sleep-disordered breathing – a static-charge-sensitive bed study. Submitted to Sleep Medicine 7/2008

INTRODUCTION

In Western societies, sleep-disordered breathing (SDB) is an important health problem leading to decreased quality of life, and increased co-morbidity and mortality (Young et al., 2002; Marin et al., 2005). It is also an important contributor to traffic accidents (Terán-Santos et al., 1999), and increases the health-care costs for several years prior to the diagnosis (AlGhanim et al., 2008). Despite the marked recent advancement in our understanding of the pathogenesis and clinical consequences of SDB, a majority of those affected remain undiagnosed.

SDB was originally thought to be a "male disorder". Although SDB has a male predominance (Young et al., 1993), recent data indicate that it is also a common disorder in females, especially after menopause (Dancey et al., 2001; Resta et al., 2003). Importantly, despite development of the diagnostic and treatment options of SDB during the last three decades, the clinical picture and diagnosis of the disorder are still based on the typical symptoms and findings of men with SDB. Therefore, women are likely to be unrecognised and underdiagnosed because of an "atypical" symptom profile (Kapsimalis and Kryger, 2002a). Indeed, women with SDB challenge our SDB diagnosis and treatment parctices.

In spite of the growing knowledge that upper airway dysfunction during sleep may be either complete or partial upper airway obstruction, nearly all studies in this field define SDB and its severity in terms of the apnea-hypopnea index (AHI). AHI measures the frequency of periodic obstructive events. Partial upper airway obstruction is a state of flow-limitation which does not increase the AHI but associates with symptoms. Therefore, the incidence and severity of SDB in women are underestimated when defined by the AHI. Women with SDB have a lower AHI in all age groups than men. However, women are frequently symptomatic with a low AHI, the suggested cut-off point for clinical significance being 2 for women (Young et al., 1993). This implies that factors other than the AHI are likely to contribute to the symptoms of female SDB. Our clinical experience and accumulating scientific data suggest that partial upper airway obstruction plays a key role in female SDB (Polo-Kantola et al., 2003).

Menopause is a known hallmark in a woman's life span, not only in terms of permanent cessation of menstruation, but also in terms of increased risk for cardiovascular and other chronic diseases (Bixler et al., 2001; Moe, 2005). Previously, SDB was conceived as a disorder of loud snoring, nocturnal breathing pauses and excessive daytime sleepiness. Today there is compelling evidence that SDB is a significant risk factor for cardiovascular disease and mortality (Marin et al., 2005). However, there is a lack of studies addressing the impact of menopause on the burden of co-morbidities in women with SDB.

Women with a low AHI but with clinically significant and symptomatic partial upper airway obstruction frequently remain undiagnosed and untreated. Missing the diagnosis may be a result of relying on a conventional sleep study (e.g. polygraphic sleep study

with a thermistor) which is not able to detect partial upper airway obstruction. Further, even though a static-charge-sensitive bed or nasal prongs connected to a pressure transducer may have been included in the set-up of the sleep study, the clinical significance of partial upper airway obstruction (flow limitation) and patient's symptoms may be overlooked. One reason for this could be the current thinking that sleepiness, the cardinal symptom of SDB, is due to arousals from sleep, which are not as common in partial obstruction as in obstructive sleep apnea (Saaresranta et al., 2001). As a result, the severity of SDB based on a low AHI alone will be interpreted as mild, and the patient left without treatment. However, even mild SDB is associated with increased morbidity (Young et al., 1997). These cases of "mild SDB" may include a notable proportion of patients with partial obstruction. No studies have evaluated the impact of type of SDB (partial obstruction vs. conventional obstructive sleep apnea) on the burden of co-existing diseases in SDB.

To overcome SDB, we need clinically cost-effective diagnostic methods, effective treatment modes and good intervention strategies to prevent SDB or its progression in all its forms. The aim of the present study was to evaluate the impact of menopause and gender on the manifestation of SDB in terms of breathing pattern, co-morbidity profile and long-term adherence to nasal continuous positive airway pressure (CPAP). Another aim was to evaluate the clinical relevance of partial upper airway obstruction compared to obstructive periodic breathing (conventional sleep apnea) in terms of adherence to CPAP therapy, as well as the spectrum and prevalence of co-existing diseases. This work attempts to provide clinical principles for identifying the women who would benefit from active treatment of SDB.

REVIEW OF THE LITERATURE

1. Sleep-disordered breathing (SDB)

Sleepmedicine is growing rapidly as a clinical discipline on the basis of the increasing recognition of sleep-disordered breathing. The discovery of sleep apnea as episodes of obstructive, central and mixed apneas was reported in 1965 in Germany (Jung et al., 1965) and in 1966 in France (Gastaut et al., 1966) independently. It took two more decades to understand the clinical relevance of SDB and to find an effective treatment (Fujita et al., 1981; Sullivan et al., 1981). Nowadays, the prevalence of SDB in adults is estimated to be 4% in middle-aged men and 2% in women (Gislason et al., 1988; Young et al., 1993; Kripke et al., 1997). However, these studies have used thermistors to detect respiratory events, whereas now there is a growing body of evidence showing that inspiratory flow-shape analysis from nasal flow prongs is a better tool to distinguish respiratory events, especially partial upper airway obstruction (Norman et al., 1997; Aittokallio et al., 2001). According to the Health 2000 survey in Finland, 7% of the Finnish adult population reported weekly appearance of apnea episodes during sleep (13% of men and 3% of women), whereas only 2% of men and 0.5% of women had physician diagnosed SDB (Aromaa and Koskinen, 2002). With growing obesity, the prevalence of SDB (defined as an apnea-hypopnea index > 5) in adults may be as high as 20% (Young et al., 2002). Because epidemiologic studies have focused solely on obstructive sleep apnea, the prevalence of partial upper airway obstruction is largely unknown. In a Finnish study of 65 healthy obese postmenopausal women, the incidence of partial upper airway obstruction was 17% which is surprisingly high (Polo-Kantola et al., 1999).

1.1. Definition of obstructive sleep-disordered breathing

Obstructive apnea episodes are defined as cessation of airflow for at least 10 seconds despite the continuing breathing efforts. To score an apnea there must be a drop of 90% or more in airflow from baseline. No arterial oxyhemoglobin desaturation is needed, and at least 90% of the event's duration must meet the amplitude reduction criteria for apnea (Iber et al., 2007). *Hypopnea* is an episode that lasts for at least 10 seconds with either a 30% reduction in thoracoabdominal movement or airflow as compared with normal baseline with 4% or more arterial oxyhemoglobin desaturation, or a 50% reduction in thoracoabdominal movement or airflow as compared with normal baseline with 3% or more arterial oxyhemoglobin desaturation, and in both cases at least 90% of the event's duration must meet the amplitude reduction criteria for hypopnea (Iber et al., 2007). *The apnea-hypopnea index (AHI)* is the total sum of the apnea and hypopnea episodes divided by hours of sleep. *Respiratory effort-related arousal (RERA)* is defined as a sequence of breaths characterized by increasing respiratory effort or flattening of the nasal pressure waveform leading to an arousal from sleep (Iber et al., 2007). The event lasts for at least 10 seconds and it does not meet the criteria for apnea or hypopnea. *The respiratory disturbance index (RDI)* is the sum of RERA, apnea and

hypopnea events per hour. RERA is presumed to have the same underlying pathophysiology as apneas and hypopneas and is thus included under the definition of obstructive sleep apnea syndrome (OSAS) (American Academy of Sleep Medicine, 2005). The conventional method to detect breathing disorders during sleep is a full night, 12-channel polysomnogram (PSG) including the following parameters: electroencephalogram (EEG), electrooculogram (EOG), electromyogram (EMG), oronasal flow, chest wall effort, body position, snore microphone, ECG, and arterial oxyhemoglobin saturation (American sleep Disorders Association, 1997).

1.2. Definition of partial upper airway obstruction

The literature provides various definitions for partial upper airway obstruction during sleep depending mostly on the set-up of a sleep study and the detection methods used to measure various phenomena.

Increased respiratory resistance (IRR) is an abnormal breathing pattern characterised by prolonged (from 1 min up to 30 min) episodes of nonperiodic obstructions, with slowly increasing intrathoracic pressure variations (Polo et al., 1991; Polo et al., 1992) (Fig. 1). IRR is often accompanied by sustained arterial oxyhemoglobin desaturation and terminated by movement arousal (Polo, 1992). To be registered with a static-charge-sensitive bed (SCSB) an IRR episode requires at least a 20 cmH_2O intrathoracic pressure variation (Kirjavainen et al., 1996). IRR corresponds to prolonged episodes of obstructive hypoventilation and should not be confused with shorter episodes of UARS. IRR reflects partial upper airway obstruction and is diagnosed with a SCSB, which is a non-invasive method to detect breathing, heart beats and body movements without any electrodes placed on the subject (see Methods). This is important in detecting long episodes of IRR without any irritation of the esophageal balloon and early arousals because of it.

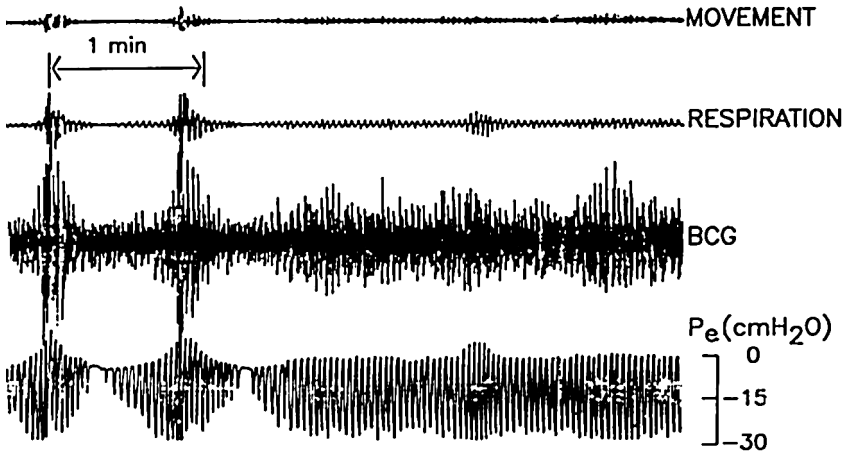

Figure 1. Increased respiratory resistance (IRR) is an abnormal breathing pattern characterized by prolonged (from 1min up to 30 min) episodes of nonperiodic obstructions, with slowly increasing intrathoracic pressure variations. With permission from Polo et al., 1991. BCG = ballistocardiogram, Pe = esophageal pressure.

Upper airway resistance syndrome (UARS) was described by Guilleminault in 1993 (Guilleminault et al., 1993). These patients had typical symptoms of OSAS. They may or may not have been snorers but had no apneas or hypopneas on polysomnography. Instead, they had short events of increased negative esophageal pressure during inspiration, terminating with an arousal. The diagnostic criteria for UARS have not been established and there is no agreement that UARS is a separate entity. To diagnose UARS, nocturnal polysomnography should include additional measurements like esophageal pressure monitoring (Bao and Guilleminault, 2004).

Flow limitation is a term referring to abnormal inspiratory air flow shape during partial upper airway obstruction (Aittokallio et al., 2001). When upper airway narrowing develops after falling asleep, a normal rounded inspiratory flow shape will change to a flowlimited one, which is characterized by plateau flow throughout the middle part of inspiration. The plateau flow during inspiration indicates that the upper airway behaves like a collapsible tube (Starling's resistor's physiological phenomenon) (Fig. 2). The area under the inspiratory flow curve displays the inspiratory volume. Prolonged episodes of nonperiodic partial upper airway obstruction are characterized by constant flow limitation with gradually decreasing inspiratory volumes, often terminated with arousals. Flow limitation is measured with nasal prongs (cannula) connected to a pressure sensor. Detection of flow limitation is used with success in some nasal CPAP devices to autotitrate the CPAP to a level controlling not only episodes of obstructive apnea but also episodes of partial upper airway obstruction.

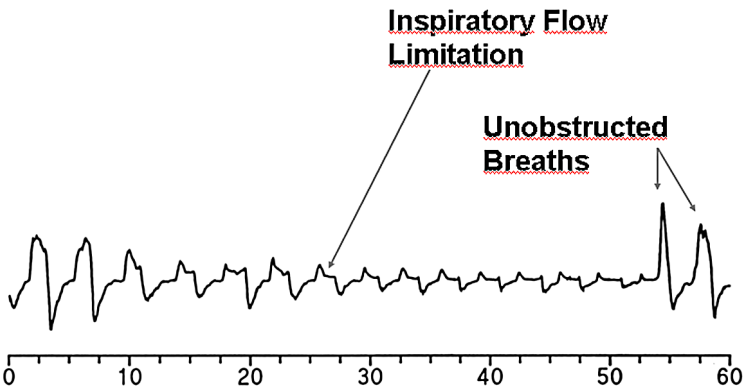

Figure 2. Flow limitation measured with nasal prongs during one minute (Starling's resistor's physiological phenomenon).

1.3. Pathophysiology and etiology

The pathophysiology of SDB is not fully understood but it is believed to result from a combination of changes in upper airway anatomy and in neural activation mechanisms intrinsic to sleep. The pharynx is a very compliant structure of three regions: nasopharynx (the area between nasal turbinates and the hard palate), oropharynx (the area from the tip of the soft palate to the epiglottis) and hypopharynx (the area from the base of the tongue to the larynx) (Fig. 3). The tendency of the upper airway to collapse

can be expressed quantitatively by P_{crit} (pressure surrounding the pharyngeal airway, critical value for the transmural pressure). When airways are exposed to atmospheric pressure (zero-level), an elevation of P_{crit} above zero would cause obstruction, whereas a decrease in P_{crit} below zero would increase the airway patency (Gleadhill et al., 1991). The size of the upper airway depends on the balance between forces that would collapse the airway and forces that would maintain airway patency. Collapsible forces include negative intraluminal pressure and increased extraluminal pressure (airway suction), and the counteracting force is contraction of pharyngeal dilator muscles.

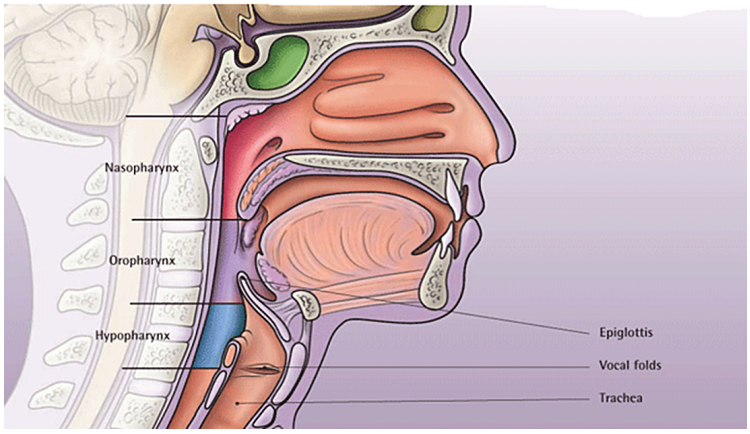

Figure 3. Anatomy of pharynx.

First, the sleep-wake state in the pathogenesis of SDB is highlighted by the fact that disordered breathing events only occur during sleep, even in patients with severe SDB. During sleep the activity of dilating muscles is relatively suppressed and associated changes in the mechanics and reflex activity of the muscles occur, causing a rise in P_{crit} and greater tendency for the upper airway to narrow during inspiration (Worsnop et al., 1998; Malhotra et al., 2000).

Second, since the upper airway lacks a rigid structural support, the size of the airway is dependent on the position of the soft tissue structures of the oropharynx. Because of gravity, in the supine position the tongue and soft palate move posteriorly, reducing the oropharyngeal area and predisposing to collapse (Malhotra et al., 2004). Lung volume is known to influence pharyngeal airway calibre and this influence is clearer in SDB patients than in subjects without SDB (Hoffstein et al., 1984). When the lung volume decreases to almost residual volume, the pharyngeal cross-sectional area decreases and pharyngeal resistance increases (Brown et al., 1986; Series et al., 1990). Larger lung volumes cause caudal traction of the trachea and soft tissues in the upper airway, “tracheal tug”, which in the supine position, and especially in obese patients, is reduced and predisposes to upper airway collapse (Van de Graaf, 1988).

Third, anatomic differences in the pharyngeal airway between patients with SDB and controls have been reported, patients with SDB having smaller airway lumen than

controls (Schwab et al., 1995; Schellenberg et al., 2000). This may be caused by genetic influence (small skeletal boundary for tissues surrounding the upper airway), soft tissue abnormalities (long uvula or soft palate, large tongue), or obesity affecting pharyngeal size by deposition of fat around the airway or by altering muscle orientation and function (Partinen et al., 1988).

Fourth, instability of respiratory control may lead to periodic breathing, and compromised airway patency can occur at the nadir of the ventilatory cycle when an imbalance of forces may occur between upper airway muscles and thoracic pump muscles (Hudgel et al., 1987).

Gender seems to influence the resistance and collapsibility of the upper airway although the evidence is conflicting. Men are thought to have a larger pharyngeal size than women and thus lower resistance (Brown et al., 1986; Brooks and Strohl, 1992). However, pharyngeal resistance has been measured to be twice as high in men as in women which, on the other hand, can suggest gender differences in the airway mechanics (White et al., 1985). It has also been reported that changes in the pharyngeal cross-sectional area are more dependent on lung volume, and increases in pharyngeal resistance in response to load are greater in men than in women (Brown et al., 1986; Brooks and Strohl, 1992; Pillar et al., 2000). In females, hormonal status might influence the upper airway dilator activity during inspiratory resistive loading in such a way that premenopausal women have greater genioglossal activity compared with postmenopausal women or age-matched men (Popovic et al., 1995; Popovic et al., 1998; Driver et al., 2005).

1.4. Prevalence and incidence

When reviewing the epidemiology of SDB, three issues must be kept in mind. First, the majority of the epidemiologic studies have used the AHI without symptoms of SDB as a definer of SDB. Second, most of these studies have used thermistors to detect a respiratory event. This is known to be a less sensitive method than nasal prongs with a pressure transducer to distinguish respiratory events, especially flow limitation, i.e. partial upper airway obstruction (Norman et al., 1997; Aittokallio et al., 2001). Third, there are very little objective epidemiologic data on partial upper airway obstruction. However, a growing body of evidence shows that partial upper airway obstruction is clinically significant and, thus, the AHI underestimates the overall prevalence of SDB (Polo 1992; Hosselet et al., 2001; Cracowski et al. 2001). Prevalence estimates are also vulnerable to marked differences depending on the study population used. The most important studies comparing the prevalence and severity of SDB between pre- and postmenopausal women are reviewed in Table 1.

Table 1. Studies comparing pre- and postmenopausal women with sleep-disordered breathing.

Author	Study design	Subjects	HT	Findings	Comments
Block et al., 1980	Cross-sectional clinical	n=68 F: PreMP 18 PostMP 20 M: 30	Not used	PostMP: sleep duration and stage 3 sleep, breathing episodes, hypopnea, desaturation ↑; postMP SDB frequency similar to men	Definition of MP state with menses, age >50 yr
Wilhoit et al., 1987	Cross-sectional clinical	n=53 F: PreMP 8 PostMP 13 M: 32	Not used	PreMP: OSA patients more obese and more hypercapnic than postMP women and men	Definition of MP state with menses, hormone levels, age >56 yr. BMI>30 kg/m^2
Leech et al., 1988	Cross-sectional clinical	n=118 F: PreMP 12 PostMP 29 M: 77	NA	No menopause effect on OSA. Women had fewer completed occluded events and apneas were shorter than in men	Definition of MP state with reported history of MP, BMI>30 kg/m^2
Young et al., 1993	Cross-sectional general	n=602 F: 250 M: 352	NA	50-60 yr women had higher AHI>5 than younger women AHI>5: F 9% and M 24%, SDB: F 2% and M 4%	No definition of MP state
Millman et al. 1995	Cross-sectional clinical	F: PostMP 13 PreMP 12	NA	BMI or severity of OSA the similar in post and preMP	Definition of MP state with menses, surgery. BMI>30 kg/m^2
Carskadon et al., 1997	Interventional study in general population with parallel groups	F: PreMP 13 PeriMP 4 PostMP 14	Not used	No menopause effect on OSA induced with nasal occlusion test	Definition of MP state with hormonal assays, menses.
Ware et al., 2000	Cross-sectional clinical	n=430 F: PreMP 54 PeriMP 120 PostMP 41 M: 215	NA	PostMP had more apneic events than preMP and periMP (present only in stage 2 sleep!)	Definition of MP state with age groups: 18-39, 40-59, 60-88 yr. BMI>30 kg/m^2

Author	Study design	Subjects	HT	Findings	Comments
Bixler et al., 2001	Cross-sectional general	n=1000 F: PreMP 503 PostMP 495 M: 741	PostMP: 183 on HT	SDB (AHI>10+symptoms): preMP 0.6%, postMP 1.9%, postMP with HT 0.5%, postMP without HT 2.7%, men 3.9%	Definition of MP state with menses
Dancey et al., 2001	Cross-sectional clinical	F: PreMP 797 PostMP 518	Not used	AHI>10: Post 49%, pre 20%, AHI>20: Post 28%, pre 10% PostMP higher severity of OSA than preMP	Definition of MP state with age: preMP<45, postMP>55 yr. BMI>30 kg/m^2
Durán et al., 2001	Cross-sectional general	n=2148 F: 1098 M: 1050	NA	Prevalence of OSA increased with age in both genders SDB: F 3%, M 3.4%	No definition of MP state
Netzer et. al., 2003	Cross-sectional clinical	F: PreMP 27 PostMP 26	Not used	PostMP and preMP with SDB had lower levels of progesterone, estradiol and 17-OH progesterone compared with women without SDB (=AHI>10+sleepiness+snoring/restless sleep)	Definition of MP state with hormone levels. BMI>30 kg/m^2
Resta et al., 2003	Cross-sectional clinical study of obese patients	n=230 F: PreMP 89 PostMP 59 M: 82	Not used	Higher prevalence and severity of SDB (RDI>10+ sleepiness) in postMP (67.8%) than in preMP (31.5%)	Definition of MP state and use of HT questioned. PostMP were more obese than preMP. BMI>30 kg/m^2
Young et al., 2003	Cross-sectional general	F: 1.PreMP 498 2.PeriMP 125 3.PeriMP or postMP 37 4.PostMP 375	1. Not used 2. 29 3. 25 4. 231	OSA (AHI>5 or >15): 2.6 or 3.5 times higher in postMP than in preMP	Definition of MP state with menses, surgery, HT, FSH level, vasomotor symptoms
Ip et al., 2004	Cross-sectional general	F: 1532	Used	Menopause correlated with increasing AHI	Definition of MP state and use of HT questioned.

Abbreviations: AHI=apneahypopnea index, clinical=clinical study population, F=female, general=general study population, HT=hormone therapy, M=male, MP=menopause or menopausal, NA=not available, OSA=obstructive sleep apnea measured with AHI alone, PeriMP=perimenopausal, PreMP=premenopausal, PostMP=postmenopausal, SDB=sleep-disordered breathing measured with AHI and symptoms of SDB,

In the earlier prevalence studies reviewed by Lindberg and Gislason (2000), the prevalence of undiagnosed SDB (AHI over 5) in Western countries varied from 0.3% to 5% in the adult population. In more recent large population-based studies of SDB, prevalences were estimated to be 17-26% in men and 9-28% in women for at least mild SDB (AHI over 5), while 7-14% of men and 2-7% of women had at least moderate SDB (AHI over 15) (Young et al., 1993; Bixler et al., 1998 and 2001; Durán et al., 2001). When taking into account the symptoms of SDB, the prevalence varied between 3.4-4% in men and 1.2-3.4% in women, making men 2 to 3 times more likely to have symptomatic SDB than women. The prevalence of UARS is yet unknown but estimates of 10-15% of patients with snoring and excessive daytime sleepiness have been made (Guilleminault et al., 1995; Loube and Andrada, 1999).

In the Cleveland Family Study, the incidence in men was overall greater than in women. With age, the risk in women increased steadily but in men only modestly. As a result of this, the gender difference in the incidence of SDB disappears by the age of 50 years (Tisher et al., 2003).

In addition to the gender differences in the anatomy and physiology described in the previous pathophysiologic section, sex hormones are likely to partly explain the differences in SDB prevalence between men and women, and between premenopausal and postmenopausal women. A clear gender difference in prevalence of SDB is reported especially between middle-aged men and premenopausal women but the difference diminishes between the same age range of men and postmenopausal women (Durán et al., 2001; Resta et al., 2003; Ip et al., 2004). With increasing age (over 60 years) in both genders, the prevalence of SDB is 2 to 4 times higher than in the middle-aged population (Redline 1998; Duran et al., 2001; Bixler et al., 1998 and 2001). In the studies carried out before 2000, the results were conflicting concerning the differences in SDB prevalence when looking at the effect of menopause. Many of them found no direct effect of menopause per se (Leech et al., 1988; Millman et al., 1995; Carskadon et al., 1997), whereas others found SDB more prevalent in postmenopausal than premenopausal women (Block et al., 1980; Young et al., 1993). Indirect menopausal effects on SDB prevalence were more frequent episodes of apnea, hypopnea and oxygen desaturations in postmenopausal than in premenopausal women (Block et al., 1980; Ware et al., 2000), or apneas were shorter and not so often completely occlusive in women as in men (Leech et al., 1988). Most of these studies had a small sample size, menopausal state was defined only by age, and possible hormone treatment (HT) was not taken into account. More recent studies have clearly demonstrated that postmenopausal women have higher prevalence and severity of SDB than premenopausal women (Dancey et al., 2001; Young et al., 2003; Resta et al., 2003; Ip et al, 2004).

Progesterone is a known respiratory stimulant hormone the secretion of which ceases after menopause (Zwillich et al., 1978; Skatrud et al., 1978). Conversely, androgens like testosterone may worsen breathing and promote SDB (Saaresranta and Polo, 2002; Liu et al., 2003). Possibly, the prevalence of SDB is related to the ratio of progestational and androgenic hormones, the ratio being high in premenopausal women, and low or reversed in men and postmenopausal women. Netzer and co-

workers (Netzer et al., 2003) reported that both premenopausal and postmenopausal women with SDB (AHI over 10) had lower levels of progesterone, 17-OH progesterone and estradiol compared with women without SDB (AHI under 10). Even when age and BMI were taken into account, HT alleviated SDB prevalence. In a population-based study, SDB prevalence was 0.6% in premenopausal women and 1.9% in all postmenopausal ones, but adjustments for age or body habitus were not included in the analyses (Bixler et al., 2001). When taking into account HT, postmenopausal women with HT had a 0.5% prevalence of SDB, while without HT it was 2.7%, while men's prevalence was 3.9% (Bixler et al., 2001). The Sleep Heart Health Study found that HT (estrogen or estrogen + progestin) is associated with lower AHI levels in postmenopausal women (Shahar et al., 2003).

1.5. Risk factors

Obesity is a well known and documented risk factor for SDB and there is little controversy over the causal role of excess body weight in SDB (Young et al., 1993; Durán et al., 2001; Ip et al., 2004). Weight reduction in obese patients with SDB decreased the severity of the AHI (Rajala et al., 1991; Strobel and Rosen, 1996; Lojander et al., 1998), while weight gain increased the AHI in a longitudinal study (Peppard et al., 2000). Obesity has been hypothesized to affect breathing in many ways, including alterations in the anatomy of the upper airway structure or function, respiratory drive and load compensation disturbances, and obesity-induced hypoxemia (Strobel and Rosen, 1996). Because women are more frequently obese than men, the prevalence of SDB should be higher in women than in men but the epidemiologic evidence shows the opposite (Kapsimalis and Kryger, 2002b).

The location of adipose tissue seems to be more important. Millman and co-workers (Millman et al., 1995) found that the AHI correlated best with upper-body obesity, measured as the sum of the subscapular and triceps skin fold, whereas despite similar BMI and waist circumference, men had a greater degree of upper-body obesity with smaller hip circumference, higher waist-to-hip ratio and a larger subscapular skin-fold thickness. Differences in premenopausal and postmenopausal women were not found. Gender differences in fat deposition of the neck might play a role in male predominance of SDB. With MRI techniques, the total neck soft-tissue volume was greater in men than in women, and the necks of men contain a higher proportion of fat than do their bodies as a whole, while the reverse is true for women matched for BMI (Whittle et al., 1999).

Smoking may have several mechanisms by which it affects SDB. Smoking may cause an increase in sleep instability and airway inflammation and the acute effects of nicotine favor increased upper airway tone but this is reversed during overnight nicotine withdrawal, causing a rebound effect (Wetter et al., 1994). Current smokers are three times more likely to have SDB than never smokers (Wetter et al., 1994), and smoking predicts the development of snoring in younger men (Lindberg et al., 1998). Controversially, The Sleep Heart Health Study reported an inverse association between current smoking and SDB after adjusting for several factors including BMI and age

(Newman et al., 2001). They speculated the finding that patients with severe SDB may have been more prone to quit smoking.

Nasal congestion is usually due to rhinitis, often of allergic origin and due to anatomic abnormalities (Lojander et al., 1999). There is some evidence that nasal congestion is a risk factor for SDB from studies that objectively measured nasal resistance (Young et al., 1997; Lofaso et al., 2000; Liistro et al., 2003). In a recent study of a small male population with sleep apnea and nasal obstruction, an intervention with a topical decongestant and an external dilator strip reduced mouth breathing during sleep and obstructive sleep apnea severity, but did not effectively alleviate obstructive sleep apnea (McLean et al., 2005).

Anatomic abnormalities have been found to predispose to SDB. Large tonsils and uvula correlate with RDI (Schellenberg et al., 2000). A long distance between the mandibular and hyoid bone or a long width of the posterior airway space have also been significant predictors of elevated RDI (Partinen et al., 1988). In a recent study from Sweden (Svensson et al., 2006), a low soft palate, retrognathia, the uvula touching the posterior wall in a supine position and at least a 75% collapse at the soft palate during Müller maneuver were predictors of SDB (defined as AHI $\geq$ 10) in normal weight women, but not in overweight women.

Male gender is a risk factor for SDB but menopause is the most important endocrine risk factor for SDB in women (see Chapter 2). Polycystic ovary syndrome (PCOS) is an *endocrine disorder* resulting in high androgen secretion and predisposing to insulin resistance and obesity. The combination of these three in PCOS women increases the risk of SDB to 30 times that of women without PCOS (Vgontzas et al., 2001; Fogel et al., 2001). SDB is common in many other endocrine disorders like acromegaly, hypothyroidism, and Cushing's syndrome (Saaresranta and Polo, 2003). An increasing body of evidence shows that SDB is linked with metabolic syndrome, insulin and leptin resistance.

1.6. Clinical features

The diagnostic criteria for adult OSAS are defined according to the international classification criteria (American Academy of Sleep Medicine, 2005). OSAS patients complain of excessive daytime sleepiness or falling asleep unintentionally, fatigue, unrefreshing sleep, or insomnia. The patient wakes holding his/her breath, gasping or choking, and his/her bed partner reports frequent snoring or episodes of obstructed breathing during sleep. A polysomnogram demonstrates more than five obstructive apneas, hypopneas or respiratory-associated arousals per hour and there is evidence of respiratory effort during all or a portion of each respiratory event. Finally, no other disorder or used medication explains the above symptoms. Associated features include loud snoring, obesity, systemic hypertension, pulmonary hypertension, congestive heart failure, sleep fragmentation, recurrent awakenings from sleep, sleep-related cardiac dysrhythmias, nocturnal angina, morning headaches, gastroesophageal reflux, nocturia, depression, impaired quality of life, impaired concentration, diabetes, and metabolic syndrome.

Snoring and witnessed apneas reflect the pathophysiologic narrowing of the upper airways (Kales et al., 1985). In population studies, 25% of men and 15% of women are habitual snorers (Lugaresi et al., 1980). Snoring increases progressively with age; 60% of men and 40% of women are habitual snorers between ages 41-65 years (McNicholas, 2005), but snoring has a poor diagnostic value for SDB or its severity (Hoffstein and Szalai, 1993). Women tend to report snoring less frequently than men even with the same severity of SDB (Redline et al. 1994; Young et al., 1996; Valipour et al., 2007). Men are more likely to report apneas than women, and women are more likely to report bed partner's apneas than men (Redline et al., 1994; Kapsimalis and Kryger, 2002a; Larsson et al., 2003). Some reasons for this discrepancy may be that snoring and apneas are not "ladylike" symptoms or that women pay more attention to their bedpartner's sleep and more easily report the nightly events than men. This can lead to under-recognition of female SDB.

Sleep fragmentation due to repeated arousals from apneas and hypopneas is thought to be the cause of *excessive daytime sleepiness (EDS)* in SDB (Kingshott et al., 1998; Bennett et al., 1999). Although SDB is a common cause of EDS, it is not very useful as a clinical feature for diagnosing SDB (Flemons and McNicholas, 1997). Sleepiness in patients with SDB can be midafternoon drowsiness after a good meal or falling asleep while eating or driving. SDB with severe EDS is a known risk for motor vehicle accidents (Young et al., 1997; Teran-Santos et al., 1999; Horstmann et al., 2002). Male patients with SDB express sleepiness but females tend to describe their sleepiness with words like fatigue, lack of energy or tiredness (Ambrogetti et al., 1991; Chervin, 2000). This can be one reason why women's SDB may be missed in primary care because they fail to report the typical sleepiness of SDB (Kapsimalis and Kryger, 2002a; Jordan and McEvoy, 2003). The standard measure of EDS is the *multiple sleep latency test (MSLT)* which quantifies the sleepiness as a tendency to fall asleep by measuring the speed of falling asleep (Carskadon et al., 1986). A behavioral measure of sleepiness is the *Epworth Sleepiness Scale (ESS)*, a questionnaire about the tendency to fall asleep in settings where SDB patients typically report falling asleep (Johns, 1993).

Morning headaches and SDB have a long-recognised association. Morning headache occurs in 18-27% of patients with SDB upon awakening compared to 5% of the general population (Ulfberg et al., 1996; Paiva et al., 1997; Göder et al., 2003). The relationship between morning headaches and SDB is complex and the cause-effect mechanism is not clear, although it is thought to be related to cerebral vasoconstriction because of oxygen desaturations in SDB (Loh et al., 1999). In some studies, female patients with SDB complain more of morning headaches than male patients (Ambrogetti et al., 1991; Young et al., 1996), but in others there is no difference (Shepertycky et al., 2007). One reason for this controversy may be that SDB has different presentations between genders (Kapsimalis and Kryger, 2002a).

"Sleep troubles" like difficulties falling asleep, awakenings during the sleep, insomnia, nightmares or sweating during the night are also symptoms of SDB, although not so typical. These atypical symptoms are more common among female than male patients with SDB; again making it harder for the clinician to suspect SDB in a woman presenting with these symptoms (Shepertycky et al., 2005; Valipour et al., 2007).

Nocturia is a relatively common clinical feature in SDB; 28% of patients report four to seven urination trips per night. Increased intra-abdominal pressure induces increased secretion of atrial natriuretic peptide which, in turn, contributes to nocturia (Umlauf and Chasens, 2003). SDB severity predicts the nocturic frequency (Hadjuk et al., 2006), and nasal CPAP treatment abolishes the nightly symptom (Umlauf and Chasens, 2003).

The prevalence of g*astroesophageal reflux* (GER) in patients with SDB (54-76%) is significantly higher than in the general population (10%) (Zanation and Senior, 2005). However, no temporal or causal relationship between the two has been demonstrated. Age and obesity are the same risk factors for both. In SDB, the obstructive events during the night cause an increased transdiaphragmatic pressure gradient allowing increased lower esophageal sphincter relaxation. Additionally, the acid clearance is prolonged during sleep (Kasasbeh et al., 2007). Nasal CPAP treatment in patients with SDB and GER has decreased the GER symptoms especially during the night (Green at al., 2003) but there is also some evidence that GER treatment may improve SDB severity (Zanation and Senior, 2005).

Periodic leg movements in sleep *(PLM)* is a sleep-related phenomenon with periodic episodes of repetitive movements of the lower extremities (Hornyak et al., 2006). The prevalence of PLM in the general population is 3.9%, being higher in women than in men, 4.6% vs. 3.1%, respectively, and subjects with PLM were more often snorers than subjects without PLM (Ohayon and Roth, 2002). Among the population with suspected SDB, the prevalence of PLM is as high as 24% (Chervin, 2001). In a recent report, women had higher scores for PLM along with psychiatric sleep disorders and narcolepsy than men, but women with an AHI > 15/h had as high scores for SDB, PLM and narcolepsy as men with an AHI > 15/h (Valipuor et al., 2007). Menopause (defined by age cutpoint of 50 years) had no effect on PLM expression (Valipour et al., 2007).

Symptoms of *depression* in SDB are common, but also the incidence of SDB is increased in subjects with depression (Ohayon, 2003; Farney et al. 2004). It has been speculated that the severe fatigue and sleepiness of patients with SDB might be misinterpreted as symptoms of depression, or that the adverse effects of SDB might actually cause clinical depression (Schwartz et al., 2005). There is also a significant gender-related difference in depression or other psychiatric symptoms in SDB. Female subjects express these symptoms or are treated for depression more often compared to males. Also women with severe SDB have higher depression scores compared to those with mild SDB (Young et al., 1996; Pillar and Lavie, 1998; Shepertycky et al., 2005; Valipour et al., 2007).

Cognitive function impairment has been reported and measured by several studies reviewed in a resent article by Engleman and Douglas (2004) but the impact of nasal CPAP treatment on cognitive function is still controversial (Weaver and Chasens, 2007). Cognitive function impairment in SDB is thought to be caused by either nocturnal hypoxemia or daytime sleepiness (Beebe and Gozal, 2002; Verstraeten, 2007).

1.7. Severity

The clinical severity level of SDB is specified by two components: objective findings in a sleep recording and subjective daytime sleepiness with functional disability. According to the American Academy of Sleep Medicine Task Force and the Institute for Clinical Systems Improvement guidelines' severity criteria, the rating should be based on the most severe component (American Academy of Sleep Medicine Task Force, 1999; Institute for Clinical Systems Improvement, 2007). Polysomnographic obstructive breathing events (measured as AHI and arterial oxyhemoglobin saturation) and sleepiness and their severity grading are shown in Table 2. However, in many papers, the severity of SDB is defined based only on the AHI.

Table 2. The severity criteria for obstructive sleep apnea syndrome (OSAS) based on the most severe component of the three (AHI, SaO_2 during sleep, sleepiness). Modified from American Academy of Sleep Medicine Task Force (1999) and Institute for Clinical Systems Improvement (2007) guidelines.

Severity of OSAS	Polysomnographic findings as AHI	SaO_2 during sleep	Sleepiness
MILD	5-15	Mean ≥ 90 % and Min ≥ 85 %	Unwanted sleepiness or involuntary sleep episodes occur during activities that require little attention (watching TV, reading, or travelling as a passenger). Symptoms produce only minor impairment of social or occupational function.
MODERATE	15-30	Mean < 90 % and Min ≥ 70 %	Unwanted sleepiness or involuntary sleep episodes occur during activities that require some attention (concerts, meetings, or presentations). Symptoms produce moderate impairment of social or occupational function.
SEVERE	> 30	Mean < 90 % and Min < 70 %	Unwanted sleepiness or involuntary sleep episodes occur during activities that require more active attention (eating, conversation, walking, or driving). Symptoms produce marked impairment of social or occupational function.

Objectively observed sleep abnormality is not always linked with subjective symptoms or vice versa. Patient's symptoms and their effects on daytime functioning are especially important when assessing the severity of partial upper airway obstruction because polysomnographic findings may be mild or normal. As the AASM Task Force reports, currently there are only a few good prospective studies on estimating the correlation between the AHI and severity of SDB (Young et al., 1997). The AHI alone is not a good indicator of SDB severity and it also correlates poorly with the patient's symptoms (Flemons and McNicholas, 1997). This lack of relationship between the

AHI and symptoms of SDB is probably due to the multifactorial origin of symptoms. The AHI has also been criticized as a too simple variable to measure SDB severity because it takes into account apneic or hypopneic events (obstructive sleep apnea) but is unable to measure arousals or flow limitation (partial upper airway obstruction) which can also cause sleep fragmentation and SDB symptoms (Hudgel, 1986; Polo, 1992; Cracowski et al., 2001). In the search for alternatives to the AHI as a measure of severity of SDB we need indexes which also take into account partial obstruction. By using the SCSB, it is possible to extend respiratory analysis during sleep to distinguish various patterns of both periodic breathing and partial upper airway obstruction (see Methods; Polo, 1992).

Sleepiness is the cardinal symptom of SDB, and the Epworth Sleepiness Scale (ESS) score progressively increases with an increasing AHI. These findings are independent of age or sex (Young et al., 1993; Gottlieb et al., 1999). Also snoring without SDB has been associated with sleepiness (Gottlieb et al., 2000). However, the majority of patients with SDB (defined as AHI 5 or more) did not complain of sleepiness, only 22% of females and 17% of males reported it (Young et al., 1993). This implies that conventional polysomnografic events of SDB do not correlate well with sleepiness, and that there are some other reasons than SDB that associate with sleepiness. Bixler and co-workers reported that in the general population depression is the major risk factor for sleepiness, other risk factors being obesity, diabetes and young age (Bixler et al., 2005). They emphasised the importance of evaluating the mental health issues and metabolic syndrome whenever a patient complains of sleepiness, regardless of SDB. There is also a lack of adequate prospective studies that have validated severity criteria for sleepiness (American Academy of Sleep Medicine Task Force, 1999).

Because cardinal measures of severity of SDB (AHI and daytime sleepiness) lack specificity and sensitivity, it is crucial to take into account the whole clinical picture of the suspected SDB patient when assessing the clinical severity of SDB and modes of treatment.

1.8. Treatment

The principle medical therapy for SDB is nasal continuous positive airway pressure (CPAP) administered through a nasal or facial mask or nasal pillows. Obesity is closely linked with SDB and thus weight reduction and other healthy lifestyle modifications have to be emphazised in the treatment. Oral appliances and surgical treatments are effective only for a carefully selected group of patients. Many pharmagological agents have been studied but no effective medication for SDB has yet been found (Hedner et al., 2008).

1.8.1. Nasal continuous positive airway pressure (CPAP)

Nasal CPAP is the treatment of choice for SDB. It acts as a pneumatic splint to elevate and maintain a positive pressure in the upper airway during inspiration and expiration (Sullivan et al., 1981). Nasal CPAP causes enlargement of the airway by dimensional changes of the lateral pharyngeal walls, and it increases the tone of upper airway dilator muscles, thus inhibiting the susceptibility to collapse (Issa and Sullivan, 1984).

Nasal CPAP improves both subjective and objective neurobehavioral symptoms of SDB (Patel et al., 2003). The benefit of nasal CPAP treatment has been found to be greater in moderate to severe cases of SDB compared to mild cases, even though the AHI has improved with treatment (Monasterio et al., 2001; Barnes et al., 2002; Patel et al., 2003). On the other hand, in SDB with the AHI of over 30 but without subjective daytime sleepiness, nasal CPAP did not improve quality of life or objective measures of neurobehavioral symptoms (Barbé et al., 2001). This inconsistency may be attributed to other reasons for sleepiness than SDB while being treated with nasal CPAP: differences in motivational factors with symptomatic and symptomless SDB patients, or that objective measures of daytime impairments are not sensitive enough for subjective sleepiness (Monasterio et al., 2001; Patel et al., 2003). The American Academy of Sleep Medicine Report recommends nasal CPAP for the treatment of mild to severe SDB, and it is also indicated for improving self-reported sleepiness or quality of life or as an adjunctive therapy to lower blood pressure in hypertensive patients with SDB (Kushida et al., 2006).

Nasal CPAP therapy is the most effective method to treat SDB but the adherence to the therapy is challenged by technological (problems caused by mask and device) and psychosocial (long-lasting treatment, spouse involvement, treatment follow-up) aspects. Nasal CPAP adherence ranges from 50% to 84% (Grote et al., 2000; Sin et al., 2002) depending on the criteria used for good adherence and how the data of usage are collected (self-reported use, type of time clock in CPAP device). The commonly used definition of clinically good adherence is nasal CPAP usage of more than 4 hours per night for more than 70% of days (Engleman et al., 1994). It is well established that nasal CPAP adherence is poor in patients with mild symptoms of SDB (Engleman et al., 1999; Rosenthal et al., 2000). Other factors found to negatively influence nasal CPAP adherence are lack of perceived benefit, side effects from CPAP (mask irritations, persistent air leakage), previous uvulopalatopharyngoplasty, nasal obstruction and claustrophobia (Engleman and Wild, 2003). Interestingly, pressure intolerance is not a common complaint among nasal CPAP users. Predictive factors for good nasal CPAP adherence are increased severity of SDB, higher AHI, greater daytime sleepiness, perceived symptomatic benefit (Engleman and Wild, 2003) and good adherence to the treatment from the very beginning (Budhiraja et al., 2007a). Better adherence may be achieved by interventions such as individual education about SDB and nasal CPAP, mask adjustments, early interventions for side effects, early and regular clinic visits, spouse involvement or objective monitoring of adherence (Engleman and Wild, 2003).

Reports of age and gender as predictive factors for nasal CPAP use are conflicting. Sin and co-workers found increasing age and female sex associated with better nasal CPAP adherence, while McArdle and his group found the opposite (McArdle et al., 1999; Sin et al., 2002). The majority of the studies of nasal CPAP adherence are conducted with predominantly male subjects and thus do not have enough power to find a gender difference. No previous reports of nasal CPAP adherence in partial upper airway obstruction exist.

1.8.2. Lifestyle modifications

Obesity is one of the main risk factors for SDB; *weight loss* reduces apneic and hypopneic events and abolishes SDB symptoms (Rajala et al., 1991; Strobel et al., 1996; Lojander et al., 1998; Peppard et al., 2000). Weight loss should be recommended for all obese SDB patients regardless of other treatment modes. It has been reported that a 10% weight loss predicts a 26% decrease in AHI and by means of a cognitive-behavioral weight loss program, a satisfactory weight loss with improvement of SDB is achieved (Peppard et al., 2000; Kajaste et al., 2004).

Alcohol consumption and benzodiazepines, as well as other *sedatives* or medications that induce weight gain (antipsychotics, antiepileptics, and hormones) may exacerbate SDB (Berry et al., 1995; Scanlan et al., 2000). *Smoking* may cause difficulties in initiating or maintaining sleep, and airway obstruction by nasopharyngeal oedema and airway inflammation (Strollo et al., 2005). SDB patients should be encouraged towards good *sleep hygiene* and to avoid *sleep deprivation* which otherwise may also worsen SDB (Strollo et al., 2005). *Sleeping position* affects upper airway stability in SDB patients, and lateral positioning during sleep stabilises the upper airway (Neill et al., 1997).

1.8.3. Oral appliances and surgical treatment

The rationale for oral appliances is to increase the airway space, stabilize the position of mandibula and advance that of the tongue, thus reducing the collapsibility of the upper airway (Ng et al., 2003). Oral appliances are inexpensive, well tolerated and possible side-effects are reversible after cessation of treatment. They are a good treatment of choice for the snorer and the patient with mild to moderate SDB who is not compliant with nasal CPAP. However, oral appliances are usually less effective with severe SDB (Johnston et al., 2002).

The goal of surgical treatment is to provide a site-specific increase in upper airway size and a decrease in airway resistance, thus reducing the workload of breathing. The three major regions of surgical treatment are nose, soft palate and tongue base. Surgical techniques include tracheostomy, nasal reconstruction, uvulopalatopharyngoplasty (UPPP), tongue reduction, genioglossus or bi-maxillary advancement, maxillary and mandibular osteotomy, and the newest technique, temperature-controlled radiofrequency. Before starting the surgical treatment, the indications and risks of the procedure have to be carefully evaluated to provide the best outcome. Surgical treatment plays a limited role in the treatment of SDB because of its disappointing long-term efficacy. (Powell et al., 2005)

2. Female gender and sleep-disordered breathing – what differs from men?

The concept of obstructive sleep apnea was first described and defined in males. Findings and symptoms are simply extrapolated to females without taking into account special factors like differences in control of breathing and different hormonal environment.

2.1. Hormonal changes in women

2.1.1. Menstrual cycle

The normal menstrual cycle lasts 28 days starting with the menses on day 1. Ovulation occurs in the middle of the menstrual cycle dividing it into two phases: a follicular phase and a luteal phase. During the follicular phase, ovarian follicles grow and estrogen level rises, peaking just before ovulation. This triggers luteinising hormone secretion and ovulation occurs. After ovulation, the progesterone hormone dominates together with estrogen, but if no fertilization occurs, hormone levels drop and the menstrual cycle starts again (Armitage et al., 2005). Although women subjectively report sleeping difficulties during the menstrual cycle, in polysomnographic sleep studies, there are only few differences in sleep architecture: an increase in sleep spindle frequency and a small decrease in rapid eye movement (REM) sleep in the luteal phase compared with the follicular phase (Driver et al., 1996; Moline et al., 2003). In the follicular phase, upper airway resistance increases compared to the luteal phase, thus causing menstrual-cycle-dependent mild partial upper airway obstruction in women (Driver et al., 2005).

2.1.2. Pregnancy

During pregnancy, estrogen and progesterone levels are high, ensuring less collapsibility of the upper airway (Saaresranta and Polo, 2003). On the other hand, in the pregnant woman, the upper airway becomes narrower, the nose stuffier and the function of the diaphragm deteriorates compared to a non-pregnant one, thus predisposing to snoring and SDB (Saaresranta and Polo, 2003). Pregnancy affects sleep because of the subjective discomfort of nausea or vomiting, the growing uterus, fetal movements, urinary frequency, backaches etc. (Moline et al., 2003). In sleep studies during pregnancy, more frequent awakenings and total wake time during the night, as well as decreased slow wave sleep have been reported (Moline et al., 2003). It is also known that during pregnancy 15-20% of women report a new onset of snoring, whereas less than 5% report snoring before pregnancy, and chronic pregnant snorers are more likely to exhibit UARS (Franklin et al., 2000; Guilleminault et al., 2000). Snoring in pregnancy is associated with pre-eclampsia and pregnancy-induced hypertension (Franklin et al., 2000). Nikkola and colleagues found no significant sleep apnea or episodes of hypoxemia in women with multiple pregnancy (Nikkola et al., 1996). On the other hand, obese pregnant women are at greater risk of SDB compared with non-obese pregnant women (Maasilta et al., 2001).

2.1.3. Menopause

Menopause is defined as permanent cessation of menstruation because of depletion of ovarian follicles. Clinical menopause is defined retrospectively 12 months after the final menstrual period. Menopause occurs at a median age of 51 years for all Finnish women (Luoto et al., 1994), but ranges in Western countries from 40 to 58 years (Moe, 2005). Smoking, obesity, menarche age, duration of breastfeeding and use of oral contraceptives influence the age at which menopause occurs. During the

perimenopausal stage, ovarian function starts to change, causing irregularities in menstruation. This stage starts two to eight years before the cessation of menstruation and lasts until 12 months after the final menses. The postmenopausal stage starts after the menopause and lasts through the remaining life span of a woman. The perimenopause and the part of the postmenopausal period with climacteric symptoms comprise the climacterium (Greendale et al., 1999).

Hormonal changes during the menopausal transition are not abrupt. It is a dynamic process consisting of complex and interactive changes in the endocrine and central nervous system. The perimenopausal stage is characterised by elevated follicle-stimulating hormone (FSH) levels and variable menstrual cycle length. Inhibins A and B are negative feedback regulators of FSH. During the menopausal transition, FSH levels increase first because of a decrease in secretion of inhibin B, which may cause elevated luteinizing hormone (LH) and estrogen levels (Santoro, 2005). Later on, FSH levels increase because of the absence of estrogen and progesterone that would normally inhibit FSH secretion by negative feedback on the hypothalamus (Moe, 2005). The postmenopausal stage is characterised by high FSH (> 30 IU/l) and LH levels, low levels of estrogen and progesterone, and more than 12 months since the final menstruation. After 2-3 years of menopause, LH levels start to decrease (Longcope et al., 1986). In premenopausal women, the main estrogen is estradiol (E2) derived from the ovaries. After menopause, most estrogens are derived from androstenedione and aromatised to estrone (E1) in adipose tissue (Grodin et al., 1973). Therefore, estrogen concentrations can be at the same level as during the premenopause in very obese postmenopausal women (Kirchengast, 1994). The normal feedback regulation of female hormones is presented in Figure 4.

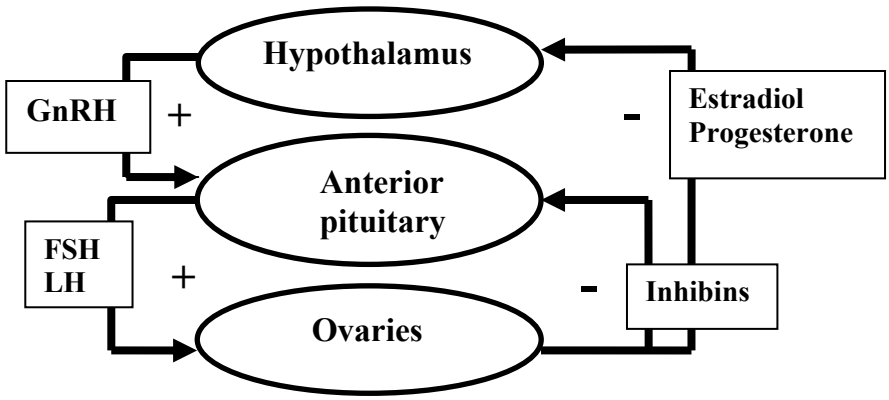

Figure 4. Normal feedback regulation of female hormones. FSH=follicle-stimulating hormone, LH=luteinizing hormone, GnRH=gonadotropin-releasing hormone, + positive feedback, - negative feedback.

In the Western countries, women live for nearly 80 years and therefore spend about one third of their life in the postmenopausal phase. The well known vasomotor symptoms of menopause include hot flashes and night sweating (Freedman, 2005). Sleeping problems are reported by up to 73% of postmenopausal women. Other

menopausal symptoms and signs include urinary incontinence, vaginal atrophy, reduced sexual function and depression (Dzaja et al., 2005). All these symptoms may start years before the menopause, during the perimenopausal phase, also causing sleep problems and fatigue (Moline et al., 2003). The prevalence of SDB rises among postmenopausal women so that the well-documented gender gap in SDB prevalence begins to narrow from the female/male ratio of 1:3.3 to 1:1.44 (Bixler et al., 2001). Strong associations have also been found with menopause and obesity, hypertension, thyroid dysfunction and cancers (Moe, 2005).

2.2. Influence of menopause on symptoms of SDB

Poor sleep quality is linked with middle age in women and attributed to the menopause, but the results are inconsistent (Owens and Matthews, 1998; Kravitz et al., 2003; Young et al., 2003; Redline et al., 2004). In older age, sleep may be affected by age-related problems like chronic pain, depression or other diseases. SDB is associated with sleep architecture alterations like more light sleep, less deep sleep and increased arousals. These associations are stronger in men than in women, suggesting important sex differences in sleep physiology (Redline et al., 2004).

The gender differences in symptoms have been discussed in the clinical features section (section 1.6.). Premenopausal women with SDB are heavier than postmenopausal ones matched for RDI. Indeed, obesity becomes a less important risk factor for women after menopause (Redline et al., 1994; Young et al., 1996). In one study, all (100%) postmenopausal women with HT and SDB and all premenopausal women with SDB were obese, but it was true for only 49.4% of postmenopausal women without HT but with SDB (Bixler et al., 2001). Few studies address symptom differences between pre- and postmenopausal women with SDB. In an older study, the clinical complaints of pre- and postmenopausal SDB women were compared (Guilleminault et al., 1988). Premenopausal women tended to report more morning headaches and night terrors (75% vs. 60% and 50% vs. 21%, respectively) and less severe EDS (56% vs. 71%) than postmenopausal ones. In another old study, the symptoms of premenopausal women with SDB were characteristic of the syndrome: loud snoring and EDS (Wilhoit and Suratt, 1987). In a questionnaire study of the general population in Sweden, 1.4-7.4% in the age groups of premenopausal women (aged 20-44 yrs) reported snoring as a problem, as did 3.2-14.4% in the age groups of postmenopausal women (aged 50-69 yrs) (Larsson et al., 2003). Relatives were concerned about witnessed apneas in 0.9-2.2% in the age groups of premenopausal women and in 2.1-6.5% in the age groups of postmenopausal women. In a recent questionnaire study, no differences were found in answers regarding symptoms of sleep apnea, periodic leg movement or psychiatric sleep disorder between women under 50 years compared with women over 50 years old, when the AHI was taken into account (Valipour et al., 2007).

2.3. Influence of menopause on findings of SDB

Subjective sleep quality is impared after menopause in women (Young et al., 2003). Studies to assess sleep before and after menopause with objective sleep measures like

polysomnography or actigraphy are few. An actigraphy study found more frequent arousals during the night in perimenopausal women compared to premenopausal ones (Baker et al., 1997). Polysomnographic studies have not shown any objectively detectable decline in sleep quality, although subjectively disrupted sleep and daytime fatigue are common complaints among postmenopausal women (Young et al., 2003; Sharkey et al., 2003). There is a clear mismatch between subjective and objective data on sleep and menopause, which has been called "sleep state misperception". The reason for this misperception is not known but one possibility is that polysomnography is not sensitive enough to measure sleep quality (Polo, 2003).

3. Co-morbidities and SDB

Tables 3-6 review the co-morbidity data of SDB studied mostly in recent years. Recent, original articles on studies comparing co-morbidity in general and SDB populations are included. Studies comparing co-morbidity in SDB between pre- and postmenopausal women or between partial upper airway obstruction and periodic obstructive breathing do not exist.

3.1. Cardiovascular co-morbidities and diabetes mellitus type 2 in SDB

SDB is a highly prevalent disease in the population and it is frequently coexisting undiagnosed in patients with some other diseases. The typical patient with SDB is an obese, middle-aged male or postmenopausal female, all features which also increase cardiovascular risk, making it hard to assess the independent role of SDB in cardiovascular diseases. Studies trying to assess these associations have had methodological limitations like small sample sizes, co-morbid conditions, medication used, lack of control groups, and lack of longitudinal study designs. However, nowadays there is evidence of an association between SDB and cardiovascular diseases or risk (Shamsuzzaman et al., 2003; Caples et al., 2007).

3.1.1. Pathogenesis in cardiovascular co-morbid diseases and diabetes mellitus type 2 in SDB

SDB includes periodic obstructive breathing and partial upper airway obstruction, characterized by increased respiratory effort despite total or partial upper airway obstruction. In central sleep apnea (CSA), both respiratory efforts and airflow are absent. CSA is mainly linked with heart failure and is not otherwise discussed in this thesis. The mechanisms underlying cardiovascular diseases in patients with SDB are not fully understood; the pathogenesis is most likely a multifactorial process. SDB causes hypoxemia, reoxygenation, hypercapnia, arousals, and sleep deprivation due to episodes of apneas and hypopneas, and abrupt intra-thoracic pressure changes resulting from inspiratory effort against the closed upper airway. These can trigger the intermediary mechanisms for cardiovascular diseases, including sympathetic nervous system overactivity, inflammatory pathways, endothelial dysfunction, metabolic dysregulation, oxidative stress, and increased coagulation (Fig. 5) (Shamsuzzaman et al., 2003; Caples et al., 2007).

Table 3. Selected recent studies of sleep-disordered breathing and cardiovascular co-morbidities.

Author	Study design	Disease	Subjects	Findings	Adjustments	**Age** (years, mean or range) **BMI** (kg/m^2, mean or range)	Comments
Young et al., 1997	Prospective population- based	Hypertension	n=1060 F/M: NA	Hypertension linearly increased with increasing AHI	Age, sex, body habitus (height, weight, waist, hip girth, neck)	Age 30-60 BMI NA	
Bixler et al., 2000	Controlled cross-sectional population-based	Hypertension	n=1741 F: 1000 M: 741	SDB associated with hypertension in young and middle-aged, no sex or MP difference	Age, BMI, sex, menopause, HT, alcohol use, smoking, race	Age 47 BMI 27	Snoring postmenopausal with HT had reduced risk for hypertension!
Grote et al., 2000	Cross-sectional clinical population- based	Hypertension	n=599 F: 51 M: 548	< 50yr SDB increases the risk by 2% for every RDI unit	Age, BMI, RDI	NA	Each yr of age increased the risk by 6%, gender effect NA, BMI increased risk by 6%
Lavie et al., 2000	Prospective population- based	Hypertension	n=2677 F: 728 M: 1949	Each apneic event/h added the risk of hypertension by 1%	Age, sex, AHI, neck circumference	Age 49 BMI 31	
Nieto et al., 2000	Cross-sectional population- based	Hypertension	n=6132 F: 52.8%	SDB increased the risk of hypertension in a dose response manner (max 37%)	Age, sex, BMI, neck circumference, WHR, smoking, alcohol use	Age >40 BMI 29	Sleep Heart Health Study
Peppard et al., 2000	Prospective longitudinal population- based	Hypertension	n=1189 (baseline) F: 45 %	Mild to moderate SDB had 2-3-fold risk for hypertension compared to subjects without SDB	Habitus (BMI, waist, hip, neck, skin folds), age, sex, smoking, alcohol use	Age 46 BMI 29	4 and 8 yr follow-up, BP > 140/90 pathologic, The Wisconsin Sleep Cohort Study
Marin et al., 2005	Prospective controlled population- based	Fatal/non-fatal cardiovascular events and stroke	M:1651	Cardiovascular events ↑ in untreated severe SDB vs. in healthy M. CPAP reduced risk	Age and BMI	NA	Mean follow-up time 10.1 yr, only men investigated
Hedner et al., 2006	Case-controlled population- based	Hypertension	n=344 F: 170 M: 174	OSA M had 2.6-2.9-fold risk for hypertension and hypertensive M 2.3-fold risk for OSA, risk not ↑ in F	Age, BMI, smoking, WHR	Age in groups 59-64 BMI in groups 27-30	F were all postmenopausal , methodology: nasal pressure cannula used
Lindberg et al., 2007	Controlled cross-sectional population-based	Hypertension	F: 6779	EDS+snoring: 1.8- fold risk for hypertension	BMI, alcohol use, smoking, physical activity	Age 45 BMI 24	Self-reported data of snoring and EDS Age>50 risk 1.5 and age<50 risk 3.4-fold for hypertension
Koskenvuo et al., 1987	Prospective population- based (The Finnish twin cohort)	Ischemic heart disease and stroke	M: 4388	Snoring a 1.7-fold risk for ischemic heart disease, also predicted stroke with ischemic heart disease together with 2.1-fold risk	Age, BMI, hypertension, smoking, alcohol use	Age 40-69 BMI NA	Questionnaire about snoring, hospital records for end points

Author	Study design	Disease	Subjects	Findings	Adjustments	**Age** (years, mean or range) **BMI** (kg/m^2, mean or range)	Comments
Hung et al., 1990	Case-control study	Ischemic heart disease	M: 101 and 53 male controls	AI >5.3 was independent 23-fold risk for myocardial infarction	Age, BMI, hypertension, cholesterol level, smoking	NA	
Mooe et al., 1996	Case-control study	Coronary artery disease (CAD)	M: 142 and 50 male controls	OSA independently associated with CAD	Age, hypertension, BMI, smoking, DM	Age 60 BMI 27	Only AHI or ODI>5% used, no symptoms
Mooe et al., 1996	Case-control study	CAD	F: 102 and 50 female controls	OSA independently associated with CAD	Age, hypertension, BMI, smoking, DM	Age 61 BMI 28	Only AHI or ODI>5% used, no symptoms
Peker et al., 1999	Case-control study	CAD	n=62 and 62 controls F: 18 M: 44	Prevalence of OSA ↑ 3.1-fold in middle-aged and elderly patients with CAD	Age, sex, BMI	Age 69 BMI 28	
Peker et al., 2006	Prospective clinical population- based	CAD	n=308 F: 63 M: 245	OSA patients 4.6-fold risk of CAD	Age, sex, hypertension, DM, current smoking	Age 49 BMI NA	Incidence study, 10 yr follow-up, efficient OSA treatment reduced risk
Sorajja et al., 2008	Cross-sectional population- based	CAD	n=202 F: 30% M: 70%	Presence and severity of SDB independently associated with coronary artery calcification	Age, sex, traditional coronary risk factors	Age 50 BMI 32	
Javaheri et al., 1998	Prospective clinical trial with heart failure patients	Heart failure (HF)	M: 81	Stable HF related to increased OSA (40% central and 11% obstructive apnea)	No adjustments	Age in groups 40-41 BMI 28	Stable HF, HF+OSA risk for arrhythmias, atrial fibrillation and low LVEF
Sin et al., 1999	Cross-sectional clinical trial with HF patients	HF	n=450 F: 68 M: 382	HF related to central and obstructive apnea in both genders, SDB less in F than M	Sex, age, BMI, LVEF, AF, $TcCO_2$	Age 60 BMI 29	Male sex and BMI risk for OSA; in M BMI and in F age dominant risk factor HF. AF, age, low $TcCo_2$ risks for CSA in both genders.
Shahar et al., 2001	Cross-sectional study of community-dwelling subjects	HF, stroke and CAD	n=1023 F: 426 M: 597	SDB associated strongly (2.4 fold) with HF and (1.6 fold)with stroke, less strongly with CAD	Age, sex, race, smoking, DM, hypertension, BMI	Age in groups 61-66 BMI 26-31	Findings persisted even with low AHI
Ferrier et al., 2005	Clinical trial with HF patients	HF	n=53 F: 12 M: 41	SDB very common in HF patients (OSA 53% and CSA 15%)	No adjustments	Age 60 BMI 28	LVEF 34% Stable HF, outpatients. atrial fibrillation, desaturation, sleep disruption and higher urinary norepinephrine levels associated with OSA/CSA and low LVEF with CSA

Author	Study design	Disease	Subjects	Findings	Adjustments	**Age** (years, mean or range) **BMI** (kg/m^2, mean or range)	Comments
Javaheri et al., 2006	Prospective study of HF patients	HF	M: 100	HF patients had average AHI 44/h but no symptoms (CSA 37% and OSA 12%), significant desaturations and ↓quality of sleep.	No adjustments	NA	Snoring and obesity correlated to OSA but not to CSA. AF, nocturnal arrhythmias, low LVEF and low CO_2 correlated to CSA. 20% of HF patients have PLMS.
Schulz et al., 2007	Cross-sectional prospective study of HF patients	HF	n=203 F: 51 M: 152	SDB prevalence 71% (OSA 43% and CSA 28%);	No adjustments	Age 65 BMI 28	Stable HF patients,LVEF<40%, OSA related to ESS, desaturations, BMI. CSA related to atrial fibrillation and low CO_2.
Arzt et al., 2005	Prospective cross-sectional population-based	Stroke	n=1475 F: 666 M: 809	SDB (about 4-fold risk) and stroke have significant relationship. AHI >20/h increases 3-fold risk of 1.stroke in 4 yr	Age, sex, BMI, hypertension and DM	Age 47 BMI 30	Partly Wisconsin Sleep Cohort Study
Bassetti et al., 2005	Prospective study of acute stroke patients	Stroke	n=152 F: 49 M: 103	46% of stroke patients had SDB (AHI+symptoms)	No adjustments	Age 56 BMI 26	SDB related to DM, night- time stroke onset, macroangiopathy as cause of stroke. Stroke severity does not predict SDB
Yaggi et al., 2005	Prospective observational cohort study	Stroke and death	n=1022 F: 294 M: 728	OSA associated with increased incidence (2.0 x) of stroke or death independently	Age, sex, race, BMI, smoking, alcohol use, AF, DM, hyperlipidemia	Age in groups 59-61 BMI in groups 31-34	Age >50 yr, median 3.4-yr follow-up
Elwood et al., 2006	Prospective population- based cohort study	Stroke and heart disease	M: 1986	Sleep disturbances related to stroke (3- fold risk) and EDS related to ischemic heart disease	Age, social class, smoking, alcohol consumption, BMI, neck circumference	Age 55-69 BMI NA	Questionnaire study, 10-yr follow-up. The Caerphilly Cohort
Munoz et al., 2006	Prospective, longitudinal population- based study	Stroke	n=429 F: 47.3% M: 52.7%	Severe OSA (AHI>30) independent risk for stroke (2.5-fold) in elderly population	Age, sex, hypertension, DM, AF, smoking, alcohol, BMI, cholesterol	Age 77 BMI 28	Victoria Sleep Project, 6-yr follow-up
Gami et al., 2004	Prospective study of cardiologic patients	Atrial fibrillation (AF)	n=463 F: 185 M: 278	AF related to OSA with 2.2-fold risk	BMI, neck circumference, hypertension, DM	Age in groups 68-71 BMI in groups 30	The Berlin questionnaire used
Porthan et al., 2004	Prospective case-controlled study of AF patients	AF	n=59 F: 11 M: 48	OSA common in AF patients (32%) but not more common than in case control group (29%)	Controls matched for sex, age, cardiovascular morbidity	Age 59 (25-84) BMI NA	No differences in sleep recordings between AF and control group No gender difference measured

Author	Study design	Disease	Subjects	Findings	Adjustments	**Age** (years, mean or range) **BMI** (kg/m^2, mean or range)	Comments
Mehra et al., 2006	Cross-sectional case-controlled community- based study of SDB patients	AF	n=566 with SDB n=228 no SDB n=338 F: about 50%	SDB patients had 4 times more AF than none-SDB	Age, sex, BMI, CAD	Age in groups 69-71 BMI in groups 29-30	Sleep Heart Health Study
Gami et al., 2007	Retrospective longitudinal cohort study of suspected SDB patients	AF	n=3542 F: 1193 M: 2349	BMI, OSA male gender and desaturations predict AF within 5 yrs of OSA diagnosis in patients <65 yrs	Age, sex, coronary heart disease, BMI, desaturations	Age 49 BMI 33	5-yr follow-up

Abbreviations: AF=atrial fibrillation, AHI=apnea-hypopnea index, AI=apnea index, BMI=body mass index, CAD=coronary artery disease, CPAP=continuous positive airway pressure, CSA=central sleep apnea, DM=dibetes mellitus, EDS=excessive daytime sleepiness, ESS=Epworth Sleepiness Scale, F=female, HF=heart failure, HT=hormone therapy, LVEF=left ventricular ejection fraction, M=male, MP=menopause, NA=not available, OSA=obstructive sleep apnea, PLMS=periodic leg movements in sleep, SDB=sleep-disordered breathing, $TcCO_2$=transcutaneous carbon dioxide

Table 4. Selected recent studies of sleep-disordered breathing and endocrinologic co-morbidities.

Author	Study design	Disease	Subjects	Findings	Adjustments	**Age** (years, mean or range) **BMI** (kg/m^2, mean or range)	Comments
Elmasry et al., 2000	Prospective population- based	Diabetes mellitus (DM) type 2	M: 2504	Snorers: 2-fold risk for DM vs. non-snorers. Obesity increases risk	Age	Age 30-69 BMI NA	Follow up 1984-1994, Questionnaire survey of habitual snoring.
Al-Delaimy et al., 2002	Prospective longitudinal study of nurses	DM type 2	F: 69 852	Occasional or regular snoring associated with increased risk (1.2-1.6-fold) of DM	Age, BMI, WHR, smoking, hypertension, HT, alcohol use	Age 40-65 at baseline BMI in 3 groups 24-28	Follow up 10 yr, Questionnaire survey of habitual snoring, The Nurses' Health Study.
Punjabi et al., 2004	Cross-sectional study of community-dwelling subjects	Glucose intolerance and insulin resistance	n=2656 F: 54.3% M: 45.7%	SDB independently associated with (1.3-1.5-fold risk) glucose intolerance and insulin resistance	Age, sex, BMI, waist circumference, smoking, sleep duration	Age 68 (60-75) BMI 27 (27-31)	The Sleep Heart Health Study Severity of SDB, hypoxemia during sleep and arousals were independently associated with insulin resistance.
Reichmuth et al., 2005	Longitudinal cross-sectional population-based	DM type 2	n=1387 F/M: NA	DM independently more prevalent in SDB (AHI >15) patients (3-4-fold risk).	Age, sex, waist circumference	Age 49 yr BMI 29	Follow up 4 yr, PSG used. The Wisconsin Sleep Cohort Study
Lindberg et al., 2007	Cross-sectional population- based	DM type 2	F: 6779	EDS+snoring risk factor for DM, EDS only a risk factor for DM	BMI, alcohol use, smoking, physical activity	Age 45 BMI 24	Self-reported data of snoring and EDS
Tuomilehto et al., 2008	Cross-sectional population- based	DM type 2	n=4500 F: 2250 M: 2250	DM 3 times more prevalent in symptomatic SDB patients in M, NOT in F	Age, BMI, sedative medication or antidepressant, smoking	Age 60 BMI 28	
Valham et al., 2008	Cross-sectional population- based	DM type 2	n=7905 F: 4047 M: 3858	Habitual snoring had 1.6-fold risk and witnessed apnea 3.3-fold risk of DM in F but not in M. Witnessed apnea had 3.8-fold risk of DM in M of 25-54 yrs	Age, smoking, BMI, waist circumference	Age 53 BMI 27	Questionnaires used to define SDB and DM
Lin et al., 1992	Cross-sectional clinical study of OSA and hypothyroid patients	Hypothyroidism	n=65 (OSA) + 20 (hypot.) OSA F: 10 M: 55 Hypot. F: 18 M: 2	25% of hypothyroid patients had OSA; 3.1% of OSA patients had hypothyroidism	No adjustments	NA	Snoring improved after 1yr of hormone replacement All hypothyroid patients snored. Thyroid hormone corrected AI, SaO_2, arousal index, movement index after 4 months.
Pelttari et al., 1994	Case-control study of hypothyroid patients	Hypothyroidism	n=26 and 188 controls	SDB increased in hypothyroid patients because of obesity and M gender	Age, sex, BMI	Age 43 BMI 29	SCSB used

Author	Study design	Disease	Subjects	Findings	Adjustments	**Age** (years, mean or range) **BMI** (kg/m^2, mean or range)	Comments
Kapur et al., 1998	Cross-sectional case-control study of OSA patients	Hypothyroidism	n=336 and 1713 controls F: 22% M: 78%	Tendency of increased hypothyroidism in F and < 50 yr patients of OSA	Age, sex	Age 52 Mean weight 102 kg	NO significant result!
Skjodt et al., 1999	Cross-sectional clinical SDB population	Hypothyroidism	n=200 F/M: NA	Hypothyroidism prevalence in all 1.5% and in OSA patients 2.4%	No adjustments	NA	Screening for hypothyroidism required
Miller and Husain, 2003	Cross-sectional clinical SDB population	Hypothyroidism	F: 118	Prevalence of hypothyroidism 9.3% in OSA F vs. general F 5.9%. NO significant result!	No adjustments	Age 62-64 BMI 36-42	Age, BMI and RDI similar between hypothyroid and euthyroid groups, PSG used
Jha et al., 2006	Prospective clinical hypothyroid population	Hypothyroidism	n=50 F: 29 M: 21	30% had SDB, after replacement treatment SDB improved	No adjustments	Age 34 BMI 25	PSG used

Abbreviations: AHI=apneahypopnea index, BMI=body mass index, DM=diabetes mellitus, EDS=excessive daytime sleepiness, F=female, HT=hormone therapy, M=male, NA=not available, OSA=obstructive sleep apnea, PSG=polysomnogram, RDI=respiratory disturbance index, SaO_2= arterial oxyhemoglobin saturation, SCSB=static-charge-sensitive bed, SDB=sleep-disordered breathing, WHR=waist hip ratio

Table 5. Selected recent studies of sleep-disordered breathing and chronic obstructive pulmonary co-morbidities.

Author	Study design	Disease	Subjects	Findings	Adjustments	**Age** (years, mean or range) **BMI** (kg/m^2, mean or range)	Comments
Larsson et al., 2001	Cross-sectional population-based	Asthma and COPD	n=4648 F: 2299 M: 2349	Snoring 2-fold and apneas 2-3 fold in COPD and asthma patients	Age sex, smoking,	Age 20-69 BMI NA	Questionnaire study
Sanders et al., 2003	Prospective cohort	COPD	n=5954 F: 3138 M: 2816	OSA prevalence similar in mild COPD or no COPD patients	Age, sex, height, weight, race, smoking	Age in groups 62-66 BMI in groups 27-29	OSA=RDI>10 or 15, no symptoms included
Bednarek et al., 2005	Cross-sectional population-based	COPD	n=676 F: 320 M: 356	No differences in COPD prevalence in OSA or non-OSA groups. No relationship between AHI and airflow limitation.	No adjustments	Age 57 BMI F: 29 M: 29	Full PSG, spirometry, ERS guidelines used for COPD
Ekici et al., 2005	Cross-sectional population-based	Asthma	n=7469 F: 3920 M: 3549	Asthma symptoms correlated with snoring (1.5 fold) and apnea (2.2 fold) and all 3 together impair QL	Sex, age, BMI, smoking, income, education	Age in groups 43-46 BMI in groups 26-27	Questionnaire study
Teodorescu et al., 2006	Clinical cross-sectional population of asthmatics	Asthma	n=115 F: 79 M: 36	EDS associated with OSA symptoms, M gender but not asthma severity	Sleep apnea scale score, M gender, asthma severity	Age 47 BMI 31	No differences between M and F Questionnaire study with medical records for asthma diagnosis and spirometry
Karachaliou et al., 2007	Cross-sectional population-based	Asthma and COPD	n=1501 F: 609 M: 892	Not asthma but COPD patients had 1.3-2-fold more SDB symptoms	BMI, apneas, ESS, frequent snoring	Age 61 BMI 27	Questionnaire, medical records, physician interview of respiratory and sleep disorders, spirometry

Abbreviations: AHI=apneahypopnea index, BMI=body mass index, COPD=chronic obstructive pulmonary disease, EDS=excessive daytime sleepiness, ESS=Epworth Sleepiness Scale, ERS=European Respiratory Society, F=female, M=male, NA=not available, OSA=obstructive sleep apnea, PSG=polysomnogram, QL=quality of life, RDI=respiratory disturbance index

Table 6. Selected recent studies of sleep-disordered breathing and epilepsy and psychiatric co-morbidities.

Author	Study design	Disease or condition investigated	Subjects	Findings	Adjustments	**Age** (years, mean or range) **BMI** (kg/m^2, mean or range)	Comments
Beran et al., 1999	Cross-sectional clinical population	Epilepsy	n=50 F: 15 M: 35	79% of epilepsy patients had SDB, 84% had SDB and 48% retained epilepsy diagnosis	No adjustments	Age 46 BMI 30	BMI>30, snoring and elderly age risks for SDB in patients with epilepsy
Malow et al., 2003	Prospective pilot study of clinical population	Epilepsy	n=13 adults and 5 children	46% of adults and 60% of children had OSA	No adjustments	Age in adults 20-56 and in children 14-17 BMI NA	CPAP therapy reduced seizures by 45%
Manni et al., 2003	Cross-sectional clinical epilepsy population	Epilepsy	n=283 F: 146 M: 137	Epilepsy patients had 10.2% OSA: 15.4% of M and 5.4% of F	Sex, BMI, age	Age 34 BMI NA	Epilepsy+OSA patients older, BMI↑, M, sleepier, than patients with epilepsy alone
Höllinger et al., 2006	Retrospective longitudinal clinical population of epilepsy and OSA patients	Epilepsy	n=29 epilepsy (out of 557 OSA) F: 4 M: 25	5% of OSA patients had epilepsy	No adjustments	In epilepsy group: age 56 BMI 28,	CPAP therapy reduced seizures in 30% of patients
Pillar et Lavie, 1998	Cross-sectional sleep-clinic population	Psychiatric symptoms	n=2271 F: 294 M: 1977	No association between OSA and depression or anxiety but F had higher scores for depression and anxiety than M	Age, RDI	Age 48 BMI 29	SCL-90 psychiatric questionnaire used
Ancoli-Israel et al., 1999	Cross-sectional clinical population of psychiatric patients	Psychiatric disorders	n=52 F: 17 M: 35	48% had OSA, aged 65-76 schizophrenia patients had more severe OSA compared to healthy controls	Age, BMI	Age 60 BMI 29	
Sharafkhaneh et al., 2005	Retrospective cross-sectional study of veterans	Psychiatric disorders	n=4 060 504 M: > 90%	In OSA group 21.8% had depression (2.7-fold risk), 5.1% psychosis (1.4-fold risk) compared to non-OSA	Age, sex, ethnicity	Age 58 BMI NA	2.9% had OSA, 7.4% of depressed had OSA compared to 2.9% of non-depressed, 1.6% of psychotic had OSA compared to 1.2% of non-psychotic

Abbreviations: BMI=body mass index, CPAP=continuous positive airway pressure, F=female, M=male, NA=not available, OSA=obstructive sleep apnea, RDI=respiratory disturbance index

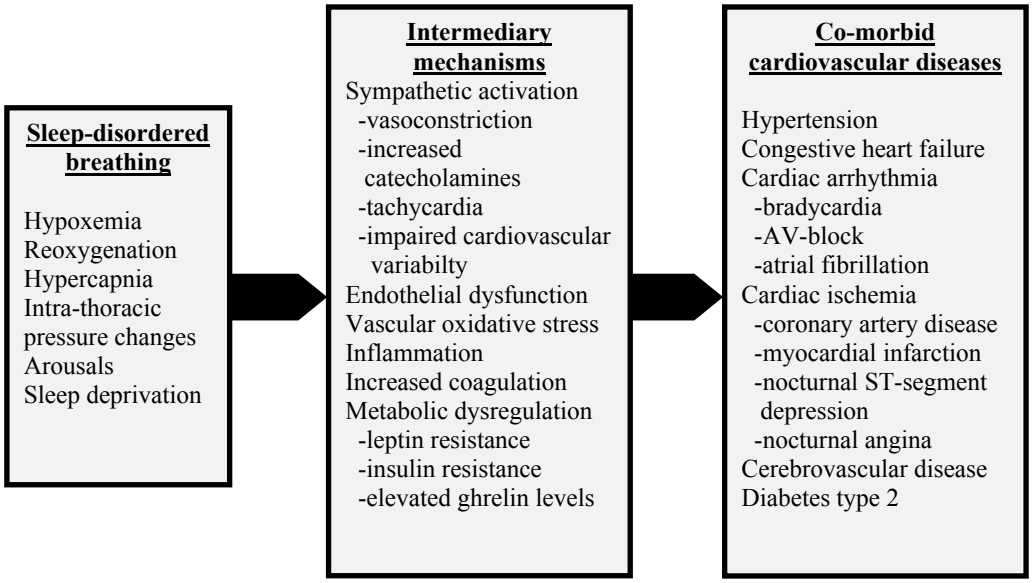

Figure 5. The mechanisms between sleep-disordered breathing and co-morbid cardiovascular diseases (Modified from Shamsuzzaman et al. JAMA 2003).

3.1.1.1. Cardiovascular and metabolic effects of SDB

Repetitive episodes of apneas, hypercapnia and intrathoracic pressure changes during the night cause increased sympathetic activity and vasoconstriction, and a consequent rise in systemic and pulmonary artery pressure, increased left ventricular afterload, and changes in cardiac output (Sajkov et al., 1994; Narkiewicz and Somers, 2003). There is also evidence of augmented sympathetic activity during wakefulness, which may contribute to the cardiovascular pathophysiology (Narkiewicz and Somers, 2003). Furthermore, negative intrathoracic pressure alters cardiac filling and cardiac function such in a way that there is a reduction in stroke volume and cardiac output and decreased baroreflex sensitivity in patients with SDB (Shamsuzzaman et al., 2003; Ryan et al., 2007). Frequent *arousals* cause sleep fragmentation and sleep deprivation which have been associated with metabolic and inflammatory dysregulation (Spiegel et al., 2005; Irwin et al., 2006).

3.1.1.2. Mechanisms of diabetes mellitus type 2 and cardiovascular diseases in SDB

Sympathetic activation. Patients with SDB have high levels of sympathetic nerve traffic and these are present even during daytime in wakefulness (Narkiewicz and Somers, 2003). One mechanism that may enhance the sympathetic activation in SDB during daytime is decreased baroreflex sensitivity (Ryan et al., 2007). Increased sympathetic activation causes more rapid pulse rate, decreased heart variability and increased blood pressure, all of which have been linked to risks of cardiovascular diseases (Narkiewicz and Somers, 2003).

Endothelial dysfunction. The vascular endothelium maintains the balance between vasoconstriction and vasodilatation. A shift in this balance towards vasoconstriction leads to damage to the arterial wall, and endothelial dysfunction occurs (Shamsuzzaman et al., 2003). Obstructive episodes of apneas and hypopneas may act as stimuli for the release of vasoconstrictive substances like endothelin. Nitric oxide is a vasodilator which is decreased in patients with SDB (Budhiraja et al., 2007b). Endothelial dysfunction was found to occur in response to cardiovascular risk factors and to proceed in the development of atherosclerosis (Ross, 1999). A gender difference was found in the endothelial dysfunction. Flow-mediated vasodilatation was more impaired in females with SDB than males, implying that females with SDB may be more vulnerable to cardiovascular diseases than men (Faulx et al., 2004). Treatment with nasal CPAP may improve the endothelial function (Ohike et al., 2005).

Vascular oxidative stress. Repetitive periods of upper airway collapse result in cyclic periods of hypoxia/reoxygenation which, in turn, cause increased activation of polymorphonuclear neutrophils. They adhere to the endothelium and release free oxygen radicals (Lavie, 2003; Lavie et al., 2004). This has been found in both human and animal models (Lavie, 2003; Dematteis et al., 2008). Further, free oxygen radicals are supposed to make an important contribution to the development of cardiovascular disease, linking cardiovascular co-morbidity with SDB (Yamauchi and Kimura, 2008). Short-term effective use of nasal CPAP therapy seems to fully reverse the increased oxygen radical release in patients with SDB (Schulz et al., 2000).

Inflammation. Systemic inflammation plays a pivotal role in all stages of atherogenesis, from foam cell to plaque formation to rupture and, ultimately, to thrombosis (Libby et al., 2002). The most important markers of systemic inflammation include C-reactive protein (CRP), tumour necrosis factor (TNF)-α and interleukin (IL)-6. All these inflammatory markers are elevated in patients with SDB (Yokoe et al., 2003; Minoguchi et al., 2004). Hypoxia and sleep deprivation may evoke the production of inflammatory cytokines and CRP. Nasal CPAP therapy decreases the levels of IL-6 and CRP (Yokoe et al., 2003).

Increased coagulation. Increased circulating levels of coagulation factors have been reported in patients with untreated SDB (Robinson et al., 2004). This may also increase the risk of clot formation, atherosclerosis and cardiovascular diseases. There is some but not consistent evidence that nasal CPAP therapy can reduce coagulability in patients with SDB (Robinson et al., 2004; von Känel et al., 2006). This suggests that SDB may be causally associated with increased coagulability.

Metabolic dysregulation. SDB-related factors that may be associated with metabolic dysfunctions include increased sympathetic activity, sleep fragmentation and intermittent hypoxia. Metabolic dysregulation can predispose to both weight gain and cardiovascular risk.

Impaired glucose tolerance is associated with SDB. Patients with SDB, independent of obesity, have high levels of fasting blood glucose, insulin, and glycosylated haemoglobin and increased insulin resistance (Vgontzas et al., 2005). On the other

hand, sleep deprivation, sympathetic activation and leptin resistance are associated with impaired glucose intolerance (Spiegel et al., 2005; Vgontzas et al., 2005). Nasal CPAP therapy has not shown any consistent improvement in glucose tolerance (Punjabi et al., 2003; West et al., 2007), until recent data showing that regular use of nasal CPAP with effective pressure improved insulin sensitivity during a 2.9-year follow-up (Schahin et al., 2008).

Leptin is an adipocyte-derived hormone that regulates body weight through suppressing appetite and promoting satiety (Saaresranta and Polo, 2003). Although the independent relationship of leptin and SDB requires more investigation, there is some evidence of an association. Several studies report high levels of leptin in patients with SDB. Obesity or nocturnal hypoxemia have been the main determinants for hyperleptinaemia, and BMI the main confounding factor (Patel et al., 2004; Barceló et al., 2005; Tatsumi et al., 2005). Changes in leptin levels have been linked with cardiac sympathetic function, and CPAP therapy markedly decreases leptin levels (Shimizu et al., 2002).

Ghrelin is a hormone that influences appetite and energy homeostasis but also has effects on cardiovascular and gastric functions (Hosoda et al., 2006). Human obesity is associated with decreased ghrelin levels that increase after weight reduction acting as an antagonist of leptin. In patients with SDB, ghrelin levels have been elevated and then have decreased after two days of nasal CPAP therapy (Harsch et al., 2003). Sleep restriction is associated with decreased leptin, increased appetite and ghrelin levels (Spiegel et al., 2004). In humans, ghrelin decreases systemic vascular resistance and increases cardiac index and stroke volume index concomitantly, causing a reduction in arterial pressure but no change in heart rate or mean pulmonary arterial pressure (Lely et al., 2004).

3.1.2. Hypertension

There is strong evidence that SDB is an independent risk factor for hypertension; this is acknowledged in recommendations where SDB is to be ruled out as a cause of hypertension (Chobanian et al., 2003). The Wisconsin Sleep Cohort study was the first large prospective population study to show the causal association of SDB in the development of hypertension (Peppard et al., 2000). They found that patients with mild to moderate SDB had a two- to three-fold risk of developing new hypertension in a four-year follow-up after adjusting for age, sex, body habitus, smoking and alcohol consumption. Regular or occasional snoring with or without excessive daytime sleepiness increases the risk of hypertension by 1.3-1.8 times in women, independently of major confounding factors (Hu et al., 1999; Lindberg et al., 2007). In men with UARS without classic apneas and drops in oxygen saturation, repetitive increases in both systolic and diastolic blood pressures during sleep occur as a result of increased airway resistance (Guilleminault et al., 1996). This emphasizes that UARS, often accompanied with snoring, may play a role in the development of hypertension. A dose-response association between the severity of SDB (measured as increasing AHI or RDI) and the presence of hypertension has been found in many studies (Young et al., 1997; Lavie et al., 2000; Grote et al., 2000; Nieto et al., 2000; Peppard et al., 2000).

Age and BMI are the major confounding risk factors for both SDB and hypertension. In patients with SDB, increasing BMI and old age (over 65 years) decreased the association between SDB and the prevalence of hypertension (Young et al., 1997; Bixler et al., 2000; Hedner et al., 2006). To emphasize the clinical importance of SDB regarding prevalence of hypertension, even mild SDB has been found to add a slight risk of hypertension (Young et al., 1997).

There are few studies investigating gender differences regarding SDB and hypertension and even fever studies addressing this issue in pre- and postmenopausal women. Hedner and co-workers found that male patients with SDB had an independent association with hypertension, while in women there was a similar tendency but it was not as strong and significant as in men (Hedner et al., 2006). They speculated that because their women were almost all postmenopausal in age, this could have accounted for the propotionally higher number of women with SDB, therefore resulting in a dilution of the association between SDB and hypertension in women. Postmenopausal, snoring women who used HT had a reduced risk of hypertension but the risk of hypertension in postmenopausal women without HT was similar to that of men (Bixler et al., 2000). This implies that hormonal factors may contribute to gender differences regarding the associations of SDB and hypertension.

3.1.3. Ischemic heart disease

SDB induces stress situations that can predispose to ischemic heart disease. Nightly episodes of hypoxemia, hypercapnia, increased sympathetic activation and blood pressure may evoke myocardial ischemia and coronary artery disease (CAD). In the early studies with a male population, snoring increased the risk of ischemic heart disease by 1.7-fold and an apnea index over 5.3 increased the risk of myocardial infarction 23-fold after adjustment for hypertension, BMI and smoking habits (Koskenvuo et al., 1987; Hung et al., 1990). With similar age and BMI in men and women, patients with SDB (defined as AHI $\geq$ 14 in men and AHI $\geq$ 5 in women) had similar 4.5- and 4.1-fold risks for CAD, respectively (Mooe et al., 1996a and 1996b). An increased prevalence of SDB was found in middle-aged and elderly patients with CAD compared to sex-, age- and BMI-matched subjects without CAD, although traditional risk factors were adjusted for (Peker et al., 1999). In longitudinal studies, untreated SDB worsened the prognosis of patients with CAD, whereas patients with CAD and SDB receiving treatment had a better clinical course compared with those who refused the treatment (Mooe et al., 2001; Milleron et al., 2004; Peker et al., 2006).

Recently, it has been found that even in patients without clinical CAD, the presence and severity of SDB are independently associated with the presence of coronary artery calcification (Sorajja et al., 2008). In the Sleep Heart Health study, the prevalence of CAD increased with even a mildly elevated AHI but there was a plateauing of the effect size at a moderately increased AHI (Shahar et al., 2001). Firstly, this implies that even mild SDB has considerable public health implications. Secondly, the plateauing may indicate that the effect of SDB on CAD risk is fully realized at some level or that the AHI is not a proper tool to capture the relevant pathogenetic factors. Patients with untreated severe SDB (AHI $\geq$ 30) have a significantly higher incidence of fatal and

non-fatal cardiovascular events than healthy controls matched for age and BMI, and treatment with nasal CPAP reduces the risk (Marin et al., 2005). Male populations dominate in the studies and no gender differences have been found in associations of SDB with CAD. Taken together, even mild SDB should be taken into account when considering risk factors for CAD as SDB can be easily diagnosed and in many cases is effectively treatable.

3.1.4. Heart failure

The relationship between SDB and heart failure (HF) is complex since they may exacerbate each other. Hypoxemia, catecholamine surges and increased blood pressure due to SDB may predispose to congestive HF. On the other hand, HF could contribute to the pathogenesis of SDB in the form of obstructive or central apneas (Caples et al., 2005). Both SDB and HF are common diseases and thus it is clinically relevant to assess the association between SDB and HF, and to be able to maximise the treatment effect. In studies of patients with stable HF, the prevalence estimates of SDB varied from 11 to 53%, and the isolated prevalence estimates of CSA varied from 15 to 40% (Javaheri et al., 1998; Sin et al., 1999; Ferrier et al., 2005; Javaheri et al., 2006; Schultz et al., 2007). Patients were all middle-aged or older, male gender dominated and obesity was also common (mean BMI 28-31 kg/m^2). In one study with HF patients, women had 26% lower occurrence of SDB than men, while the relative occurrence of both CSA and obstructive sleep apnea were greater in men than in women (Sin et al., 1999). CSA risk factors, atrial fibrillation (AF), increasing age and hypocapnia during sleep did not differ between genders but in women increasing age and hypocapnia were more strongly related to CSA than in men (Sin et al., 1999). Similar risk factors for CSA were also found in other studies, but gender differences were not investigated (Ferrier et al., 2005; Javaheri et al., 2006; Schultz et al., 2007).

Cross-sectional data from the Sleep Heart health study showed a strong association (2.4-fold risk) of SDB with HF, the finding persisting even with low AHI measures (Shahar et al., 2001). This implies again that the AHI may not be the proper parameter to measure the severity or consequences of SDB. Nasal CPAP therapy for a three-month period has improved left ventricular ejection fraction in patients with SDB and HF, but the long-term effects of nasal CPAP are still not known (Mansfield et al., 2004; Egea et al., 2007).

3.1.5. Atrial fibrillation

SDB and nocturnal disturbances of cardiac rhythm including AF, heart block, ventricular ectopy, sinus bradycardia, and atrioventricular block have been linked together (Shamsuzzaman et al., 2003; Mehra et al., 2006). Hypoxemia, pressure changes and apnea episodes may predispose to the development of AF. SDB is also a risk factor for hypertension, CAD and HF all of which are known to precipitate AF (Peppard et al., 2000). Patients with AF have an over two-fold risk for SDB although this is not confirmed by all studies (Gami et al., 2004; Porthan et al., 2004). A pathogenetic role for SDB is suggested by the four-fold increase in the prevalence of AF in subjects with AHI over 30, after age, sex, BMI and CAD were adjusted for (Mehra et al., 2006). Obesity is

a common risk factor for both SDB and AF. Gami and co-workers studied whether SDB increases the risk of incident AF independently of obesity (Gami et al., 2007). They found that SDB, increasing BMI and nocturnal desaturations are all independent predictors of AF. Furthermore, they found an age-dependent effect where age under 65 years and SDB along with nocturnal desaturations strongly predicted the incidence of AF within five years of its diagnosis (Gami et al., 2007). In these presented studies, no gender effect was found or even measured. Finally, the clinical relevance of the role of SDB in AF is highlighted by the high rate of recurrence of AF in inadequately CPAP-treated patients with SDB (Kanagala et al., 2003).

3.1.6. Stroke

A pathogenetic involvement of SDB in cerebrovascular disease is suggested by nocturnal oxygen desaturations and endothelial changes, including occurrence of atherosclerotic plaques in the arteries of patients with SDB (Shamsuzzaman et al., 2003). Prospective data show that SDB is associated with a 2-4-fold risk of developing a stroke after a follow-up varying from 4 to 10 years, and this was also seen in elderly (70-100 years of age) patients (Artz et al., 2005; Yaggi et al., 2005; Elwood et al., 2006; Munoz et al., 2006). Especially moderate to severe SDB (AHI greater than 20-30) was associated with stroke (Artz et al., 2005; Munoz et al., 2006). Also increasing incidence of stroke and/or death with increasing severity of SDB was observed after a median follow-up of 3.4 years (Yaggi et al., 2005) and in a large cross-sectional study (Shahar et al., 2001). These findings support the view that SDB precedes and increases the risk of the occurrence of stroke. In one prospective study of stroke patients, SDB (AHI over 30) was associated with diabetes, night-time stroke onset and macroangiopathy as a cause of stroke (Bassetti et al., 2006). They also found that SDB improved after the acute phase of stroke and was associated with increased mortality in the post-stroke phase. Finally, only about 15% of patients adhered to the long-term nasal CPAP therapy. However, it was not possible to prove any benefit of nasal CPAP treatment in stroke patients with SDB (Bassetti et al., 2006). None of these studies found any gender difference.

3.1.7. Pulmonary arterial hypertension

Pulmonary hypoxic vasoconstriction was first demonstrated about sixty years ago. It may result from pulmonary vascular remodeling and potentially be the major mechanism contributing to the development of pulmonary arterial hypertension (PAH) (Golbin et al., 2008). Varying PAH defining methods, confounding factors like aging and obesity, and difficulties in finding appropriate control subjects, make it difficult to study the associations between PAH and SDB (Golbin et al., 2008). PAH prevalence estimates in SDB vary from 17% to 53% and, in general, PAH seems to be mild (Atwood et al., 2004). Chronic obstructive pulmonary disease can cause secondary PAH and only two studies excluded COPD patients from the study population (Sajkov et al., 1999; Bady et al., 2000). The largest epidemiologic study consists of 220 mostly male subjects with SDB, of whom 17% had PAH (Chaouat et al., 1996). Population-based data are still lacking and no gender differences have been investigated. In a recent study of 23 OSA patients and 10 control subjects, severe OSA caused day-time

PAH without significant heart or lung diseases, and nasal CPAP therapy reduced pulmonary arterial hypertension (Arias et al., 2006).

3.1.8. Diabetes mellitus type 2

There are multiple mechanistic pathways involved in the interaction between SDB, obesity, and metabolic derangements. Upper airway obstruction causing hypoxia and oxygen desaturation may increase catecholamine and cortisol levels, which induce insulin resistance and thereby diabetes mellitus (DM) type 2 (Oltmanns et al., 2004; Tasali and Ip, 2008). AHI and minimum oxygen saturation as markers of SDB severity have been associated with insulin resistance (Ip et al., 2002), while in large cross-sectional population studies, the risk of glucose intolerance, insulin resistance and DM type 2 were found to be 2-4-fold after adjustment for age, sex and body habitus (Punjabi et al., 2004; Reichmuth et al., 2005). However, no causal effect could be detected between SDB and development of DM (Reichmuth et al., 2005).

In prospective studies of snoring as a risk of DM, occasional and regular snoring increased about two-fold the risk of developing DM compared to never snorers, and obesity with SDB increased the risk further (Elmasry et al., 2000; Al-Delaimy et al., 2002). A population study of 593 male and female subjects assessing the relationship of glucose intolerance to SDB (defined by EDS or snoring questions) found that snoring but not EDS was statistically more prevalent in subjects with DM or impaired glucose regulation, more so in diabetics (Renko et al., 2005). They found no gender difference. In a recent Finnish cross-sectional study of associations between SDB and obesity in a large male-female general population, DM and glucose intolerance were investigated (Tuomilehto et al., 2008). Probability of SDB was assessed with questionnaires about sleeping habits. They found an independent risk of DM type 2 in middle-aged men with SDB after adjustments for age, BMI, smoking habits and central nervous system-affecting medication. In women, there was only a trend but no significant association between SDB and DM type 2. They argued that the large number of women under 65 years in their female population diminished the association because SDB is more prevalent in women older than 65 years of age (Tuomilehto et al., 2008). Contrary to the Finnish study, another recent Nordic survey of the general population showed that SDB (defined as snoring and witnessed apneas) is associated with DM in women but not in men in general after adjustments for age, smoking, BMI and waist circumference (Valham et al., 2008). One exception was that in men younger than 55 years, witnessed apneas were related to an almost 4-fold risk of DM. They speculated that elderly men might have had more co-morbidity and lower life expectancy than women, and therefore men had died because of relationships between co-morbidity, SDB and DM. They also speculated that hormonal differences between genders could have affected the results (Valham et al., 2008). Nasal CPAP effects on markers of DM are inconsistent (see section 3.1.1.2.).

3.2. Non-cardiovascular co-morbidities in SDB

Cardiovascular diseases are the main co-morbidities of SDB but there is a growing body of evidence suggesting that other diseases may also associate and contribute to

SDB. Recent and selected studies of various non-cardiovascular co-morbidities have been gathered in Tables 4-6.

3.2.1. Chronic obstructive pulmonary diseases

SDB and chronic obstructive pulmonary diseases (COPD and asthma) are common diseases and frequently coexist. It is suggested to be an overlap syndrome, and that patients have both conditions by chance (Fleetham, 2003). SDB and COPD have a common risk factor, namely smoking, and hypoxemia and poor sleep quality are consequences of both conditions (Saaresranta et al., 2005; Weitzenblum et al., 2008). Hypothetical mechanisms linking SDB and asthma include obesity, local and systemic inflammation, cardiovascular sequelae of SDB and gastroesophageal reflux (Kasasbeh et al., 2007).

There are inconsistent data on associations of SDB or symptoms related to SDB in patients with COPD and/or asthma. In questionnaire studies, snoring was found to be 1.5-2 times and apneas 2 to 3 times more prevalent in COPD and/or asthma patients compared to non-COPD/asthma patients when at least age, sex and smoking habits were adjusted for (Larsson et al., 2001; Ekici et al., 2005). In other questionnaire studies, symptoms of SDB were not related to asthma or its severity, while patients with COPD had more symptoms of SDB (Teodorescu et al., 2006; Karachaliou et al., 2007). No gender differences were found (Teodorescu et al., 2006). The largest study to date to assess the SDB prevalence in COPD is the Sleep Heart Health Study (Sanders et al., 2003). It found that the prevalence of SDB was the same in patients with or without mild COPD. No gender difference was investigated (Sanders et al., 2003). Nor was any epidemiologic relationship found in COPD prevalence between patients with or without SDB, when SDB and COPD were defined on the basis of a full polysomnography and the European Respiratory Society guidelines, respectively (Bednarek et al., 2005). However, the risk of significant desaturations during sleep in patients with overlap syndrome is increased compared to those without SDB and COPD (Sanders et al., 2003; Bednarek et al., 2005). Taken together, the current evidence suggests that when SDB and chronic obstructive pulmonary disease coexist, it is a result of chance alone. Clinically, it is important to consider overnight oximetry in most COPD/asthma patients, irrespective of whether they have SDB symptoms or not, to exclude significant desaturations and SDB during sleep.

3.2.2. Hypothyroidism

Patients with SDB have symptoms like EDS, fatigue, snoring, decreased libido, depressed mood, headache and obesity, mimicking symptoms of accompanying hypothyroidism (Kapur et al., 1998; Skojt et al., 1999). It has been suggested that hypothyroidism may be related to the development of SDB but the mechanism is not clear (Saaresranta and Polo, 2002). Obesity in both diseases and myxedema in hypothyroidism narrow the upper airway. Further, low respiratory drive and hypoventilation in hypothyroidism may be the reasons for the increased prevalence of SDB in patients with hypothyroidism (Saaresranta and Polo, 2002). The prevalence of SDB in patients with hypothyroidism varied between 25-30%, and in another study

there was a similar trend but the result was not significant (Lin et al., 1992; Kapur et al., 1998; Jha et al., 2006). In a study of a female population, hypothyroidism tended to be more prevalent in women with SDB (9.3%) compared to the general population (5.9%) (Miller and Husain, 2003). In a Finnish study, SDB was increased among hypothyroid patients because of obesity and male gender (Pelttari et al., 1994). Thyroxin replacement therapy reverses SDB in a majority of patients with hypothyroidism (Saaresranta and Polo, 2002; Jha et al., 2006). From the clinical point of view, screening for hypothyroidism among patients with SDB is recommended (Skjodt et al., 1999).

3.2.3. Epilepsy

The coexistence of epilepsy and SDB has been reported previously (Beran et al., 1999; Manni et al., 2003). These two disorders can aggravate the clinical cause of each other. Sleep fragmentation, hypoxemia and sleep deprivation in SDB can exacerbate seizures in patients with epilepsy, whereas epileptic seizures can induce apneas (Herman, 2006). Also epileptic drugs can adversely affect SDB by decreasing upper airway muscle tone and arousal threshold or by inducing weight gain (Cicolin et al., 2006). The occurrence of SDB in patients with epilepsy is high but varies a lot from 10% to 79% depending on the study population (Beran et al., 1999; Malow et al., 2003; Manni et al., 2003). In a clinical series of epilepsy patients, women (5.4%) had less SDB than men (15.4%), and patients with SDB and epilepsy were older, heavier and sleepier than patients with epilepsy alone (Manni et al., 2003). Effective treatment of SDB with nasal CPAP reduced the seizure frequency significantly (Malow et al., 2003; Höllinger et al., 2003). No causal link between SDB and epilepsy has yet been proven but a possible temporal relationship has been found in the study by Höllinger (2003). They analyzed the temporal relationship between the onset of SDB symptoms and an increase in seizure frequency. In two thirds of their patients, seizure frequency increased after the onset of symptoms of SDB.

3.2.4. Psychosis and depression

Depression is the most common psychiatric disorder that has been linked with SDB, whereas there is sparse and inconsistent knowledge of associations between psychosis and SDB (Saunamäki and Jehkonen, 2007). SDB may be associated with depression through symptoms of SDB (EDS, sleep problems, concentration difficulties, social withdrawal) or other factors related to SDB (obesity, co-morbidity) (Saunamäki and Jehkonen, 2007).

Increased prevalence of psychosis in patients with SDB may have two possible explanations. First, SDB patients have damage to the prefrontal cortex and may therefore be more fragile and prone to psychotic disorders (Beebe and Gozal, 2002). Second, treatment of psychosis often induces weight gain, thus contributing to the occurrence of SDB. The prevalence estimates of depression and psychosis in patients with SDB were high, 22% and 5% respectively, when age, sex, and ethnicity were taken into account as confounding factors (Sharafkhaneh et al., 2005). An older study of psychiatric symptoms found no association between SDB and depression or anxiety

although women had higher scores for depression and anxiety than men (Pillar and Lavie, 1998). In a small sample of schitzophrenic patients, in the elderly (65-76 years), the prevalence of psychosis was higher than in age-matched healthy controls (Ancoli-Israel et al., 1999). Recent data on psychiatric patients suggest that symptoms of depression and psychosis often collaborate, and vulnerability to psychosis increases the risk of depression (Salokangas et al., 2007). Although there are no consistent data on the effect of nasal CPAP treatment on psychiatric disorders, in patients with SDB some decline in depressive symptoms and anxiety has been shown (Saunamäki and Jehkonen, 2007). From the clinical point of view, SDB should be evaluated before starting a treatment in the middle-aged, obese patient with depressive symptoms and it should be remembered that postmenopausal women may be especially vulnerable to symptoms fitting both disorders.

3.2.5. Glaucoma

It has been speculated that repetitive prolonged apneas and nocturnal arterial blood pressure variations in SDB can cause impaired optic nerve head blood flow and direct damage to the optic nerve, thus causing glaucoma. Older studies showing a positive association of SDB in patients with glaucoma have been criticized because of small patient numbers or lack of polygraphic sleep studies (Mojon et al., 1999; Onen et al., 2000). Recent studies have overcome these problems, and they could not find an association between SDB and glaucoma after adjustments (Geyer et al., 2003; Girkin et al., 2006). In a recent study in patients with SDB compared to healthy controls, glaucoma was found in 5.9% of SDB patients and none in controls (Sergi et al., 2007). The studies used mostly male-dominated study populations and no gender difference was found.

3.2.6. Gastroesophageal reflux (GER)

GER and SDB share the same risk factors and increased prevalence estimates of GER in patients with SDB have been published (Zanation and Senior, 2005; Kasasbeh et al., 2007). GER is discussed further in the section on clinical features of SDB.

3.2.7. Restless leg syndrome (RLS)

RLS is characterised by unusual, unpleasant sensations in the lower extremities, an urge to move the legs and movement-induced relief of the sensations (American Academy of Sleep Medicine, 2005). The RLS diagnosis with typical symptoms is clinical but it is often accompanied by periodic, stereotypical leg movements (PLM) (Hornyak et al., 2006) (PLM is discussed in section 1.6.). The prevalence estimates of RLS vary between 5-13% in the general population. Patients with RLS are more likely to be females, middle-aged or older, suffering psychiatric conditions or sleep disorders and with poorer quality of life than non-RLS subjects (Allen et al., 2005; Phillips et al., 2006; Ulfberg et al., 2007). In peri- and postmenopausal women with complaints of disturbed sleep, 53% had episodes of apnea, RLS, or both, which were the major predictors of poor sleep efficiency rather than hot flashes (Freedman and Roehrs, 2007). Patients with RLS symptoms do discuss their symptoms with a physician but

only a small proportion receives the right diagnosis (6.2%) and treatment (Allen et al., 2005).

3.3. Different co-morbidities of SDB in females

The overall co-morbidity data of SDB in females is sparse because most studies have been done with male populations or gender differences have not been evaluated. Studies comparing the differences in co-morbidity of SDB between pre- and postmenopausal women are almost non-exsistend.

In women with mild to moderate SDB or even occasional snoring, a two- to three-fold risk of hypertension has been found compared to women without SDB or snoring (Peppard et al., 2000, Lindberg et al., 2007). There are contradictory data of associations between DM type 2 and SDB in women. One study found no gender difference, another only a trend in women, while a third found an association between SDB and increased risk of DM in women but not in men (Renko et al., 2005; Tuomilehto et al., 2008; Valham et al., 2008). Among hypothyroid patients, SDB was less common if you were female and had normal weight (Pelttari et al., 1994). Female patients with epilepsy have less SDB than males with epilepsy (Manni et al., 2003). In other co-morbid diseases of SDB, no gender differences have been found between CAD, stroke, COPD/asthma, depression, psychosis or glaucoma and SDB. Gender differences in associations between AF, PAH and GER and SDB have not been investigated.

AIMS OF THE STUDY

The aims of the present study were to investigate:

1) the impact of menopause on the manifestation of sleep-disordered breathing in terms of signs, symptoms, and breathing pattern

2) the determinants of the gender differences in partial upper airway obstruction and periodic obstructive breathing and their associations with age and BMI

3) the occurrence of partial upper airway obstruction in age- and BMI-matched male-female pairs and its impact on CPAP adherence

4) the differences in co-morbidities between male and female patients with partial upper airway obstruction or periodic obstructive breathing during sleep and to compare their prevalences to population prevalences

5) the differences in co-morbidities between pre- and postmenopausal women with SDB

6) the impact of type of SDB on the prevalence of co-morbidities in male and female patients

SUBJECTS AND METHODS

1. Subjects

1.1. Female patients (studies I-IV)

All the women who were included in the studies were referred to the pulmonary clinic at the Turku University Central Hospital for the first time because of snoring, episodes of witnessed apneas, EDS or other clinical symptoms suggesting SDB. They underwent a diagnostic sleep study with the SCSB during the years 1994-1998. Using our pulmonary sleep database, we included 601 consecutive women. Information on age, weight, height, BMI and neck circumference was retrieved from the sleep database. The hospital records were screened for the signs and symptoms of SDB. When available, information on other diseases, smoking habits, use of medication with potential interaction with breathing, menopausal state and flow-volume spirometry were also retrieved from the hospital records. Background information was further clarified by the posted questionnaire battery.

The menopausal status (pre- or postmenopausal) definition was based on data from the hospital records (medical history, ovarian surgery, etc.) or self-reported history of last menstruation time in a questionnaire (postmenopause defined as the last menstruation more than one year previously). If these data were not available, age with a cut-off point of 55 years was used. Women over 55 years of age were considered postmenopausal.

1.2. Male patients (studies II-IV)

We used the same pulmonary sleep database in the Turku University Central Hospital as with female patients and searched for male patients with similar body mass index (BMI) (±2 kg/m^2) and age (±3 years) as the women. All the male patients suffered from some of the main symptoms of SDB such as EDS, witnessed apneas, snoring or morning headaches. They underwent a diagnostic sleep study with the SCSB during the years 1994-2000. Out of the 304 matched pairs found from the database, 233 had complete data for the purpose of the study. The questionnaire battery was not sent to male patients and the hospital records were not investigated.

1.3. Characteristics of the subjects

Out of 601 women, 207 (34.4%) were considered premenopausal and 394 (65.6%) postmenopausal (Fig. 6). After omitting sleep studies as not available or in incompatible format, 469 (78.0%) SCSB sleep studies remained available for the study. Hospital records were screened in 587 (97.7%) patients. The rest of the hospital records were so often in use clinically that they were not available for study. The questionnaire was sent to 577 women because 24 had died since the sleep studies. After one reminder, 451 (78.2%) returned the questionnaire. The characteristics of females with SDB (n=393) are presented in Table 7. Premenopausal women (40.5%)

were more often smokers than postmenopausal ones (23.6%). SDB was diagnosed in 262 out of 304 postmenopausal women (86.2%), and in 131 out of 165 premenopausal ones (79.4%). About 40% of the postmenopausal women reported that they were currently using or had previously used hormone replacement therapy (estrogen or progesterone alone or in combination).

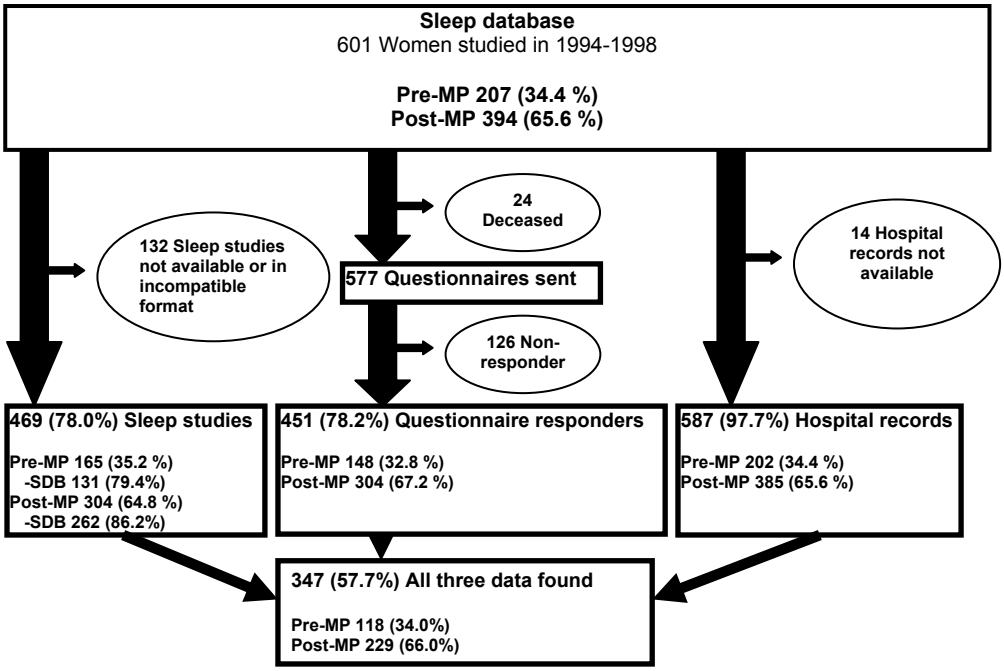

Figure 6. Flow chart of the female study subjects. MP = menopause, SDB = sleep-disordered breathing

Table 7. Characteristics of the 393 out of 469 women, in whom sleep-disordered breathing was found during more than 5% of time in bed.

Characteristic	Postmenopause		Premenopause		
	n	Mean (range)	n	Mean (range)	p
Age (years)	262	62.5 (33-85)	131	46.2 (18-55)	**<0.001**
Height (cm)	261	161.8 (136-178)	131	162.9 (148-178)	0.091
Weight (kg)	261	87.3 (41-144)	131	88.6 (37-165)	0.574
BMI (kg/m^2)	261	33.3 (18.1-61.0)	131	33.3 (12.4-57.1)	0.973
Neck circumference (cm)	134	39.0 (31-49)	65	39.6 (33-52)	0.383
FEV_1 (L)	226	2.1 (0.6-3.7)	113	2.6 (0.7-3.9)	**<0.001**
FEV1% (%)	224	82.5 (21-128)	114	84.8 (23-116)	0.321
FVC (L)	226	2.7 (0.6-4.6)	113	3.3 (0.8-4.9)	**<0.001**
FVC% (%)	224	87.7 (33-138)	114	88.5 (27-119)	0.681

* Two-sample t-test, significant p-values in bold

FEV_1 = forced expiratory volume in one second

FEV1% = FEV_1 as percentage of predicted value

FVC = forced vital capacity

FVC% = FVC as percentage of predicted value

N values vary depending on the availability of data.

Out of 304 age- and BMI-matched male-female pairs, 233 had complete data for the study. The mean age for male-female pairs was 55.8 years (SD 10.4) in men, and 56.2 years (SD 10.3) in women. The mean BMI for men and women was 31.4 kg/m^2 (SD 5.5) and 31.5 kg/m^2 (SD 5.5), respectively. The distributions of pairs according to age and BMI are presented in Figures 7 and 8, respectively. SDB was diagnosed in 203 women (87.1%), in 219 men (94.0%), and in 192 pairs (82.4%) (Fig. 9).

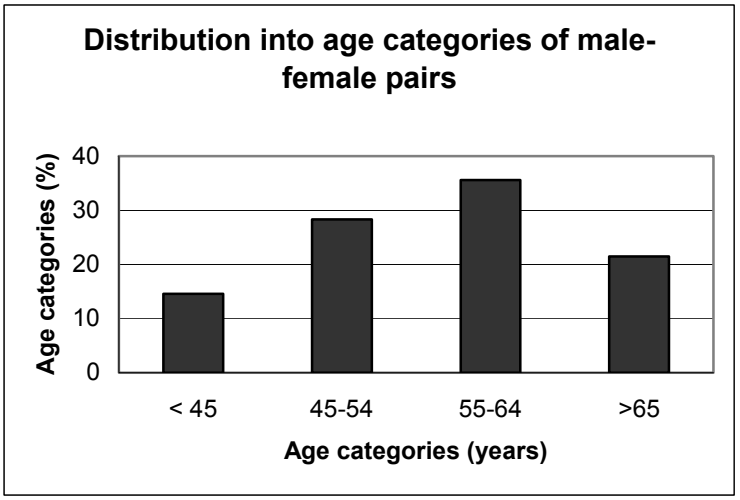

Figure 7. Distribution of 233 male-female pairs into four age categories.

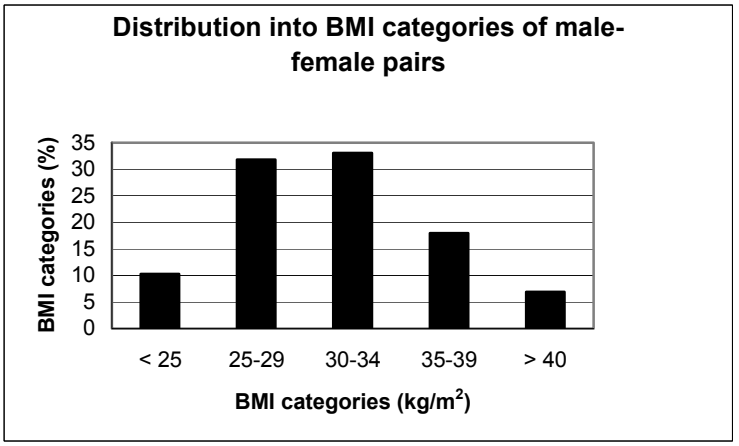

Figure 8. Distribution of 233 male-female pairs into five BMI categories.

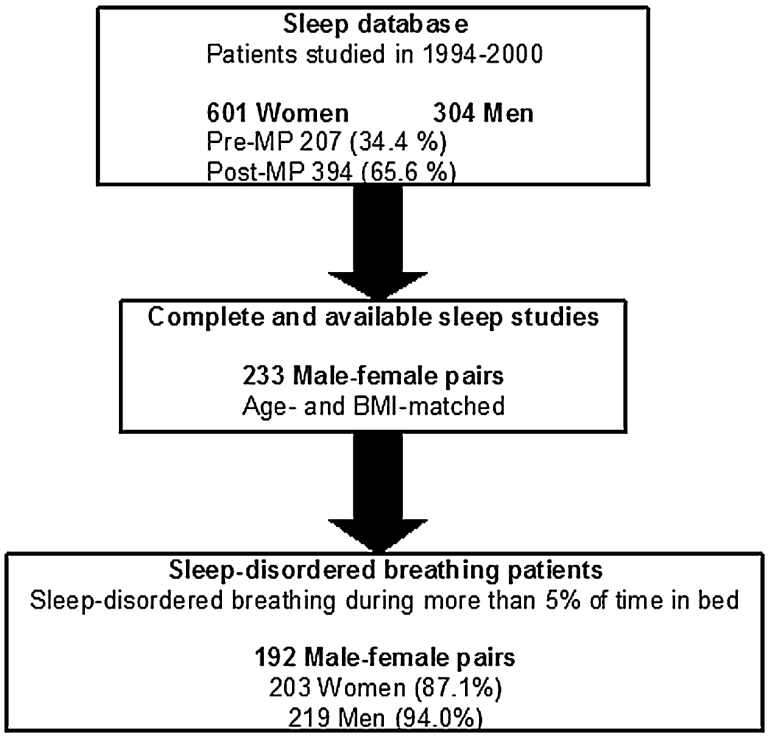

Figure 9. Flow chart of the male-female pairs. MP = menopause

2. Methods

2.1. Questionnaire (study I)

The questionnaire battery that was sent to 577 women out of the 601 had 107 items (14 open and 93 structured ones) to obtain background information, focusing on previous medical history (including detailed gynaecologic history) and medication used, smoking habits, use of alcoholic beverages and coffee, nasal congestion and information on social status. Selected elements from the Basic Nordic Sleep Questionnaire (BNSQ) were also included in the questionnaire battery (Partinen and Gislason, 1995). (Appendix 1)

2.2. Sleep study: Static-charge-sensitive bed (studies I-IV)

All the overnight sleep studies included the static-charge-sensitive bed (SCSB, Bio-Matt®, Biorec, Turku, Finland) and simultaneous oximeter recordings (BCI-oximeter ECG-monitor, Model 3101, CAT 3101A, Waukesha, Wisconsin, USA). The SCSB is a non-invasive, validated method to monitor breathing, heart beats and gross body movements in bed without any electrodes attached to the subject (Alihanka et al. 1981; Polo 1992). The SCSB consists of a movement sensor that is placed under a normal foam mattress (Fig. 10). The sensor charge is modified by static charge layers, moving in conjunction with body movements, resulting in potential difference. The potentials

are amplified, filtered and recorded to obtain three types of movements: gross body movements, respiratory movements and heart beats. The filtration frequencies are in three bands, 0.25 – 0.9 Hz, 0.3 – 16 Hz and 6 – 16 Hz.

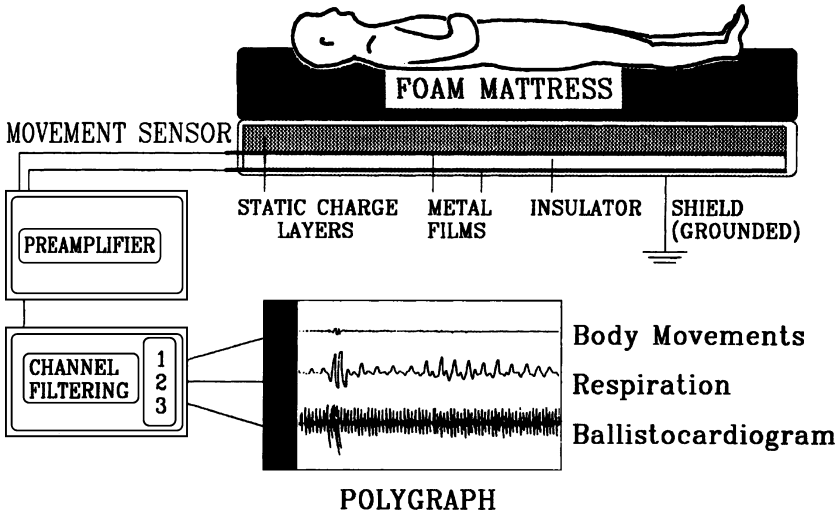

Figure 10. The static-charge-sensitive bed (SCSB) (Polo 1992).

2.2.1. The measurements of breathing patterns and body movements

The SCSB recordings were visually analyzed by two independent scorers to distinguish normal breathing from four types of periodic breathing patterns or prolonged episodes of increased respiratory resistance (IRR) pattern, using established and earlier reported principles (Polo et al., 1988; Polo et al., 1992). The IRR episodes are prolonged periods of obstructive hypoventilation (from one minute up to 30 minutes), with slowly increasing intrathoracic pressure variations and increasing intensity of the snoring sound (Polo et al., 1991; Fig. 1). Often the IRR is accompanied by sustained arterial oxyhaemoglobin desaturation and terminated by a movement arousal (Polo, 1992). Percentage of time was preferred to event-index-based calculations because the episodes of IRR do not present as repetitive events. On the SCSB recording, the episodes of obstructive apnea and hypopnea manifest as the OP-2 and OP-3 patterns (Polo et al., 1988). P-1 and OP-1 patterns represent periodic breathing with moderate or high respiratory effort, respectively (Polo, 1992). Periodic limb movements (PLM) were also analyzed from the SCSB signal (Rauhala et al., 1996). PLM was defined as body movements which were a part of a series of four or more consecutive movements with a duration of 0.5-5 s and with an interval of 5-90 s (Coleman, 1982). The breathing abnormalities or periodic movements were quantified within three-minute epochs and the frequencies of the abnormal epochs were expressed as percentage of time in bed (TIB). TIB indices greater than 5% were considered clinically significant.

To enable comparison of the conventional AHI with the patterns of the SCSB recordings, we used the estimated AHI (AHI_{est}). The following equation was used: the episodes of obstructive apnea and hypopnea on the SCSB recording manifest as the OP-2 and OP-3 patterns. Five percent of time with OP-2 or OP-3 patterns equals an

AHI of 5 / h, presuming that the duration of an apnea or hypopnea cycle is 36 s on average. With a shorter average apnea cycle length the AHI_{est} underestimates, and with longer apnea cycles, overestimates the AHI.

2.2.2. Measurement of arterial oxyhemoglobin saturation (SaO_2)

The overnight oximeter recordings with finger probe were analyzed with UniPlot software (Unesta Oy, Turku, Finland), which reports the minimum, median and maximum SaO_2, and the frequencies of the oxygen desaturation events of 4%-unit or more per hour of recording (ODI_4). A decrease of 4 percentage units or more from the preceding stable SaO_2 level was defined as a hypoxic event (Block et al., 1979).

2.3. Data on nasal CPAP adherence (Study III)

The information on nasal CPAP use (pressure, hours of actual use) was derived from a database at the time of initiation and one year thereafter. Objective adherence data were collected on each visit and measured by a nasal CPAP unit compliance meter which calculates the actual hours used. The average nightly use was calculated over the period between the two consequent visits. Permanent device user was defined as nasal CPAP use of one year or longer. The limit of one year was chosen because the possible placebo effect of treatment was not likely to last so long.

2.4. Definition of a co-morbid condition (Study IV)

The cumulative information on co-morbidities was gathered from the Finnish Statistics on Medicines, annually provided by the National Agency for Medicines and the Social Insurance Institution. This medicine reimbursement system covers all permanent Finnish residents, regardless of age, wealth or area of residence. It consists of three categories: the Basic Refund Category, and the Lower and Higher Special Refund Categories. The two latter categories include chronic illnesses where drug treatment is needed to maintain the patient's health status, and where the drug restores or replaces normal bodily functions. To qualify for a reimbursed drug belonging to either of the two Special Refund Categories, the patient has to provide a separate statement from his/her own doctor to prove his/her need for such medication. The medical criteria for a drug reimbursement are stricter than the diagnosis and treatment criteria. Therefore, the number of patients using the drug is higher than the number of patients meeting the criteria for the Special Refund reimbursement.

In study IV, the year 2000 reimbursement data of the general population were used. The data of the study subjects' Special Refund Categories (89 in total) from 1994 to 2000 were analyzed. The data of reimbursements of recipients were divided into age groups of ten years and was accordingly matched to the age of the study population. Most reimbursements of medicines for chronic illnesses are ongoing without an expiry date, and the data cover only those recipients who were entitled to Special Refund Category all year around and who had also bought these medicines.

2.5. Statistical analyses

Statistical calculations were performed using SAS System for Windows, release 8.02 (SAS Institute, Cary, NC). P-values less than 0.05 were considered statistically significant.

Study I. Two-sample t-test was used to test the differences between pre- and postmenopausal women regarding patients' characteristics. Univariate associations between variables were tested using chi-squared test or logistic regression. Associations between the manifestation of SDB in terms of signs, symptoms and breathing pattern and the dependent variable of menopause status were analysed using multivariate logistic regression analysis. The results were quantified by calculating odds ratios (OR) with 95% confidence intervals (95% CI). Multivariate linear models where FVC (FVC%) and FEV_1 (FEV_1%) were dependent variables and ODI_4, smoking and menopausal status explanatory variables were used. All multivariate models were adjusted for age.

Study II. The differences in breathing patterns between men and women were tested with Wilcoxon signed rank test. Associations of age and BMI with SDB patterns were analyzed using logistic regression analysis. Age and BMI were used as explanatory variables in logistic models. The dependent variables IRR, P-1, OP-1 and PMS were divided into three categories (the first quartile, the second and third quartiles combined, and the fourth quartile). These ordinal dependent variables were analyzed with cumulative logistic regression (Hosmer and Lemeshow, 2000). OP-2 and OP-3 were dichotomized due to the high proportion of 0 values and analyzed with binary dichotomic logistic regression. Logistic models were performed separately for men and women.

Study III. The differences in breathing patterns between men and women were tested with Wilcoxon signed rank test. Comparisons of CPAP use and pressure between genders were made using a linear mixed model by taking into account matched pairs, defining pair as a random factor (McCulloch and Searle, 2001). The differences in CPAP use and pressure between patients with pure IRR and periodic breathing were tested with two-sample t-test, and the difference in duration of CPAP treatment was tested using Mann-Whitney U test.

Study IV. The differences in breathing patterns between men and women were analysed using Wilcoxon signed rank test and between pre- and postmenopausal women using Mann-Whitney U-test. Chi-squared test was used to test the difference in the proportion of partial upper airway obstruction, periodic obstruction and special refunds between pre- and postmenopausal women. Special refunds between age- and BMI-matched male-female pairs were compared with conditional logistic regression. Associations of the manifestation of SDB in terms of breathing patterns, age and BMI with the special refund categories were analysed using multivariate logistic regression analysis. The results were quantified by calculating odds ratios (OR) with 95% confidence intervals (95% CI). Age-standardized prevalence of diseases per 100 persons with 95% confidence interval (CI) was calculated using the direct method.

The year 2000 reimbursement data of the general Finnish population were used as reference.

3. Designs of the studies

All studies were retrospective and cross-sectional using a clinical population from the database of the pulmonary sleep department of Turku University Central Hospital. In study IV, the year 2000 reimbursement data of the general Finnish population were used as controls.

4. Ethical aspects

The study protocols were approved by the Joint Commission on Ethics of Turku University and Turku University Central Hospital. Permission to study the hospital records was obtained from the Head of the Department of Pulmonary Diseases in Turku University Central Hospital. Written informed consent was obtained from all female subjects answering the survey. Reimbursement data on medication for co-morbidities were obtained with permission of the National Agency for Medicines and the Social Insurance Institution.

RESULTS

1. Effect of gender

1.1. Type of SDB

SDB (defined as breathing abnormalities more than 5% of TIB) was diagnosed in 192 pairs (82.4%), in 219 men (94.0%) and in 203 women (87.1%) out of 233 male-female pairs. The occurrence of the various breathing abnormalities was first determined as percentage of TIB (median and interquartile range IQR) (Table 8). Breathing abnormalities were encountered during 21.8% and 31.7% of TIB in women and in men, respectively ($p<0.001$). The proportions of different types of breathing abnormalities varied between genders. The median percentage of partial upper airway obstruction of TIB was 10.5% in women and 7.5% in men ($p=0.174$). Periodic obstructive breathing (defined as P-1, OP-1, OP-2 and OP-3 together) was less common in women (5.8% (IQR 10.7) vs. 15.6% (IQR 23.6) of TIB, $p<0.001$).

Table 8. Sleep-disordered breathing (SDB) abnormalities during time in bed (TIB) in 233 male-female population.

n=233	**Women** (mean,IQR)	**Men** (mean,IQR)
Patients with SDB	203 (87.1%)	219 (94.0%)
Proportion of SDB of TIB*	21.8% (IQR 40.0)	31.7% (IQR 44.4)
Partial upper airway obstruction of TIB	10.5% (IQR 36.0)	7.5% (IQR 26.3)
Periodic obstructive breathing of TIB*	5.8% (IQR 10.7)	15.6% (IQR 23.6)

Values are n (%) or median (IQR) = interquartile range, *$p<0.001$

The contribution of the various breathing patterns to the overall breathing abnormalities in each subject was determined (Fig. 11). Partial upper airway obstruction was the most common breathing abnormality; it was more common in females than in males representing (mean ± SD) 50.2% ± 40.8 of all breathing abnormalities in women and 37.2% ± 36.4 in men ($p<0.001$), whereas all patterns of periodic obstructive breathing together accounted for 49.8% ± 40.8 in women and 62.6% ± 36.4 in men of all breathing abnormalities ($p<0.001$). Periodic obstructive breathing P-1 contributed less in women than in men (24.2% ± 32.1 and 34.5% ± 33.4, $p<0.001$). The proportion of OP-1 averaged 21.1% ± 29.1 in women and 14.7% ± 21.7 in men ($p=0.034$). The proportions of OP-2 and OP-3 were significantly lower in women than in men (3.0% ± 9.4 vs. 7.9% ± 17.0, $p<0.001$ and 1.5% ± 5.7 vs. 5.6% ± 13.3, $p<0.001$, respectively). OP-2 and OP-3 patterns are compatible with conventional episodes of obstructive apnea.

Knowing that age and BMI are two major risk factors for SDB, we looked at the age and BMI associations of different breathing patterns in 3D format (Fig. 12A-F) and tested the significances as odds ratios (Tables 9A and 9B). The IRR frequency increased in the age group of over 65 years ($p=0.037$) or BMI 35 - 39 kg/m^2 ($p=0.046$), but not in women with BMI over 40 kg/m^2. Men with BMI over 40 kg/m^2 had a higher IRR frequency ($p=0.017$), and age over 65 years tended to explain this ($p=0.053$) (Fig.

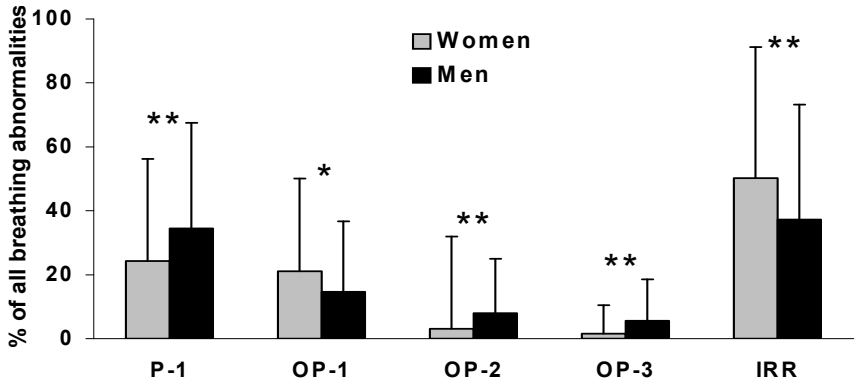

Figure 11. The average (± SD) contribution of the various breathing abnormalities to the overall breathing abnormalities in each patient. P-1, OP-1, OP-2 and OP-3 are forms of periodic breathing, whereas IRR represents partial upper airway obstruction during sleep. *p<0.05, **p<0.001.

12A). In women, an increase of neither BMI nor age was associated with change in P-1 (Fig. 12B). In men, contrary to IRR, P-1 was more frequent in the mild obesity groups ($25 \leq$ BMI < 30 kg/m^2 and $30 \leq$ BMI < 35 kg/m^2) than in the normal weight group (p=0.009 and p=0.012, respectively). In women, only during the early postmenopausal period ($55 \leq$ age < 65 years, p=0.028) was OP-1 increased (Fig. 12C). It was not associated with BMI. In men, OP-1 was most frequent in patients with BMI between 35 - 39 kg/m^2 (p=0.003). In women, neither age nor BMI was associated with OP-2 or OP-3 patterns (Fig. 12D and 12E). In men, an increase in BMI predicted more OP-2 ($35 \leq$ BMI < 40 kg/m^2, p< 0.001) and OP-3 ($35 \leq$ BMI < 40 kg/m^2, p<0.001 and BMI ≥ 40 kg/m^2, p= 0.042). Men aged between 45 and 54 had less OP-2 (p=0.046). Periodic movements in sleep were more common in women than men, 1.16% vs. 0.97%, respectively (p<0.001). PMS did not change with increasing age or with BMI in either sex (Fig. 12F).

1.2. CPAP adherence

Nasal CPAP therapy was started in 116 (49.8%) out of the 233 men and 66 (56.9%) continued therapy at the one-year check point. In 233 women, the figures were 86 (36.9%) and 52 (60.5%), respectively. The mean CPAP use was equal in both genders (in men 5.1 and in women 4.8 hours, p=0.519) but the mean pressure in the CPAP device was higher in males than in females (9.8 cmH_2O and 8.8 cmH_2O, p<0.001) with a mixed model. (Table 10)

1.3. Co-morbidity

The results of Special Refunds in the entire study population including subjects without SDB are presented in Table 11. Men had significantly more diabetes mellitus (14.2% vs. 6.0%) and less hypothyroidism (3.4% vs. 9.4%) than women. An exceptionally high prevalence was found for patients entitled to Special Refunds for asthma and/or chronic obstructive pulmonary disease (COPD) (24.0%-24.5%) or hypertension (31.8%-34.8%) in both genders.

Figure 12 A

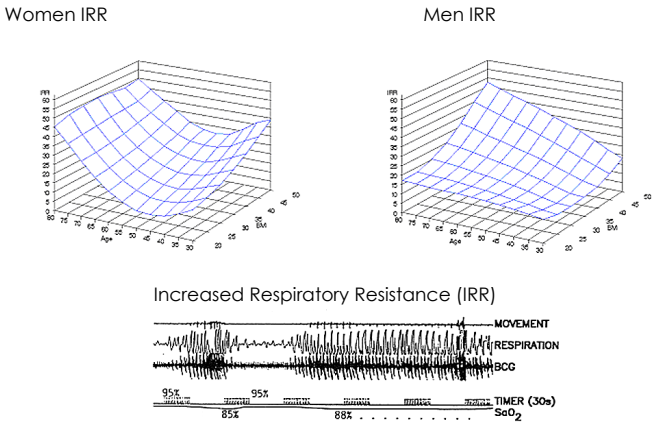

Figure 12 B

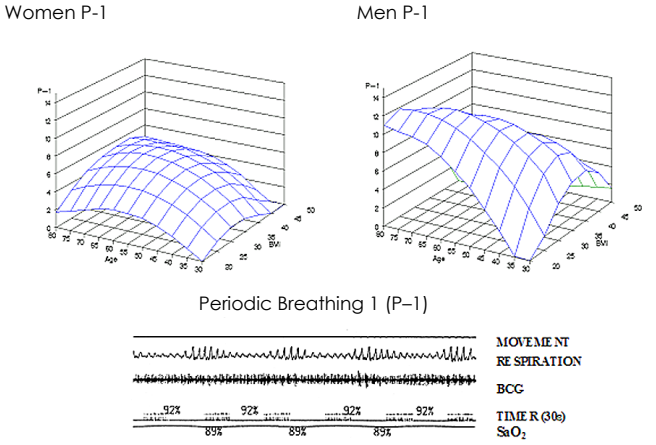

Figure 12 C

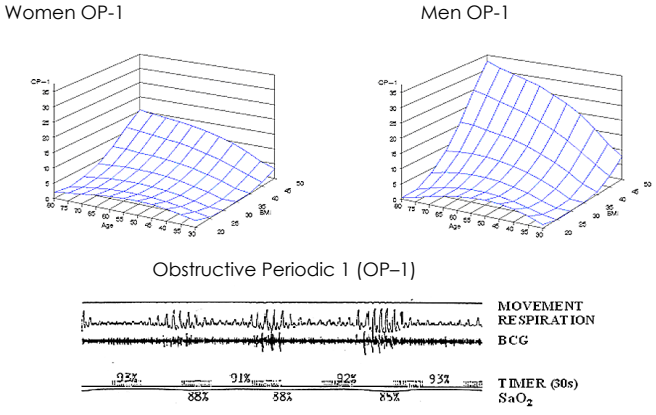

Figure 12 D

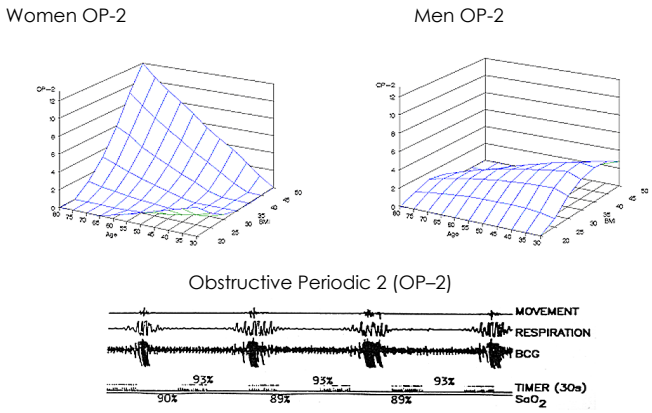

Figure 12 E

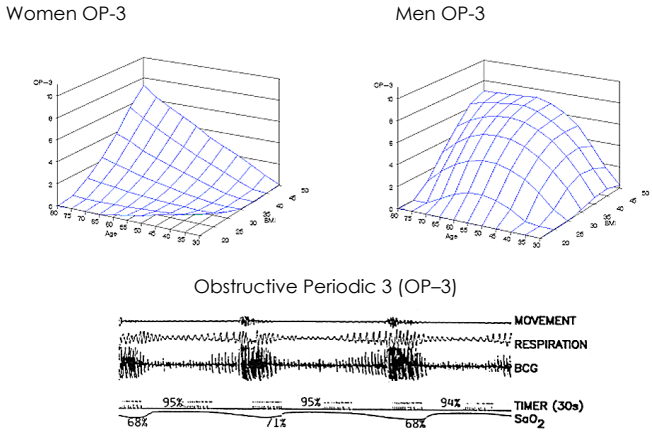

Figure 12 F

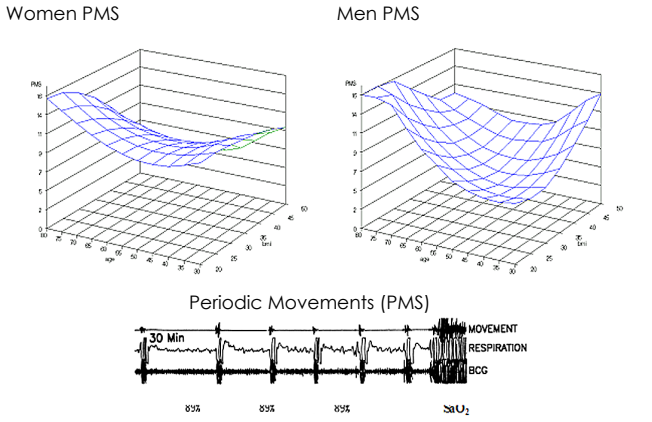

Figure 12A-F. A pattern of prolonged episodes of increased respiratory resistance (IRR) (Fig. 12A), four types of periodic breathing patterns (P-1, OP-1, OP-2 and OP-3) (Fig. 12B – E, consecutively), and a pattern of periodic movements in sleep (PMS) (Fig. 12F) of the static-charge-sensitive bed (lower panels), and the effects of age and BMI on these patterns (upper panels) in women and in men in 3-D format (n=233). BCG = ballistocardiogram, SaO_2 = arterial oxygen saturation

Tables 9A-B. Association of categorical age and BMI with periodic breathing patterns (P-1, OP-1–OP-3) and partial upper airway obstruction (IRR) in women and in men.

Table 9A .

Breathing patterns	IRR		P-1		OP-1		OP-2		OP-3	
Women n=233	**p**	**COR (CI 95%)**	**p**	**COR (CI 95%)**	**p**	**COR (CI 95%)**	**p**	**OR (CI 95%)**	**p**	**OR (CI 95%)**
Age (yrs)	0.091		0.802		0.174		0.435		**0.022**	
≤ 45		1.0		1.0		1.0		1.0		1.0
45 - 54		1.1 (0.5-2.4)		1.4 (0.6-3.0)		2.0 (0.9-4.4)		0.5 (0.2-1.5)		0.8 (0.2-3.6)
55 - 64		1.5 (0.7-3.2)		1.1 (0.5-2.3)		**2.4*** (1.1-5.3)		0.9 (0.3-2.4)		2.8 (0.7-10.7)
≥ 65		**2.5*** (1.1-5.7)		1.0 (0.4-2.3)		1.7 (0.7-4.0)		0.5 (0.2-1.6)		0.7 (0.1-3.6)
BMI (kg/m^2)	0.186		0.676		0.732		0.397		0.689	
≤ 25		1.0		1.0		1.0		1.0		1.0
25 - 29		1.2 (0.5-2.9)		1.0 (0.4-2.5)		0.9 (0.4-2.1)		2.1 (0.5-8.5)		1.4 (0.3-7.3)
30 – 34		1.7 (0.7-4.0)		1.5 (0.6-3.7)		0.8 (0.3-1.8)		1.6 (0.4-6.4)		0.9 (0.2-4.7)
35 – 39		**2.7*** (1.0-7.1)		1.5 (0.6-3.9)		0.9 (0.4-2.4)		1.9 (0.5-8.2)		1.9 (0.3-10.3)
≥ 40		1.5 (0.4-4.9)		1.3 (0.4-4.5)		1.5 (0.5-5.0)		4.6 (0.9-23.2)		1.9 (0.3-13.8)

Table 9B.

Breathing patterns	IRR		P-1		OP-1		OP-2		OP-3	
Men n=233	**p**	**COR(CI 95%)**	**p**	**COR(CI 95%)**	**p**	**COR(CI 95%)**	**p**	**OR(CI 95%)**	**p**	**OR(CI 95%)**
Age (yrs)	0.106		0.639		0.513		0.187		0.870	
≤ 45		1.0		1.0		1.0		1.0		1.0
45 - 54		1.1 (0.5-2.4)		1.5 (0.7-3.4)		1.2 (0.5-2.5)		**0.4***(0.2-1.0)		1.2 (0.4-3.2)
55 - 64		1.1 (0.5-2.4)		1.2 (0.6-2.7)		1.4 (0.6-3.0)		0.5 (0.2-1.2)		1.3 (0.5-3.4)
≥ 65		2.3 (0.99-5.3)		1.6 (0.7-3.7)		1.7 (0.7-4.0)		0.4 (0.1-1.0)		1.5 (0.5-4.3)
BMI (kg/m^2)	0.174		**0.043**		**0.018**		**0.001**		**<0.001**	
≤ 25		1.0		1.0		1.0		1.0		1.0
25 - 29		1.4 (0.6-3.4)		**3.4** (1.4-8.6)		1.5 (0.6-3.8)		1.8 (0.6-5.4)		2.6 (0.7-9.9)
30 – 34		1.5 (0.6-3.7)		**3.2** (1.3-7.8)		1.7 (0.7-4.1)		2.7 (0.9-8.1)		2.5 (0.7-9.5)
35 – 39		1.7 (0.7-4.6)		1.7 (0.6-4.4)		**4.4** (1.6-11.7)		**8.1** (2.5-26.7)		**17.4** (4.3-70.7)
≥ 40		**4.5***(1.3-15.5)		2.5 (0.7-8.7)		2.5 (0.7-8.4)		1.3 (0.3-5.9)		**5.2** (1.1-25.3)

Ordinal variables IRR, P-1 and OP-1 breathing patterns had three categories, and higher breathing pattern categories were compared to lower ones in cumulative logistic regression (COR = cumulative odds ratio). Dichotomic variables (0, >0) OP-2 and OP-3 were analyzed using dichotomic logistic regression (OR = odds ratio). Significant values in bold. * Overall p-value could not detect this difference

Table 10. The adherence data of nasal CPAP therapy in male-female pairs.

n=233	Women	Men
Nasal CPAP started	86 (36.9%)	116 (49.8%)
Permanent user	52 (60.5%)	66 (56.9%)
Mean use (h/night)	4.8 (SD 2.5)	5.1 (SD 2.1)
Mean pressure (cmH_20)*	8.8 (SD1.9)	9.8 (SD 2.1)

Values are n (%) or mean (SD) = standard deviation, *p<0.001

Table 11. The number of patients entitled to Special Refunds in different study populations.

Diseases	Men (n=233)	Women (n=233)	p-value*	Premenopausal women (n=207)	Postmenopausal women (n=394)	p-value#
Diabetes mellitus	33 (14.2%)	14 (6.0%)	**0.005**	7 (3.4%)	40 (10.2%)	**0.003**
Chronic hypertension	81 (34.8%)	74 (31.8%)	0.478	57 (27.5%)	156 (39.6%)	**0.003**
Chronic cardiac insufficiency	11 (4.7%)	9 (3.9%)	0.638	3 (1.5%)	24 (6.1%)	**0.009**
Chronic arrhythmias	13 (5.6%)	6 (2.6%)	0.100	3 (1.5%)	15 (3.8%)	0.107
Chronic coronary heart diseases	26 (11.2%)	18 (7.7%)	0.209	7 (3.4%)	39 (9.9%)	**0.004**
Asthma and/or COPD	56 (24.0%)	57 (24.5%)	0.916	64 (30.9%)	128 (32.5%)	0.695
Thyroid insufficiency	8 (3.4%)	22 (9.4%)	**0.012**	15 (7.3%)	36 (9.1%)	0.429
Connective tissue disease, rheumatoid arthritis	6 (2.6%)	13 (5.6%)	0.100	0	10(2.5%)	**0.021**
Glaucoma	6 (2.6%)	9 (3.9%)	0.410	1 (0.5%)	15 (3.8%)	**0.016**
Epilepsy	6 (2.6%)	4 (1.7%)	0.530	7 (3.4%)	11 (2.8%)	0.687
Psychosis	5 (2.2%)	11 (4.7%)	0.144	9 (4.4%)	18 (4.6%)	0.901

COPD= chronic obstructive pulmonary disease
*Comparison between men and women of study population; conditional logistic regression.
#Comparison between pre- and postmenopausal women of study population; chi-squared test.
Significant p-values in bold

When taking into account only patients with SDB and compared with the Finnish general age-standardized population, a greater proportion of men were entitled to Special Refunds for diabetes (9.3%), hypertension (28.0%), chronic arrhythmias (3.0%) and asthma and/or COPD (22.8%). Women with SDB were more often entitled to refunds for hypertension (27.1%), asthma and/or COPD (37.4%) and hypothyroidism (9.1%) than age-matched women generally (Table 12).

Increasing age and BMI were associated with increased prevalence of many cardiovascular diseases including chronic hypertertension and chronic coronary heart disease in both genders and, in addition, chronic cardiac insufficiency in women (Tables 13 and 14). In the women of the pairs, age and BMI were also associated with the prevalence of hypothyroidism. In the men of the pairs, age significantly explained the higher prevalence of diabetes, asthma and/or COPD.

Table 12. Age-standardized prevalence of Special Refunds in the study populations with sleep-disordered breathing compared to the general Finnish population by gender and menopause status.

Diseases	Men n=219*			Women n=203*			Premenopausal women n=122#			Postmenopausal women n=257#		
	Prevalence in study population (%)	95% CI	Prevalence in general population (%)	Prevalence in study population (%)	95% CI	Prevalence in general population (%)	Prevalence in study population (%)	95% CI	Prevalence in general population (%)	Prevalence in study population (%)	95% CI	Prevalence in general population (%)
Diabetes	**9.3**	5.7-13.0	3.6	4.0	1.7-6.2	3.1	3.3	0.6-6.0	1.1	**10.1**	5.2-14.9	4.6
Chronic hypertension	**28.0**	20.6-35.3	11.5	**27.1**	19.3-34.9	13.4	**18.7**	12.1-25.3	4.3	**40.8**	31.6-50.0	20.7
Chronic cardiac insufficiency	3.7	1.2-6.2	1.5	3.6	0.5-6.7	2.1	1.0	0-2.4	0.1	5.3	2.1-8.5	3.3
Chronic arrhythmia	**3.0**	1.3-4.8	1.3	1.2	0.1-2.3	1.0	0.5	0-1.5	0.1	3.4	0.5-6.4	1.6
Chronic coronary heart diseases	8.0	4.5-11.6	5.4	5.2	2.7-7.7	4.0	**2.5**	0.3-4.8	0.2	9.9	5.5-14.2	6.5
Asthma/COPD	**22.8**	13.1-32.5	3.5	**37.4**	12.1-62.8	4.8	**26.5**	10.7-42.2	3.5	**28.6**	20.9-36.3	5.9
Thyroid insufficiency	2.5	0.3-4.6	0.5	**9.1**	4.1-14.0	3.3	4.6	1.4-7.8	1.9	**11.0**	6.2-15.7	4.4
Connective tissue disease, rheumatoid arthritis	3.0	0.3-5.7	1.3	4.1	0.9-7.3	2.6	10.8	0-25.3	1.4	5.1	2.1-8.1	3.5
Glaucoma	1.9	0-3.8	1.0	3.8	0.6-7.0	1.9	0.5	0-1.5	0.2	3.5	1.2-5.7	2.9
Epilepsy	2.0	0-4.0	1.2	9.8	0-27.1	1.1	2.3	0-4.6	1.1	1.6	0-3.6	1.2
Psychosis	4.6	0-12.3	2.1	4.0	1.2-6.8	2.4	3.5	0.4-6.6	1.8	**7.9**	3.3-12.6	3.0

COPD= chronic obstructive pulmonary disease, CI=confidential interval, differing prevalence in bold.

*Number of study subjects with SDB during more than 5% of time in bed (TIB)

#Number of pre- and postmenopausal women with SDB during more than 5% of TIB and age-standardized to general population, age 25-54 years and 45-84 years, respectively

Tables 13-14. Odd ratios associated with increasing age, BMI and sleep-disordered breathing (comparing partial upper airway obstruction and periodic obstruction) of Special Refund Categories among the women and the men.

Table 13.

Women n=133	**age**		**BMI**		**Partial vs. periodic obstruction**	
Diseases	OR§	95% CI	OR§	95% CI	OR#	95% CI
Diabetes mellitus	1.02	0.94-1.12	1.06	0.90-1.24	1.22	0.19-7.75
Chronic hypertension	**1.04***	1.00-1.08	**1.11***	1.03-1.20	**0.40***	0.18-0.90
Chronic cardiac insufficiency	**1.14***	1.01-1.30	1.16	0.97-1.39	2.80	0.26-29.70
Chronic arrhythmias	1.16	0.95-1.42	1.04	0.78-1.38	NA	NA
Chronic coronary heart diseases	**1.14***	1.04-1.25	1.13	0.99-1.29	0.39	0.08-1.78
Asthma and/or COPD	1.00	0.96-1.03	1.02	0.95-1.10	**3.02***	1.31-6.99
Thyroid insufficiency	**1.06***	1.00-1.13	**1.14***	1.02-1.27	1.39	0.41-4.70
Connective tissue disease, rheumatoid arthritis	1.05	0.97-1.14	0.97	0.85-1.12	0.53	0.11-2.60
Glaucoma	1.01	0.91-1.11	0.92	0.75-1.14	NA	NA
Epilepsy	0.91	0.80-1.04	1.09	0.89-1.34	1.87	0.16-22.18
Psychosis	1.00	0.92-1.08	1.14	0.98-1.33	0.87	0.16-4.63

Table 14.

Men n=122	**age**		**BMI**		**Partial vs. periodic obstruction**	
Diseases	OR§	95% CI	OR§	95% CI	OR#	95% CI
Diabetes mellitus	**1.09***	1.02-1.16	1.09	0.99-1.21	1.75	0.53-5.72
Chronic hypertension	**1.09****	1.04-1.15	**1.16***	1.06-1.26	0.77	0.30-2.01
Chronic cardiac insufficiency	1.08	0.98-1.20	0.92	0.74-1.14	0.63	0.06-6.52
Chronic arrhythmias	1.07	0.97-1.17	1.02	0.86-1.21	1.48	0.23-9.63
Chronic coronary heart diseases	**1.14****	1.06-1.23	0.98	0.87-1.11	3.21	0.93-11.07
Asthma and/or COPD	**1.05***	1.01-1.11	1.07	0.98-1.16	**3.39***	1.32-8.73
Thyroid insufficiency	0.96	0.81-1.14	1.22	0.92-1.61	NA	NA
Connective tissue disease, rheumatoid arthritis	1.07	0.95-1.21	1.13	0.92-1.38	5.58	0.46-68.42
Glaucoma	1.00	0.90-1.12	0.96	0.77-1.20	4.51	0.39-52.77
Epilepsy	1.00	0.92-1.10	0.83	0.66-1.04	NA	NA
Psychosis	0.89	0.75-1.07	0.82	0.57-1.18	1.86	0.09-38.20

Multivariate logistic regression analyses with 95% confidence interval (CI), significant ORs in bold, *p<0.05 and **p<0.001. N-value dropped from 233 to 133 with women and to 122 with men because subjects included were predominantly partial obstruction (partial obstruction more than 5% of time in bed (TIB) and periodic obstruction less than 5% of TIB) or periodic obstruction (partial obstruction less than 5% of TIB and periodic obstruction more than 5% of TIB) patients.
COPD= chronic obstructive pulmonary disease
BMI = body mass index
SDB=sleep-disordered breathing.
NA = no values available due to zero frequencies
§ Odds ratio (OR) for one unit increase in continuous age and BMI variables
#OR for partial obstruction versus periodic obstruction

2. Effect of menopause

2.1. Type and symptoms of SDB

Breathing abnormalities during the night were frequent in both female groups (Table 15). SDB was diagnosed in 262 (86.2 %) of the postmenopausal women and in 131 (79.4 %) of the premenopausal ones (p=0.057). In postmenopausal women, the average proportion of breathing abnormalities of TIB was higher than in premenopausal women (68.1% vs. 35.8%, p<0.001). The proportion of partial upper airway obstruction of TIB did not differ significantly between premenopausal and postmenopausal women, 49.0% and 55.3%, respectively. The proportion of periodic obstructive breathing was as common in premenopausal as in postmenopausal women, 51.0% and 44.7%, respectively. However, the proportion of postmenopausal women with partial upper airway obstruction (66.1%) was higher than that of premenopausal women (50.9%, p=0.001). The proportion of patients with periodic obstruction did not differ between postmenopausal (56.3%) and premenopausal women (48.5%).

Table 15. Sleep-disordered breathing (SDB) abnormalities during time in bed (TIB) in pre and postmenopausal women.

n=469	**Premenopausal** n=165	**Postmenopausal** n=304
Patients with SDB	131 (79.4%)	262 (86.2%)
Proportion of SDB of TIB*	35.8%	68.1%
Patients with partial upper airway obstruction*	84 (50.9%)	201 (66.1%)
Patients with periodic obstructive breathing	80 (48.5%)	171 (56.3%)
Proportion of partial upper airway obstruction of TIB	49.0% (SD 41.4)	55.3% (SD 39.2)
Proportion of periodic obstructive breathing of TIB	51.0% (SD 41.4)	44.7% (SD 39.2)

Values are n (%) or mean (SD) = standard deviation, *p<0.05

The severity of SDB was higher in postmenopausal than in premenopausal women. With SDB cut-off points greater than 5% of TIB, a greater proportion of postmenopausal women received the diagnosis of SDB than in the premenopausal group (Table 16). Neither ODI_4 nor AHI_{est} could measure any significant differences in the severity of SDB between the female groups. The average ODI_4 greater than 5/h was 24.0% in postmenopausal, and 17.5% in premenopausal women, and the AHI_{est} greater than 5/h was 8.9% and 4.9%, respectively.

The prevalences of the principal signs or symptoms of sleep-disordered breathing were similar in the post- and premenopausal women (Table 17). Only nasal congestion was less frequent in postmenopausal women than in premenopausal ones. In multivariate analysis, variation of nasal congestion was determined by variation of allergic rhinitis, but not by BMI, EDS, morning headache or smoking. In univariate analysis, variation of BMI and presence of SDB explained allergic rhinitis with borderline significance (p=0.095 and p=0.058, respectively). Micrognathia/retrognathia tended to be less frequent in the postmenopausal than in the premenopausal group. In a multivariate analysis, menopause, ODI_4 over 5 or AHI_{est} did not correlate with the signs and symptoms of SDB (Table 18). Increasing BMI was associated with increasing EDS and self-reported snoring.

Table 16. Sleep-disordered breathing (SDB) in the clinical population of women investigated with static-charge-sensitive bed.

Sleep studies n=469	Postmenopausal (n=304)	Premenopausal (n=165)	P*
SDB > 5%	86.2 %	79.4 %	0.057
SDB > 20%	61.2 %	46.7 %	**0.003**
SDB > 50%	30.9 %	16.4 %	**0.001**
ODI4 > 5/h	24.0 %	17.5 %	0.098
AHI_{est} > 5/h	8.9 %	4.9 %	0.113

* Chi-squared test, significant p-values in bold, 469 out of 601 sleep studies were eligible for the analyses.
SDB = P1 + OP1 + OP2 + OP3 + IRR > 5% of time in bed (TIB). P1, OP1, OP2 and OP3 are forms of periodic breathing and IRR (increased respiratory resistance) represents partial upper airway obstruction during sleep.
ODI_4 = the oxygen desaturation events of 4%-unit or more
AHI_{est} = the sum of OP2 and OP3 equals 5 % of TIB, which equals an apnoea-hypopnoea index (AHI) of 5 per hour.

Table 17. The signs and symptoms of sleep-disordered breathing in pre- and postmenopausal women.

Total n=393	Postmenopause	Premenopause			
Dependent variable	**%**	**%**	**OR**	**95% CI**	**p***
Excessive daytime sleepiness (n=383)	74.8	79.1	0.79	0.47-1.31	0.355
Self-reported snoring (n=380)	85.3	86.1	0.94	0.51-1.72	0.836
Witnessed apnea (n=380)	52.6	49.6	1.13	0.74-1.72	0.582
Morning headaches (n= 382)	13.0	17.8	0.69	0.39-1.24	0.213
Nasal congestion (n=382)	12.3	26.4	**0.39**	0.23-0.67	**<0.001**
Micro/retrognathia (n= 382)	8.3	14.0	0.56	0.29-1.09	0.088

* Univariate logistic regression analysis, significant ORs in bold
N values vary depending on the availability of data

2.2. Co-morbidity

The entire group of postmenopausal women had more special refunds for diabetes mellitus, hypertension, chronic cardiac insufficiency, chronic coronary heart diseases and glaucoma when compared to premenopausal women (Table 11).

When comparing the reimbursements of general Finnish postmenopausal women and postmenopausal women with SDB in our study, the latter were more frequently entitled to refunds for diabetes, hypertension, asthma and/or COPD, hypothyroidism and psychosis. Similarly, premenopausal women with SDB were more often entitled to refunds for hypertension, asthma and/or COPD and chronic coronary disease (Table 12).

Table 18. Excessive daytime sleepiness, snoring, witnessed apnoeas and morning headaches explained by BMI, age, menopausal status, ODI_4 > 5/h and AHI_{est} in a multivariate logistic regression model.

Total n=393	**BMI**		**Age**		**Menopause**		**ODI_4 > 5/h**		**AHI_{est}**	
Dependent variable	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	OR	**95% CI**
Excessive daytime sleepiness (n=364)	**1.06***	1.02-1.10	0.97	0.94-1.00	1.22	0.56-2.65	0.98	0.53-1.79	0.88	0.36-2.15
Self-reported snoring (n=363)	**1.11****	1.05-1.17	0.98	0.94-1.02	1.13	0.44-2.94	0.60	0.29-1.23	2.42	0.53-11.06
Witnessed apnea (n=363)	1.01	0.98-1.05	0.99	0.97-1.02	1.35	0.72-2.52	0.87	0.53-1.43	1.48	0.69-3.17
Morning headaches (n=364)	1.01	0.97-1.06	1.00	0.96-1.04	0.73	0.31-1.71	1.09	0.55-2.15	1.23	0.46-3.29

*p < 0.05, **p < 0.001, significant ORs in bold. N varies from total of 393 because some observations were deleted due to missing values for the response or explanatory variables. OR was adjusted for BMI, age, menopause, smoking, ODI_4 > 5/h and AHI_{est}.

AHI = apnea-hypopnea index

AHI_{est} = the sum of OP2 and OP3 equals 5 % of time in bed, which equals an AHI of 5 per hour.

ODI_4 = the oxygen desaturation events of 4%-unit or more

Table 19 shows the multivariate logistic regression analyses of the entire female population. Here OR was adjusted for age, BMI, smoking, excessive daytime somnolence, snoring, morning headaches, witnessed apneas during sleep and SDB. N-value dropped to 444 from 601 due to missing values in many variables. Morning headaches were associated with lower prevalence of hypertension (OR 0.48, 95% CI 0.24-0.94), and smoking (previous or current) with increased prevalence of asthma and/or COPD (OR 1.75, 95% CI 1.12-2.74). There were no associations between SDB and the diseases after controlling for other confounding factors.

Table 19. Special Refund Categories in the large female study population and sleep-disordered breathing

Women n=444	**age**		**BMI**		**SDB vs. non-SDB**	
Diseases	OR	95% CI	OR	95% CI	OR	95% CI
Diabetes mellitus	1.02	0.98-1.06	**1.08***	1.03-1.14	4.28	0.55-33.08
Chronic hypertension	**1.06****	1.04-1.09	**1.11****	1.07-1.15	0.98	0.52-1.84
Chronic cardiac insufficiency	**1.10***	1.04-1.16	0.99	0.93-1.08	1.86	0.23-15.39
Chronic arrhythmias	**1.08***	1.01-1.16	0.91	0.81-1.02	0.75	0.08-7.21
Chronic coronary heart diseases	**1.08****	1.04-1.13	1.01	0.96-1.06	1.86	0.23-15.39
Asthma and/or COPD	**1.02***	1.00-1.04	1.03	1.00-1.06	1.93	0.43-8.70
Thyroid insufficiency	1.02	0.99-1.06	**1.05**	1.01-1.10	1.93	0.21-17.83
Connective tissue disease. rheumatoid arthritis	1.02	0.98-1.06	0.97	0.91-1.03	1.40	0.45-4.29
Glaucoma	**1.08***	1.02-1.15	0.96	0.88-1.06	1.99	0.43-9.10
Epilepsy	0.97	0.90-1.04	1.09	0.99-1.19	0.85	0.08-8.48
Psychosis	0.99	0.94-1.03	1.04	0.98-1.10	0.58	0.33-1.01

OR (odds ratio) is adjusted for age, BMI, smoking, excessive daytime somnolence, snoring, morning headache, apneas during sleep and SDB>5% of time in bed. Multivariate logistic regression analyzes with 95% confidential interval (CI) were used, significant ORs in bold, *p<0.05 and **p<0.001. N dropped from total of 601 because some observations were deleted due to missing values for the response or explanatory variables.

COPD= chronic obstructive pulmonary disease

BMI = body mass index

SDB= sleep-disordered breathing

3. Effect of type of SDB

3.1. CPAP adherence

Out of the 116 male patients starting nasal CPAP, 73 (62.9%) had IRR, 99 (85.3%) periodic breathing and 38 (32.8%) severe periodic breathing (OP-2 + OP-3) over 5% of TIB. In the female group (n=86) the figures were 61 (70.9%), 50 (58.1%) and 7 (8.1%), respectively. In men, the presence of partial upper airway obstruction did not explain permanent nasal CPAP use (66.7% continued vs. 58.0% discontinued, p=0.339) but men with periodic obstructive breathing were more likely to continue the therapy than discontinue it (90.9% vs. 78.0%, p=0.052). Women continued CPAP therapy equally if they had predominantly partial upper airway obstruction (76.9% vs. 61.8%, p=0.130) or periodic obstructive breathing (51.9% vs. 67.7%, p=0.148). The duration of nasal CPAP treatment, the hours of use or nasal CPAP pressures did not differ in either men or women when patients with pure partial upper airway obstruction (IRR > 5% and periodic breathing ≤ 5% of TIB) and patients with periodic obstructive breathing (IRR ≤ 5% and periodic breathing > 5% of TIB) were compared.

3.2. Co-morbidity

Special Refund Categories in patients with predominantly nonperiodic partial upper airway obstruction (partial obstruction more than 5% of TIB and periodic obstructive breathing less than 5% of TIB) compared with patients with periodic obstructive breathing (partial obstruction less than 5% of TIB and periodic obstructive breathing more than 5% of TIB), and the associations with age and BMI were analysed using multivariate logistic regression analysis (Tables 13 and 14). Women with partial upper airway obstruction had a lower prevalence of hypertension (OR 0.40, 95% CI 0.18-0.90) and a higher prevalence of asthma and/or COPD (OR 3.02, 95% CI 1.31-6.99) compared to those with periodic obstructive breathing, even after adjusting for age and BMI. Men with partial upper airway obstruction had a higher prevalence of asthma and/or COPD (OR 3.39, 95% CI 1.32-8.73).

DISCUSSION

The present study has its origin in clinical observations of patients, especially women, suffering from substantial symptoms of SDB without severe conventional obstructive sleep apnea. These patients tend to get good relief from their symptoms with nasal CPAP therapy. This study focuses on evaluating previously frequently neglected effects of gender, pre- and postmenopausal state and partial upper airway obstruction on the manifestation of findings, co-morbidities and adherence to nasal CPAP in patients with clinically significant SDB. A retrospective study design was used with data on sleep recordings, hospital records, questionnaires sent to women and co-morbidities from the National Agency for Medicines and the Social Insurance Institution.

According to the present study, nonperiodic partial upper airway obstruction is a common type of SDB in both genders but especially in women. Partial upper airway obstruction is not a mild form of SDB when comparing co-morbidity or adherence to nasal CPAP between patients with partial upper airway obstruction and those with periodic obstructive breathing, namely, “frank” obstructive sleep apnea.

Neither the prevalence nor the symptoms of SDB differed between pre- and postmenopausal women although postmenopausal women had more severe SDB than premenopausal women in terms of different cut-off points of SDB.

The effects of BMI and age on type of SDB between genders were different. In women, partial upper airway obstruction increased with increasing age only, but in men partial upper airway obstruction was associated with increasing age and BMI combined.

Co-morbidity with SDB was high in both genders. A novel and intriguing finding was the lower prevalence of hypertension in females with partial upper airway obstruction compared to those with conventional obstructive sleep apnea, even after adjustment for age and BMI. This reflects differences in pathogenesis between the genders and increases the concerns about using the AHI as the only marker of SDB and its severity.

1. Methodological aspects

1.1. Subject selection

Both male and female subjects were consecutively selected from our pulmonary clinic sleep database. They were all referred to diagnostic sleep studies with static-charge-sensitive bed recordings. The results of the present study can be generalised to the sleep clinic population but with caution to the general population. Because the sleep recordings were done in a pulmonary clinic, a selection bias of patients with pulmonary diseases might be present. However, a vast majority (80-90%) were referred to the sleep studies by general practitioners or specialists other than pulmonologists.

BMI greater than 30 kg/m^2 was found in 58% of male-female pairs, obesity being higher in the study population than in the general Finnish male (21%) and female (24%) population (Aromaa and Koskinen, 2002). The male-female pairs were carefully matched by age and BMI, which are the major confounding factors. However, this may have made some contribution to the prevalence of co-morbidities compared to the general population because BMI adjustment could not be used in these analyses. Age was taken into account by dividing the general population into age groups of ten years and matching them according to the age of the study population.

Information about co-morbidities of the general population was provided by the National Agency for Medicines and the Social Insurance Institution. Because SDB is not included in the diseases with reimbursed medication, it was not possible to segregate patients with SDB from the general population. However, the differences between the patients with SDB and the general population would probably have been even clearer, if we had been able to use a "SDB-free" control population. The exact menopausal status in the general female population could not be defined, but, knowing the median age of menopause among Finnish women and using the large number of control subjects, this is unlikely to have weakened our results.

1.2. Diagnosing SDB with static-charge-sensitive bed

The SCSB was developed in 1979-1981 at the Department of Physiology, University of Turku (Alihanka and Vaahtoranta, 1979; Alihanka et al., 1981). Since then, it has been validated and used regularly in clinical and investigational settings for sleep studies (Polo et al., 1988; Polo, 1992, Polo-Kantola, 1999; Saaresranta, 2000). In our pulmonary clinic, the SCSB has been the only method used for sleep studies from 1985 until 2000, and after that, together with Embla Somnologica® (Medcare Flaga hf. Medical devices, Reykjavik, Iceland) used as a cardiorespiratory polygraphy. The SCSB has a low cost/benefit ratio in diagnosing SDB. The particular advantage of the SCSB is that it is a non-invasive method without any detectors attached, and the subject is able to sleep naturally without the disturbances of thermistors or thoracic and abdominal bands. As the airflow is not monitored in the SCSB, it is not possible to determine the AHI in the conventional way. Instead, a special SCSB-based analysis was used (Polo, 1992) to detect a wide spectrum of breathing abnormalities. Four types of periodic breathing (P-1, OP-1, OP-2 and OP-3) can be distinguished accurately from the SCSB on the basis of body movements, respiratory movements and ballistocardiographic findings. P-1 and OP-1 represent periodic breathing. OP-2 and OP-3 patterns reflect episodes of obstructive sleep apnea, and these can be correlated to the AHI with specificity (61-68%) and sensitivity (98-99%) in patients with sleep apnea compared to conventional methods (Polo et al., 1988). Instead of a conventional AHI from the SCSB patterns, the estimated AHI_{est} was used in study I. In addition, the SCSB has proved to be a powerful tool in diagnosing partial upper airway obstruction, seen as increased respiratory resistance (IRR pattern) (Polo, 1992). IRR corresponds to prolonged episodes of partial upper airway obstruction without arousals and with slowly increasing CO_2 retention accompanied with increased intrathoracic variations of pressure.

Although we know that upper airway dysfunction during sleep may be either complete or partial upper airway obstruction, nearly all investigations in this field only define SDB in terms of the AHI. Because periodic breathing is a prerequisite for scoring episodes of apnea and hypopnea, factors promoting or suppressing periodic breathing may cause overestimation or underestimation of the severity of the upper airway obstruction. The AHI is a poor variable to estimate signs and symptoms of SDB in the nonapneic snoring patient, and it can be considered insufficient to estimate the severity of the upper airway dysfunction during sleep (Hudgel, 1986; Flemons and McNicholas, 1997; Cracowski et al., 2001). In the search for alternatives to AHI, there is a need for indexes which also consider partial obstruction. By using the SCSB, it is possible to extend the respiratory analysis to distinguish various patterns of periodic breathing and partial upper airway obstruction.

The recordings of the SCSB combined with an oximeter, were reanalyzed by two scorers who were blinded to the study hypothesis. The scorers were experienced in analyzing the SCSB patterns and had been originally taught and guided by the same tutor. Thus, the criteria used for the analyses were alike, and scoring bias was unlikely.

1.3. Study design and data collection

Because of the retrospective study design, no laboratory samples could be taken. Therefore, menopausal status was defined by other methods than serum hormone levels. Women 55 years or older were considered postmenopausal if hospital records or self-reported data on menstrual history in a questionnaire did not confirm otherwise. The cut-off point of 55 years was chosen because the median age for menopause in Finnish women is 51 years (Luoto et al., 1994). The questionnaire sent to women included open questions about the use and duration of HT and the trade names of the hormones. Despite the clear questions, they were poorly answered and only a rough estimate of HT could be used. HT could not be defined in the general female population either, but it was assumed that the use of hormones would be similar in both populations. In the questionnaire battery, the BNSQ, a validated and widely used questionnaire in Nordic sleep surveys, was partly included (Partinen and Gislason, 1995).

The data on nasal CPAP usage were gathered from the pulmonary clinic sleep database which was carefully updated at every control visit. The actual hours used were measured by a nasal CPAP unit compliance meter giving accurate and objective adherence data.

The data on co-morbid diseases were based on the governmental database of reimbursed medications from the National Agency for Medicines and the Social Insurance Institution. Because the criteria of reimbursement for chronic obstructive pulmonary diseases include both asthma and COPD, it was not possible to separately analyze these diseases. For the same reason, diabetes mellitus types 1 and 2 were combined in the co-morbidity data. This has to be kept in mind when comparing our results of chronic obstructive pulmonary diseases or diabetes mellitus to other than Finnish studies. However, this does not lead to a differential bias between our study

and the control population used since the same reimbursement criteria are applied to both. The public health insurance system covers all Finnish residents and criteria for medication reimbursements are stricter than normal clinical criteria for treatment. In addition, not only doctors but also pharmacists and social workers make sure that every patient entitled to reimbursed medication receives it. The use of a governmental database of reimbursed medications strengthens our results regarding the criteria of the diseases.

2. Gender differences

2.1. Differences in type of SDB and adherence to nasal CPAP treatment

Our results show that in age- and BMI-matched male-female pairs in clinical settings, the prevalence of SDB was very common in both genders (in males 94.0% and in females 87.1%). It was more common in men when looking at the proportions of breathing abnormalities of TIB (in males 31.7% and in females 21.8%). This is in agreement with previous population-based studies showing the same difference between genders (Young et al., 1993; Bixler et al., 1998 and 2001; Durán et al., 2001). The high prevalence of SDB may be explained partly by the fact that our study population was more obese than the general Finnish population. It has been estimated that with increasing obesity, SDB may be as prevalent as one in every five adults (Young et al., 2002). Our results exceeded even these estimates. Another explanation for the high prevalence of SDB in our study may be that the patient population was referred to sleep studies because of suspicion of SDB due to symptoms. During the years 1994-2000, the knowledge of SDB among general practitioners was still scarce and referring patients to sleep studies was not as common as it is today, a fact which may have caused strict referring criteria bias because probably only the women with severe symptoms of SDB would have been referred. In our study, the male-female pairs were carefully matched for age and BMI and, together with the perception of male predominance of SDB, an over-referral of women with less severe SDB and less periodic breathing, would be unlikely. In our study, the high prevalence of SDB in patients referred to sleep studies suggests that the threshold for referral is still too high. Many patients, who should be studied for their breathing problems, are not getting referral.

The type of SDB differed between genders in our study population. The median percentage of partial upper airway obstruction (IRR) was similar in men and women but periodic obstructive breathing (P-1, OP-1, OP-2 and OP-3 together) was more common in men than in women. An unexpected finding was that partial upper airway obstruction was the most common type of SDB not only in women but also in men, being 50.2% in women and 37.2% in men. Especially the proportions of OP-2 + OP-3, which are compatible with conventional obstructive apnea, were less frequent in women than in men. On the other hand, we expected women to have less of almost all patterns of periodic obstructive breathing (P-1, OP-2 and OP-3) than men. PMS was more common in the women than in the men.

Why was partial upper airway obstruction so common in our study? Previous studies have used conventional polysomnographic methods with a thermistor to diagnose SDB. In those studies, the severity of SDB has been assessed with the AHI. Both polysomnography and the AHI were developed to detect and measure apneas and hypopneas, but not partial upper airway obstruction. The SCSB used in our study is a powerful method to measure partial upper airway obstruction (Polo, 1992). The present study is the first larger-scale study focusing on the occurrence of partial upper airway obstruction. In previous reports, partial upper airway obstruction has only scarcely been investigated (Bao and Guilleminault, 2004).

Why are women more likely to have partial upper airway obstruction during sleep? By assessing the age and BMI dependencies of partial obstruction separately in men and women with three-dimensional figures, we found that women had a consistently increasing susceptibility to partial obstruction after the age of 65 years over the whole BMI range, whereas in males, partial obstruction associated with the combination of high age and high BMI. Although there were no significant linear associations, this implies gender differences in the ventilatory and upper airway control during sleep or in the arousal threshold. These possible gender influences on the resistance and collapsibility of the upper airway have been reviewed in section 1.3.

Partial upper airway obstruction is associated with general narrowing of the upper airway from the soft palate to the tongue base and hyoid bone levels, whereas obstructive sleep apnea is characterized by upper airway narrowing, focused at the soft palate level (Polo et al., 1991). Women have a smaller, stiffer and less collapsible upper airway than men with sleep apnea (Brooks and Strohl, 1992; Mohsenin, 2001; Rowley et al., 2001; Jordan et al., 2005). In addition, respiratory control may oscillate when the controler gain increases. Changing hormonal levels in women at menopause (low progesterone level) may have a stabilizing effect on the decreased respiratory drive. These mechanisms could explain why women are more prone to partial upper airway obstruction than men.

Do these findings and the high proportion of partial upper airway obstruction have any clinical relevance? In our study, nasal CPAP adherence was equal between genders at the one-year control visit. The one-year time limit for permanent use was chosen because the placebo effect of treatment would not last so long. Both men and women used the nasal CPAP adequately (the mean use was 5 hours per night). Previous studies with mild SDB (measured with low AHI) have shown low adherence to nasal CPAP therapy (Engleman et al., 1999; Rosenthal et al., 2000). Our results show the opposite, if symptomatic partial upper airway obstruction is considered a mild form of SDB. It could be argued that no difference in nasal CPAP adherence was observed because of lack of statistical power. However, since women with partial upper airway obstruction predominance tended to continue nasal CPAP therapy more often than those presenting with a smaller proportion of partial obstruction, a significant difference would only have strengthened the adherence in favor of partial obstruction. Therefore, the clinical relevance of partial upper airway obstruction is supported by the equal CPAP adherence in women with partial obstruction and

periodic obstructive breathing. Although not shown in the studies of hypertension (Li et al., 2008), women in general might be more likely to comply with the therapy presented by the doctor compared to men, and this could explain the similar adherenre to nasal CPAP in women regardless of the severity or type of SDB. However, a recent study of short-term use of nasal CPAP found no gender differences in adherence to the therapy (Budhiraja et al., 2007a).

It has to be pointed out that all our study subjects were symptomatic in terms of symptoms suggesting SDB. Although EDS is the major symptom of SDB, the majority of subjects, especially the elderly with SDB, do not have EDS (Young et al., 1993). Further, some patients with a low AHI (below 5) may complain of EDS, which can be successfully relieved by nasal CPAP (Young et al., 1993). Men also had a high proportion of partial upper airway obstruction but still they tended to adhere better to nasal CPAP when they had predominant periodic obstructive breathing. This may be due to the fact that men would be less symptomatic with partial obstruction than with periodic obstructive breathing. Thus, they were motivated to use the nasal CPAP because of the better relief of symptoms with predominant periodic obstructive breathing. Studies of SDB are conventionally done with mostly male populations using methods that do not measure partial upper airway obstruction, and studies of partial upper airway obstruction are few. This may exaggerate the male predominance in SDB and underestimate the degree of upper airway obstruction and SDB in women.

Our findings do have clinical relevance. Our results indicate that a symptomatic patient with a low AHI may have partial upper airway obstruction that should and can be successfully treated with nasal CPAP. This should be taken into consideration especially with elderly, obese and female patients. SDB in females is probably underestimated, and the AHI is not a good marker for the entire range of SDB.

2.2. Differences in co-morbidity

Our results show that the total burden of unadjusted co-morbidity of male-female pairs with suspicion of SDB is heavy. Especially diabetes, hypertension, coronary disease, asthma and/or COPD and hypothyroidism were common in both genders. Men had more diabetes and less hypothyroidism than women. The high co-morbidity in general is not surprising because our study population consisted of clinical subjects with symptoms, not the general population. Symptoms fitting SDB may also have been due to other diseases. On the other hand, the general population used as controls was not "SDB-free" (as explained in section 1.1.), a fact which probably diminished the differences between the study and the general population. The obesity of our study population probably augmented the co-morbidity burden. Both diabetes and hypothyroidism have been more prevalent in studies of patients with SDB. The gender difference in terms of hypothyroidism is in agreement with previous studies of the general population (Aoki et al., 2007). The higher prevalence of diabetes in males compared to females is not in line with previous data when taking into account the fact that the pairs were age- and BMI-matched (Narayan et al., 2003). Because of non-adjustment of other confounding factors no further conclusions can be drawn.

The present study shows a clearly increased prevalence of cardiovascular diseases (hypertension and arrhythmia), diabetes, asthma and/or COPD and hypothyroidism in patients with SDB in both genders when compared to the general Finnish population. There were some differences in the impact of age and BMI between genders concerning co-morbidities. The novelty of our results was that the co-morbidity profile of partial upper airway obstruction differed from that of obstructive sleep apnea. After adjustment for age and gender, partial upper airway obstruction was associated with a higher prevalence of asthma and/or COPD in both genders, and lower prevalence of hypertension in females, when compared to periodic obstructive breathing. Otherwise the disease profiles were the same in patients with predominantly partial upper airway obstruction or periodic obstructive breathing.

Cardiovascular diseases, especially hypertension, have been associated with SDB in many large, controled studies. SDB has been found to be an independent risk factor for hypertension, the risk being two- to three-fold compared to patients without SDB. The risk of hypertension in our patients with SDB was with in roughly the same range. In previous studies, male patients have dominated, or either male only or female only study populations have been used, and thus no clear gender differences have been found. Contrary to the majority of other studies, we found that women with partial upper airway obstruction had reduced prevalence of hypertension compared to women with periodic obstructive breathing predominance. In men, the odds ratio was 0.8, suggesting that less hypertension was also associated with partial upper airway obstruction. However, the difference was not significant. In the cross-sectional population study of Bixler and co-workers, SDB was associated with increased risk of hypertension in young and middle-aged patients without any gender differences except that snoring postmenopausal women with hormone therapy had a reduced risk of hypertension (Bixler et al., 2000). The same effect was not seen if SDB was more severe in postmenopausal women using hormone therapy. One could hypothesize that snoring postmenopausal women had suffered from partial upper airway obstruction and been thus protected from hypertension.

In the population-based case control study of Hedner and co-workers, SDB was independently associated with hypertension regardless of the severity of SDB (Hedner et al., 2006). This connection was found only in men, but not in women, indicating that there may be gender dependence in the development of hypertension in patients with SDB. They suggested two possible explanations for the lack of association between hypertension and SDB in a female population. First, the methodology used for nasal airflow measurement in their study differed from previous studies since they used both a nasal pressure cannula and a thermistor. The nasal pressure cannula is more sensitive in detecting restricted airflow than thermistors (Aittokallio et al., 2001; Teichtahl et al., 2003), and hence a larger number of patients with mild SDB were likely to be included in the study (Hedner et al., 2006). The SCSB used in our study is a powerful method to detect partial upper airway obstruction. Second, a dilution of the association between hypertension and SDB in women could have resulted from the fact that the women were mostly postmenopausal, and postmenopausal women have SDB more often than

premenopausal women. Therefore, this could have accounted for the proportionally higher number of women in their study (Hedner et al., 2006).

The reasons for less hypertension in women with partial upper airway obstruction are not clear. If partial upper airway obstruction was considered a mild form of SDB, it could affect the overall health of patients less. However, we have already discussed the fact that nasal CPAP therapy adherence was the same in patients with partial upper airway obstruction and those with periodic obstructive breathing. In addition, other co-morbidities in our study were no less associated with partial upper airway obstruction than periodic obstructive breathing. These findings suggest the theory that partial upper airway obstruction is not mild SDB.

Partial upper airway obstruction during sleep is associated with increased transcutaneously measured carbon dioxide (CO_2) levels (Rauhala et al., 2007). One possible hypothesis for explaining less hypertension in partial upper airway obstruction is CO_2 –coupled autoregulation of blood flow (Lavi et al., 2003; Lavi et al., 2006). By increasing arterial CO_2, partial upper airway obstruction could enhance local vasodilation and therefore protect against hypertension. Low sympathetic activity associating with high arterial pCO_2 could be another factor. The possibility of interaction between partial upper airway obstruction and the endothelial function makes this preliminary finding of special interest. Further studies are needed first to replicate this finding.

Chronic arrhythmias (including ventricular and supraventricular tachycardia and atrial fibrillation), were about two times more prevalent in male patients with SDB compared with the general Finnish male population, but no correlation was seen in women. This is consistent with previous studies. Atrial fibrillation is the most frequently studied type of arrhythmia that has been connected to SDB. However, the gender difference seen in our study is a novel finding. In addition to SDB, obesity and nocturnal desaturations have also predicted atrial fibrillation (Gami et al., 2007). In our study, obesity was present and male patients had more conventional apneas, probably with deeper desaturations during the night than female patients, thus explaining the gender difference. The type of SDB did not have any correlation with chronic arrhythmias.

In the present study, diabetes mellitus was two to three times more prevalent in males with SDB than in general, and increasing age but not BMI explained this connection. The type of SDB did not have any correlation. Among the female population the prevalence of diabetes was the same as in the general female Finnish population. The higher prevalence of diabetes or the markers of diabetes have been found in several studies, but gender differences only in two recent ones. Tuomilehto and co-workers found, in a population-based cross-sectional study, an association between SDB and diabetes in men but not in women after adjustment for age, BMI, smoking and central nervous system-affecting medication (Tuomilehto et al., 2008). They explained that the female group was overrepresented with women over 65 years, diminishing the association. This does not explain our results because only 21.5% of women in the pairs were over 65 years. In a Nordic questionnaire study, the results were opposite to the Finnish study regarding the gender difference (Valham et al., 2008). Both snoring

and witnessed apneas were related to diabetes in women regardless of the age group, but in men, only those younger than 55 years were witnessed apneas related to a four-fold risk of diabetes (Valham et al., 2008). They argued that hormonal factors (for example, co-existing or previous polycystic ovary syndrome) could explain some of the gender difference, or that male subjects over 65 years have more illnesses and a shorter life expectancy than their female counterparts (Valham et al., 2008). In our study, 78.5% of men were younger than 65 years, and 42.9% were younger than 55 years. Therefore, there was no overrepresentation of elderly men.

The present study shows that the prevalence of asthma and/or COPD in male and female patients with SDB was seven-fold compared to the age- and gender-standardized general population. Partial upper airway obstruction was related to a three-fold risk of asthma and/or COPD in both genders. A higher prevalence of asthma and/or COPD has been reported previously, but not consistently. In agreement with our study, no major gender differences have been found in associations between SDB and asthma and/or COPD. Because the sleep recordings were performed in a pulmonary clinic, referral bias could have occurred.

Obesity and GER are shared risk factors for SDB and asthma. Weight reduction improves pulmonary mechanics and contributes to a better control of airways obstruction (Hakala et al., 2000; Tantisira and Weiss, 2001; Gunnbjörnsdóttir et al., 2004). Inflammation-mediating cytokines (tumor necrosisfactor-alpha and interleukin-1) are associated with asthma and obesity, as well as with increased sleepiness (Tantisira and Weiss, 2001). However, in our study, the high BMI in both men and women did not explain the high prevalence of asthma and/or COPD. Because medicines for GER are not included in reimbursed medications, we were not able to disclose the impact of GER on asthma patients in our study population. The quality of sleep in patients with asthma and/or COPD is often poor (Janson et al., 1996; Saaresranta et al., 2005). Because of this, the combined symptom burden of our study population may have been high, resulting in more referrals to sleep studies.

In the present study, hypothyroidism was nearly three times more prevalent in women with SDB than in the general population. Increasing age and BMI, but not the type of SDB, independently associated with hypothyroidism in women but not in men. Previous studies of hypothyroidism are sparse, populations are small, gender differences have not been assessed, and the results of associations between SDB and hypothyroidism are inconsistent. Our results are consistent with previous studies showing the higher prevalence of hypothyroidism in women than in men. Increasing age and BMI have been linked with a higher prevalence of hypothyroidism because weight gain is often found in hypothyroidism. Our finding of gender difference in age- and BMI-matched pairs has not been reported before.

Clinically, it is important to diagnose and treat the co-morbidities of SDB regardless of wheather the patient has partial upper airway obstruction or periodic obstructive breathing. With the exception of hypertension, partial upper airway obstruction is no less related to co-morbidities than periodic obstructive breathing, which is conventionally considered a more severe form of SDB, and thus supposed to be more

closely linked with co-morbidities. Our clinical practice of treating patients with symptomatic SDB even with a low AHI seems to be relevant.

3. Menopausal differences

3.1. SDB in pre- and postmenopausal women

The prevalence of SDB was high in both pre- (79.4%) and postmenopausal (86.2%) women in the present study. The SDB was less severe in premenopausal than in postmenopausal women with different SDB cut-off points, and the same tendency was also observed in nocturnal desaturations. In women with SDB, partial upper airway obstruction was more common in postmenopausal (66.1%) than in premenopausal (50.9%) women, but no difference in periodic obstructive breathing was seen between the groups. The higher prevalence and increasing severity of SDB in terms of the AHI in postmenopausal than in premenopausal women have been recognised earlier. The older studies did not have consistent results, but the recent large population studies with careful adjustments and taking into account the use of hormone therapy, show that menopause has an impact on the prevalence of SDB (measured either by AHI alone or combined with major symptoms of SDB). The prevalences of SDB measured with an AHI greater than 5 or 10 have varied between 20-32% and 49-68% in a clinical population of pre- and postmenopausal women, respectively (Dancey et al., 2001; Resta et al., 2003). Further, one study found SDB in 83% of postmenopausal women who complained of chronic insomnia (Guilleminault et al., 2002).

Our results exceeded Dancey's and Resta's prevalence figures when measured with findings of SDB more than 5% of TIB. With a cut-off point of more than 20% of TIB, the results are more or less the same as those of Dancey and Resta, our figures being 46.7% in premenopausal and 61.2% in postmenopausal women. When using ODI_4 over 5/h or AHI_{est} over 5 as the measures for prevalence of SDB in our study population, the figures were clearly smaller. This could refer to the methodology used in our and in other studies, the SCSB being a better method to estimate the prevalence and severity of SDB compared to conventional polygraphic sleep studies. The high prevalence of SDB in our clinical population may reflect too strict referral criteria for sleep studies and underdiagnosis of SDB especially in the female population. Women tend to express their sleepiness of SDB differently from men, and they are also less likely to report restless sleep or witnessed apneas during sleep than men (Redline et al., 1994; Kapsimalis and Kryger, 2002a; Valipuor et al., 2007). The under-reporting of typical symptoms of SDB may explain the more delayed diagnosis of SDB in women and the strict referral criteria for sleep studies.

Our results are strong in that we had a large female population of 601 women whose menopausal status was defined very carefully by other means (age, history of ovariectomy and menstruation) than hormone levels, due to our retrospective study designs. The use of HT seems to alleviate SDB in postmenopausal women, reinforcing the idea that gender differences can be partly due to different levels of sex hormones (Bixler et al., 2001; Shahar et al., 2003). In fact, postmenopausal women with HT have

the same prevalence of SDB than premenopausal ones, while postmenopausal women without HT have nearly as much SDB as men (Bixler et al., 2001). Unfortunately, we were not able to calculate the exact number of women who used HT despite the questionnaire sent to the women. Therefore, we used an estimation based on the answers to the questionnaire that 40% of postmenopausal women had been previously or currently on HT (estrogen or progesterone alone or combined). Additional statistical analyses were performed to address this problem. The same statistical anlyses were performed including only HT-nonusers as regarding the major findings, and there were no changes in the results.

In addition to age and HT, obesity, smoking, nasal congestion or gynecological diseases may influence the prevalence of SDB. Obesity and upper body fat distribution with large neck circumference are thought to be risk factors for SDB (Millman et al., 1995; Dancey et al., 2001; Resta et al., 2003). After menopause women tend to gain weight perhaps due to hormonal changes, and this predisposes postmenopausal women to SDB (Young et al., 1993; Duran et al., 2001; Ip et al., 2004). In the present study, BMI was high (> 30 kg/m^2) in both pre- and postmenpausal women but neither BMI nor neck circumference differed between the groups. Thus, obesity can not explain the difference in severity seen in our study, but it may have increased the overall prevalence of SDB.

Smoking is considered to be one of the risk factors for SDB even after controling for other confounders (Wetter et al., 1994; Lindberg et al., 1998). In our study, previous or current smoking was more frequent in premenopausal (40.5%) than in postmenopausal women (23.6%), a fact which could inrease the possibility of SDB in pre- but not in postmenopausal women. Thus, in our study, smoking does not explain the greater severity of SDB in postmenopausal women, but it may have increased the prevalence of partial upper airway obstruction seen in premenopausal women. However, no differences were observed in spirometry values between postmenopausal and premenopausal women when lung volumes were expressed as percentages of predicted values.

Nasal obstruction is thought to be a risk for SDB and it has been most strongly linked with snoring regardless of AHI levels (Young et al., 2001; Liistro et al., 2003). Treatment of nasal congestion has reduced mouth breathing and the severity of SDB (Mclean et al., 2005). In our study, self-reported nasal congestion was a more common feature in premenopausal than in postmenopausal women, probably indicating the higher levels of estrogen (Haeggstrom et al., 2000).

Polycystic ovary syndrome is an endocrine disorder increasing the risk of SDB up to 30 times compared to women without PCOS (Vgontzas et al., 2001; Fogel et al., 2001). We found no differences between pre- and postmenopausal groups in history of PCOS, based on the results of the questionnaire.

3.2. Impact of menopause on symptoms of SDB

The frequencies of signs and symptoms of SDB did not differ between pre- and postmenopausal women, which is not surprising as all the women were referred to sleep studies because of suspicion of SDB. Nasal congestion was the only symptom that was significantly more prevalent in premenopausal than in postmenopausal women as stated in the previous section. In addition to possible estrogen influence, self-reported allergic rhinitis was common in both groups of women and may partly explain the nasal obstruction.

Increasing BMI explained EDS and snoring when adjusted for age, menopause, nightly desaturations, smoking and AHI_{est}. This is consistent with previous studies (Vgontzas et al., 1998). Contrary to our initial hypothesis, we found no menopausal impact on signs and symptoms of SDB in women. Neither the characteristics of the studied women (except age naturally) nor gynecological diseases showed any differences between the groups. Age is a powerful confounder. We tried to focus on this problem by analyzing separately the age group of 45-55 years with both pre- and postmenopausal women, and carried out the multivariate analyses of the different types of periodic breathing patterns, the signs and symptoms of SDB and concomitant diseases without adjusting for age (data not shown). This analysis did not alter our results and we did not find any interaction between age and menopausal state, either. Other factors including definition of menopause, BMI, neck circumference and referral bias that might have interacted with the menopausal impact on SDB have been discussed above.

3.3. Differences in co-morbidity

In the present study, the general co-morbidity burden of postmenopausal women was greater than in premenopausal women: they had cardiovascular diseases, diabetes, glaucoma and rheumatoid diseases more often than premenopausal women. This is not surprising considering that age and obesity are strong risk factors in the majority of the diseases addressed in our study. Increasing BMI and age logically explained many of the increased co-morbidity prevalences in the entire female study population. However, a high BMI does not explain the greater co-morbidity of postmenopausal women because premenopausal women were as obese as their postmenopausal counterparts. SDB per se did not associate with co-morbidities after controling for other confounders.

Our results show an increased prevalence of diabetes, hypothyroidism and psychosis in postmenopausal women with SDB, coronary heart disease in premenopausal women with SDB and hypertension, asthma and/or COPD in both compared to the general Finnish age-matched female population. These novel results increase our understanding since no previous studies have assessed the impact of menopause in women with SDB and its associations with co-morbidity. Although the study population of 601 women was originally large, the numbers of women suffering from SDB and a particular disease and belonging to either of the menopausal groups dropped to a rather small number (0-9). This was the case especially in the group of

premenopausal women and may have resulted in some statistical biases. This may be one explanation for the ten times higher prevalence of chronic coronary heart disease in premenopausal women (n=7) with SDB compared to the general Finnish premenopausal female population.

Asthma and/or COPD were associated with four- and seven-fold risks in post- and premenopausal women with SDB, respectively. This is consistent with our findings in the previous section concerning gender differences with the same model. In the same way, hypertension was found to have two- and four-fold risks, with premenopausal women with SDB having the latter. Although the prevalence of diabetes in the women of the male-female pairs was no different from that of the general population, postmenopausal women with SDB had double the risk of diabetes compared to the general postmenopausal women. Aging and obesity increase the probability DM type 2 (Elmasry et al., 2000; Lammi et al., 2007). In the multivariate analysis, increasing BMI but not age explained the prevalence of diabetes.

Interestingly, psychosis was twice as prevalent in our postmenopausal women as generally. From previous studies it is known that to some extent depression, psychosis and SDB are associated and that psychotic disorders are associated with metabolic abnormalities which are also common in patients with SDB (Saunamäki and Jehkonen, 2007; Suvisaari et al., 2007). These possible combined morbidities in the same postmenopausal women, might partly explain our finding.

SUMMARY AND CONCLUSIONS

SDB has been considered conventionally a “male” disease with episodes of apnea and hypopnea during sleep. Women with SDB have been missed or underdiagnosed because of their different symptom profile from men. The conventional polysomnogram with thermistors is not able to detect partial upper airway obstruction. Partial upper airway obstruction has been suggested to be a mild form of SDB and the patient has been left without treatment. There is quite a large and increasing body of data on co-morbidities of SDB, and even mild SDB has been linked with risk of co-morbidities and increased mortality. Therefore, the clinical relevance of partial upper airway obstruction is important. However, the data assessing partial upper airway obstruction are scarce. The aim of the present work was to inestigate the differences in presentation, symptoms and co-morbidity of SDB between the genders and between pre- and postmenopausal women. Additionally, the clinical relevance of partial upper airway obstruction compared to periodic obstructive breathing (sleep apnea) was assessed using static-charge-sensitive bed (SCSB) recordings.

The main conclusions were the following:

1) The signs and symptoms of SDB were similar between pre- and postmenopausal symptomatic women. The prevalence of SDB was high in both groups. SDB affected a greater proportion of nocturnal sleep time in postmenopausal than in premenopausal women, although the prevalence of SDB did not differ between these female groups referred for sleep studies due to suspicion of SDB. The results emphasize the importance of partial upper airway obstruction as a cause of symptoms in female SDB.

2) Partial upper airway obstruction and periodic obstructive breathing (sleep apnea) have distinct evolutions with increasing age or BMI in both men and women. In women, there is a consistently increasing susceptibility to partial upper airway obstruction after the age of 65 years over the whole BMI range, whereas in men, partial obstruction associates with the combination of high age and high BMI. These findings are likely to reflect gender differences in the ventilatory and upper airway control during sleep or in the arousal threshold, and further increase the concerns about using the AHI as the only marker of upper airway obstruction during sleep or as the index of its severity.

3) Partial upper airway obstruction is common in both sexes, but particularly in women. Differences in the types of breathing abnormalities probably reflect gender differences in the pathophysiology of upper airway control during sleep. The long-term adherence to nasal CPAP therapy was equally good in patients with predominance of partial upper airway obstruction or with conventional periodic obstruction during sleep. This implies that partial upper airway obstruction is not a mild form of SDB.

4) Concomitant diseases were common in both male and female clinical populations. The prevalence of asthma and /or COPD was seven-fold and the prevalence of

hypertension two-fold in both genders compared to the general age- and gender-matched population. Additionally, in men with SDB, diabetes and chronic arrhythmias were two- to three-fold more prevalent than in men generally. In women with SDB, hypothyroidism was three times more common than in women in general. The results emphasize the importance of the diagnosis and treatment of co-morbidities such as asthma, COPD, hypertension and hypothyroidism in both male and female patients with SDB.

5) The concomitant diseases were more common in postmenopausal than in premenpausal women. In both groups, the prevalence of hypertension was two to four times and the prevalence of asthma and/or COPD four to seven times more common than in age-matched Finnish women. In addition, postmenopausal women had a two-fold risk of diabetes, hypothyroidism and psychosis compared to age-matched postmenopausal women in general. The results futher strengthen the high co-morbidity burden associated with SDB.

6) Partial upper airway obstruction was associated with a higher prevalence of asthma and/or COPD in both genders, and a lower prevalence of hypertension in women when compared to obstructive sleep apnea. The study showed that partial upper airway obstruction was no less related to co-morbidities than periodic obstructive breathing, which is conventionally considered as a severe form of sleep apnea, and thus thought to be more often related to co-morbidities. An interesting finding was that partial upper airway obstruction was related to reduced prevalence of hypertension in women. The results emphasize the importance of the diagnosis and treatment of co-morbidities regardless of whether the patient has partial upper airway obstruction or frank sleep apnea.

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APPENDICES

Appendix 1. The subset of the Questionnaire used in the studies. The entire questionnaire included 107 items.

QUESTIONNAIRE

1. Marital status:

1. unmarried
2. married
3. cohabiting
4. divorced
5. widow

2. Do you work?

1. yes
2. no; 1) unemployed
   2) retired

3. Education:

1. elementary school
2. intermediate school
3. high school
4. vocational school
5. professional college
6. university graduate

4. Have you ever smoked daily? (more than 6 months)

1. yes
2. no

5. How many years have you smoked altogether?

(take into account periods of six months or longer, give your best estimate in years)

_____years

6. How much do you smoke now or did smoke before quitting during one day?

	How many/day?
Cigarettes	_____cigarettes
Pipe	_____pipes
Cigars	_____cigars

7. When did you smoke for the last time?

1. yesterday or today
2. two days – a month ago
3. more than one month – half a year ago
4. more than half a year – one year ago
5. more than one year ago; which year? 19___

8. The use of alcoholic beverages during the last six months:

1. none
2. 0-6 bottles of beer per week or the same amount of some other alcohol
3. 7-14 bottles of beer, 1-2 bottles of wine, ½-1 bottles of liquor or the same amount of some other alcohol per week
4. 15-24 bottles beer, 2-4 bottles of wine or 1-2 bottles of liquor per week

9. The average use of alcoholic beverages during your youth:

1. none
2. rarely
3. a few times per month
4. on weekends
5. almost daily or several times per week

10. Coffee consumption:

1. none
2. occasionally
3. less than 10 cups per day
4. more than 10 cups per day

11. Have you ever had a cough with wheezing or whistling?

1. no
2. yes, at what age? (one or more answers)
    1) before school age (under 7 years)
    2) school age (7-18 years)
    3) adult (over 18 years)

12. Have you ever had asthma?

1. no
2. yes; Has a doctor diagnosed your asthma?
    1) no
    2) yes, in 19_____(give your best estimate)

13. Have you had a long-lasting cough or increased bronchial mucus?

1. never
2. during the last 12 months
3. earlier than the last 12 months

14. Have you had recurrent or chronic nasal symptoms (sneezing, runny or stuffy nose) not related to a cold or "flu"?

1. no
2. yes

15. Have you ever had "hay fever" or other allergic nasal symptoms (sneezing, itchy, runny nose) e.g. from pollen or animals?

1. no
2. yes; Were you told by the doctor that you have hay fever or nasal allergy?
   1) no
   2) yes
   3) I cannot say

16. At what age have you had recurrent nasal symptoms or nasal allergy?

1. before school age (under 7 years)
2. school age (7-18 years)
3. adult (over 18 years)

17. Have you had recurrent chest infections?

1. no
2. I cannot say
3. yes; At what age? (one or more answers)
   1) before school age (under 7 years)
   2) school age (7-18 years)
   3) adult (over 18 years)

18. Have you ever had throat or laryngeal symptoms without tonsillitis, cold or other chest infection?

1. no
2. yes

19. At what age did you have throat or laryngeal symptoms described in question 18?
(one or more answers)

1. before school age (under 7 years)
2. school age (7-18 years)
3. adult (over 18 years)

20. Have you ever had irritation of the eyes (watering, itching, redness) also at times when you did not have a cold or "flu"?

1. no
2. yes

21. Have you ever had allergic eye symptoms (watering, itching, redness, swelling of eyelids etc.) e.g. from pollen or animals?

1. no
2. yes; Were you told by a doctor that you have an allergic eye condition?
    1) no
    2) yes
    3) I cannot say

22. Do your relatives (grandparents, parents, siblings) have nightly snoring, apneas during sleep or excessive daytime sleepiness?

1. no
2. yes, who does?_____

23. If your relatives have had symptoms of sleep apnea, have these been investigated?

1. no
2. yes

23. If your relatives have been investigated because of symptoms of sleep apnea, have they been diagnosed with sleep apnea?

1. no
2. yes

25. Have you had orthodontic treatment?

1. no
2. yes

26. Have you had any type of nasal surgery?

1. no
2. yes

27. Have you had tonsillectomy?

1. no
2. yes, at what age? _____years of age

28. What is your

1. length_____cm
2. weight_____kg

29. What was your weight at

1. 20 years of age_____ kg
2. 30 years of age _____kg
3. 40 years of age _____kg
4. 50 years of age _____kg
5. 60 years of age _____kg

30. **Mark the number if you suffer from:**

1. rheumatoid arthritis
2. fibromyalgia
3. other connective tissue disease
4. acromegaly
5. diabetes
6. hypothyroidism or hyperthyroidism

31. **Do you have other diseases and which ones?**

_____

32. **Medication in use:**

1. none
2. yes,
   Names of the drugs:_____

33. **Do you use complementary or alternative medication?**

1. no
2. yes

Names of the
medication:_____

33. **Have you been bothered by restless legs, pain or an unpleasant feeling when you are in bed?**

1. no
2. sometimes
3. always or almost regularly (5-7 nights per week)

35. **Do you wake up in the middle of the night because you have to move your legs because of pain or unpleasant feeling in your legs? Does this kind of feeling cause you insomnia?**

1. no
2. sometimes
3. always or almost regularly (5-7 nights per week)

36. **Do you have to walk during the night because of pain or unpleasant feeling in your legs?**

1. no
2. sometimes
3. every night or almost every night (5-7 nights per week)

Hormonal factors can also influence respiration.

37. **Have you been diagnosed with polycystic ovary syndrome (PCOS)?**

1. no
2. yes

38. **Have you had difficulties becoming pregnant?**

1. no
2. yes

39. **Have you had regular menstruation?**

1. no
2. yes

40. **Have you had hormonal therapy before menopause?**

1. no
2. yes

41. **Have you had hirsutism or severe acne after adolesence?**

1. no
2. yes

42. **Your age at the time of cessation of menses: _____**

43. **Have you used progestin hormone therapy?**

1. never
2. yes, name of the drug:

_____

44. **If you have used progestin therapy previously, when have you discontinued the therapy?**

Year_____

45. **Have you used estrogen hormone therapy?**

1. never
2. yes, name of the drug: _____

46. **How many months or years have you used estrogens during your life?**

_____months or
_____years

47. **If you have used estrogens previously, when have you discontinued the therapy?**

Year_____

48. **Have you used vaginal estrogen hormone therapy?**

1. never
2. yes, name of the drug:

_____

49. **If you have used vaginal estrogen therapy before, when have you discontinued the therapy?**

Year_____

50. **Have you suffered from menopausal symptoms during the last six months?**

1. no
2. seldom
3. often

51. **How long have you suffered from menopausal symptoms during lifetime?**

1. not at all
2. less than one month
3. longer than one month
4. between one to six months
5. longer than one year
6. longer than five years

52. **Did you get any therapy for the symptoms of menopause?**

1. no
2. yes

53. **How soon after the beginning of the symptoms of menopause did you seek treatment?**

1. never
2. within less than one month
3. between one and six months
4. after longer than one year
5. after longer than five years

54. **Have you had a hysterectomy?**

1. no
2. yes, year _____

55. **Have you had an ovariectomy?**

1. no
2. unilateral, year_____
3. bilateral, year_____

56. **The number of your pregnancies:**

1. births_____
2. miscarriages_____
3. abortions_____

EVERYBODY should answer the following questions but if you are using a nasal CPAP device at the moment, please answer the questions as you felt the situation was BEFORE the nasal CPAP treatment.

57. How often have you woken up from sleep during the last three months?

1. never or less than once per month
2. less than once per week
3. on 1-2 nights per week
4. on 3-5 nights per week
5. every night or almost every night

58. How well have you slept during the last three months?

1. very well
2. quite well
3. not well or badly
4. rather badly
5. badly

59. Have you used sleeping pills (by prescription) during the past three months in order to fall asleep or to avoid awakenings during the night?

1. never or less than once per month
2. less than once per week
3. on 1-2 evenings per week
4. on 3-5 evenings per week
5. every night or almost every night

The names of the drugs:_____

60. Do you feel tired in the mornings?

1. never or less than once per month
2. less than once per week
3. on 1-2 mornings per week
4. on 3-5 mornings per week
5. every morning or almost every morning

61. Do you feel tired during the daytime?

1. never or less than once per month
2. less than once per week
3. on 1-2 days per week
4. on 3-5 days per week
5. every day or almost every day

62. Have you suffered from a compulsive tendency to fall asleep at work during the last three months?

1. never or less than once per month
2. less than once per week
3. on 1-2 days per week
4. on 3-5 days per week
5. every day or almost every day

63. Have you suffered from a compulsive tendency to fall asleep during your leisure time during the last three months?

1. never or less than once per month
2. less than once per week
3. on 1-2 days per week
4. on 3-5 days per week
5. every day or almost every day

64. How often do you take naps?

1. never or less than once per month
2. less than once per week
3. on 1-2 days per week
4. on 3-5 days per week
5. every day or almost every day

65. If you take naps, how long do your naps usually last?

My naps last_____hours_____minutes

66. Do you snore? (ask your bed partner)

1. once per month or less
2. less than once per week
3. on 1-2 nights per week
4. on 3-5 nights per week
5. every night or almost every night

67. Have you had breathing pauses during your sleep (ask your bed partner)?

1. never or less than once per month
2. less than once per week
3. on 1-2 nights per week
4. on 3-5 nights per week
5. every night or almost every night

68. How many hours do you need to sleep per night (how many hours would you sleep if you could sleep as long as you wish)?

I need_____hours and _____minutes to sleep

69. Do you have morning headaches?

1. never or less than once per month
2. less than once per week
3. on 1-2 mornings per week
4. on 3-5 mornings per week
5. every morning or almost every morning

70. Do you have symptoms of reflux (e.g. burning in your chest or bad taste in your mouth)?

1. never or less than once per month
2. less than once per week
3. on 1-2 days per week
4. on 3-5 days per week
5. every day or almost every day

71. Have you noticed (or has somebody else noticed that you have) loss of memory?

1. no
2. yes