

Anna-Kaisa Juuti

SLEEP DISORDERS AND
ASSOCIATED FACTORS IN
56-73 YEAR-OLD URBAN
ADULTS IN NORTHERN
FINLAND

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ANNA-KAISA JUUTI

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ASSOCIATED FACTORS IN 56-73
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IN NORTHERN FINLAND**

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Abstract

The prevalence of self-reported obstructive sleep apnea syndrome (OSAS), habitual snoring (HS), daytime sleepiness (DS) and restless legs syndrome (RLS), and their associations with cardiovascular risk factors and depressive symptoms as well as the natural course and associated factors of habitual snoring and restless legs syndrome over a ten-year period were studied.

Two different birth cohorts in Northern Finland were investigated. In the Oulu 35 longitudinal research programme study subjects participated in two subsequent surveys conducted in 1996–1998 and 2007–2008 (61–63 and 72–73 years old subjects, respectively). The Oulu 45 study population was examined in 2001–2002 (56–57 years old subjects). The data were gathered by questionnaires, as well as laboratory and clinical measurements.

In the Oulu35 study, of the 831 baseline participants, 593 (73%) participated in the first follow-up in 1996–1998 and 457 (55%) participated in both follow-up studies. In the Oulu 45 study, the target population comprised 1 332 subjects, 995 (75%) of whom participated.

The prevalence of OSAS was 8% in the 56–57 year-old population, 4% in the 61–63 year old population, and 3% in the 72–73 year old population. These figures were 31%, 26% and 19% for HS, 16%, 9% and 11% for DS, and 18%, 21% and 15% for RLS, respectively. In a ten-year period, half of those who snored in 1996–1998 stopped snoring, and half of those who suffered from restless legs 3–7 nights/week in 1996–98 suffered from this syndrome less than once a week in 2007–2008. The 10-year incidence of new cases of both HS and RLS was 7%.

In subjects aged 56–57 and 61–63, the components of the metabolic syndrome and depressive symptoms associated with OSAS and HS, while in the follow-up study, the role of these associations diminished. Male gender was the strongest predictor of the new cases of HS, while depressive symptoms and waist circumference predicted the permanence or incidence of HS.

Depressive symptoms, DS and, weakly, waist circumference were associated with RLS in both the 56–57 year-old and in 61–63 year-old populations. Depressive symptoms were also predictive of the permanence and incidence of new RLS cases. Waist circumference also predicted new cases of RLS in the 72–73 year-old population.

Sleep disorders were quite common in 56–73 year-old subjects and their prevalence seemed to diminish as subjects aged. The components of metabolic syndrome associated with sleep disorders in middle-aged subjects, but these associations lost their significance in older age groups. Depressive symptoms predicted incidence of restless legs syndrome.

Keywords: cardiovascular risk factors, daytime sleepiness, depressive symptoms, habitual snoring, longitudinal study, obstructive sleep apnea, restless legs syndrome

Juuti, Anna-Kaisa, Unihäiriöt ja niihin yhteydessä olevat tekijät 56–73-vuotiaissa pohjoissuomalaisissa kaupunkiväestöissä.

Oulun yliopisto, Lääketieteellinen tiedekunta, Terveystieteiden laitos, PL 5000, 90014 Oulun yliopisto; Oulun yliopisto, Luonnontieteellinen tiedekunta, Matemaattisten tieteiden laitos, PL 3000, 90014 Oulun yliopisto; Oulun yliopistollinen sairaala, Yleislääketieteen yksikkö, PL 10, 90029 OY; Oulun kaupungin terveyskeskus, PL 8, 90015 Oulun kaupunki; Vaasan keskussairaala, 65130 Vaasa

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Tiivistelmä

Tutkimuksessa selvitettiin enenaikaisten hengityshäiriöiden, päiväaikaisen väsymyksen ja levottomien jalkojen esiintyvyyttä ja yhteyksiä sydän- ja verisuonitautien riskitekijöihin sekä depressioon. Jokaöisen kuorsaamisen ja levottomien jalkojen luonnollista kulkua ja siihen vaikuttavia tekijöitä selvitettiin 10 vuoden seuranta-aikana.

Tutkimusaineisto koostui kahdesta eri-ikäisestä pohjoissuomalaisesta väestöstä. Oulu35-seurantatutkimukset tehtiin vuosina 1996–1998 ja 2007–2008 (61–63- ja 72–73-vuotiaat tutkittavat). Oulu45-poikkileikkaustutkimus tehtiin vuosina 2001–2002 (56–57-vuotiaat tutkittavat). Aineisto kerättiin kyselylomakkeilla, laboratorio- ja kliinisillä tutkimuksilla.

Oulu35-tutkimuksessa 593 henkilöä (73 %) 831 kutsutusta osallistui ensimmäiseen seuranta-tutkimukseen v. 1996–1998 ja molempiin seurantatutkimuksiin osallistui 457 (55 %) henkilöä. Oulu45 -tutkimukseen osallistui 995 henkilöä (75 %) 1332 kutsutusta.

Obstruktiivisen uniapnean esiintyvyys 56–57-vuotiaalla väestöllä oli 8 %, 61–63-vuotiailla 4 % ja 72–73-vuotiailla 3 %. Jokaöisen kuorsaamisen esiintyvyys oli vastaavissa ikäluokissa 31 %, 26 % ja 19 %, päiväaikaisen väsymyksen 16 %, 9 % ja 11 % ja levottomien jalkojen 18 %, 21 % ja 15 %. Kymmenen vuoden seurannassa jokaöinen kuorsaaminen vähentyi puoleen niillä henkilöillä, jotka kuorsasivat v. 1996–1998. Vastaavasti 10 vuoden kuluttua niillä henkilöillä, joilla esiintyi levottomia jalkoja 3–7 yönä viikossa v. 1996–1998, esiintyvyys oli vähentynyt alle 1 kertaan viikossa puolella tutkituista. 10 vuoden ilmaantuvuus sekä jokaöiselle kuorsamiselle että levottomille jaloille oli 7 %.

Metabolisen oireyhtymän osatekijät ja depressiiviset oireet olivat yhteydessä obstruktiiviseen uniapneaan ja jokaöiseen kuorsaamiseen sekä 56–57-vuotiailla että 61–63-vuotiailla. Kymmenen vuoden seurannassa näiden tekijöiden vaikutus näytti kuitenkin vähentyvän. Miessukupuoli ennusti vahvimmin jokaöisen kuorsaamisen ilmaantuvuutta. Myös depressiiviset oireet ja vyötärönypäryys ennustivat jokaöisen kuorsaamisen ilmaantuvuutta ja pysyvyyttä.

Depressiiviset oireet, päiväaikainen väsymys ja vyötärönypäryys olivat yhteydessä levottomien jalkojen esiintyvyyteen sekä 56–57- että 61–63-vuotiaassa että väestössä. Depressiiviset oireet ennustivat myös levottomien jalkojen ilmaantuvuutta ja tilan pysyvyyttä ja vyötärönypäryys levottomien jalkojen ilmaantuvuutta 72–73-vuotiaana.

Unihäiriöt olivat varsin yleisiä 56–73-vuotiaissa väestöissä, ja niiden ilmaantuvuus näyttäisi vähentyvän iän mukana. Metabolisen oireyhtymän osatekijät olivat yhteydessä unihäiriöihin keski-ikäisillä, mutta vanhemmissa ikäluokissa näiden yhteyksien merkitys väheni. Depressiiviset ennustivat levottomat jalat -oireyhtymän ilmaantuvuutta.

Asiasanat: depressiiviset oireet, jokaöinen kuorsaaminen, levottomat jalat, obstruktiivinen uniapnea, päiväaikainen väsymys, seurantatutkimus, sydän- ja verisuonitautien riskitekijät

Kipu on harhaa
Kuolema on harhaa
Voima on totta
StarWars

To my beloved ones

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Abbreviations

AHI	Apnea-hypopnea index
BMI	Body mass index
BNSQ	Basic Nordic Sleep Questionnaire
CAD	Coronary artery disease
CI	Confidence interval
CVD	Cardiovascular disease
CRP	C-reactive protein
DS	Daytime sleepiness
EDS	Excessive daytime sleepiness
ESS	Epworth Sleepiness Scale
GABA	γ -aminobutyric acid
HS	Habitual snoring
hsCRP	High sensitivity c-reactive protein
IFG	Impaired fasting glucose
IGR	Impaired glucose regulation
IGT	Impaired glucose tolerance
IL-6	Interleukin 6
IRLSSG	International Restless Legs Syndrome Study Group
IRLS	International Restless Legs Syndrome Study Group Rating Scale
IRR	Increasing respiratory resistance
METS	Metabolic syndrome
MSLT	Multiple Sleep Latency Test
MWT	Maintenance of Wakefulness Test
nCPAP	nasal continuous positive airway pressure
NGT	Normal glucose tolerance
OGTT	Oral glucose tolerance test
OR	Odds ratio
OSA	Obstructive sleep apnea
OSAS	Obstructive sleep apnea syndrome
PLMS	Periodic leg movements in sleep
PLMW	Periodic leg movements while awake
PSG	Polysomnography
RDI	Respiratory disturbance index
REM-sleep	Rapid eye movement sleep
RERA	Respiratory effort-related arousal

RLS	Restless legs syndrome
SCSB	Static charge sensitive bed
SDB	Sleep disordered breathing
SHHS	Sleep Heart Health Study
SIT	Suggested immobilisation test
SSS	Stanford sleepiness scale
SWS	Slow wave sleep
T2D	Type 2 diabetes
TNF- α	Tumor necrosis factor α
UARS	Upper airway resistance syndrome
VLCD	Very low calorie diet
ZSDS	Zung self-reported depression scale

List of original articles

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

- I Renko A-K*, Hiltunen L, Laakso M, Rajala U & Keinänen-Kiukaanniemi S (2005) The relationship of glucose tolerance to sleep disorders and daytime sleepiness. *Diabetes Research and Clinical Practice* 67: 84–91.
- II Juuti A-K, Hiltunen L, Rajala U, Laakso M, Härkönen P, Hedberg P, Ruokonen A, Keinänen-Kiukaanniemi S & Läärä E (2008) Association of abnormal glucose tolerance with self-reported sleep apnea among a 57-year-old urban population in Northern Finland. *Diabetes Research and Clinical Practice* 80:477–482.
- III Juuti A-K, Läärä E, Rajala U, Laakso M, Härkönen P, Keinänen-Kiukaanniemi S & Hiltunen L (2010). Prevalence and associated factors of restless legs in a 57-year-old urban population in northern Finland. *Acta Neurologica Scandinavica* 122: 63–9.
- IV Juuti A-K, Hiltunen L, Rajala U, Laakso M, Härkönen P, Keinänen-Kiukaanniemi S & Läärä E (2011). Ten year natural course of habitual snoring and restless legs syndrome in a population aged 61–63 years at baseline. (Manuscript).

*Juuti neé Renko

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1 Introduction

Obstructive sleep apnea syndrome (OSAS), habitual snoring (HS), restless legs syndrome (RLS) and daytime sleepiness (DS) are all fairly common conditions especially in middle aged populations. In western populations, depending on population's age and definitions used in assessing these conditions, the prevalence of OSAS, HS, RLS and DS are estimated to be 1–10%, 10–50%, 5–24% and 9–26%, respectively (Tables 2, 3 and 4). The development of OSAS during ageing is yet unclear. Some studies have reported the prevalence to rise with ageing, but in e.g. a large cross-sectional population based study, Sleep Heart Health Study (SHHS), the prevalence of obstructive sleep apnea (OSA) seemed to level off after the age of 65 years (Young *et al.* 2002a and b). The prevalence of HS has been suggested to decrease after the age of 60 years (Cirignotta 1989, Honsberg *et al.* 1995, Lindberg *et al.* 1998). As regards RLS, the studies are contradictory in whether the prevalence of RLS decreases after middle age or not (Tison *et al.* 2005, Garcia-Borreguero *et al.* 2006, Broman *et al.* 2008).

DS and HS are both components of the OSAS, even though the association between HS alone with different conditions has also been studied. All of the above mentioned sleep disorders are significant public health problems and various associations with other major public health disorders, such as the components of metabolic syndrome or depression, have been suggested both in population based studies and in clinical studies. The underlying mechanisms and causal relations behind these associations are not yet fully understood. DS has been shown to lead to an increased risk of traffic accidents (Barbe *et al.* 1998, Horstmann *et al.* 2000, Teran-Santos *et al.* 1999, Young *et al.* 1997).

Despite the great amount of cross-sectional data on sleep disorders, only few longitudinal studies have been conducted on them worldwide as well as in the Finnish population. Some major problems in comparing the results of cross-sectional studies are a wide range of different definitions and tools in assessing sleep disturbances and daytime sleepiness. We studied two different birth cohorts living in the same area, and the first of which was followed-up during a 10-year period. This allowed us to investigate the natural course of sleep disorders and to compare the occurrence and associated factors between different aged populations. Because of the design of this work, we were not able to answer the questions about the mechanisms behind sleep disorders, but the data gathered provide information on the magnitude of these conditions. The results obtained

may also have some clinical implications and give some clues for the causes for further studies.

2 Review of the literature

2.1 Sleep -disordered breathing and daytime sleepiness

2.1.1 Definitions

Primary snoring

Primary snoring is defined by the International Classification of Sleep Disorders manual as “loud upper airway breathing sounds in sleep, without episodes of apnea or hypoventilation” (ICSD 1990). Snoring is a subjective impression of the listener, which should be taken into consideration when investigating snoring (Hoffstein 2005). The degree of snoring may be defined in different ways, e.g. ICSD uses the categories of mild, moderate or severe (ICSD 1990). Habitual snoring (HS) has often been defined as the subject snoring every or almost every night in e.g. the Basic Nordic Sleep Questionnaire (BNSQ) (Partinen & Gislason 1995).

Partial upper airway obstruction

There are several different definitions for partial upper airway obstruction, depending mostly on the methods used to measure this phenomenon. Increasing respiratory resistance (IRR) is a phenomenon in which there are 1–30 min episodes of nonperiodic obstructions, with slowly increasing intrathoracic pressure variations (Polo *et al.* 1992). Oxygen desaturation and termination by movement arousal are often involved (Polo 1992). IRR is diagnosed with a static charge sensitive bed (SCSB), which is a non-invasive method to measure breathing, heartbeat and body movements. Respiratory effort-related arousal (RERA) is a sequence of breaths during which there is increasing respiratory effort leading to an arousal from sleep. The events last at least 10 seconds (Iber *et al.* 2007). Nasal inspiratory airflow is usually measured via nasal prongs connected to a pressure transducer. Flow limitation can be observed as an altered inspiratory air flow shape during partial upper airway obstruction (Aittokallio *et al.* 2001).

Upper airway resistance syndrome (UARS) is a condition in which the subject often, but not always, is a snorer and has daytime symptoms such as

sleepiness (Guilleminault *et al.* 1993). In polysomnography, however, the apnea-hypopnea index (AHI) is less than 10 and there is sleep fragmentation (arousal index > 10) present (Hoffstein 2005). Currently, UARS has usually been thought to be a continuum from non-apneic, asymptomatic snorers to obstructive sleep apnea syndrome (OSAS). However, this has been contested: some researchers consider it to be an independent syndrome (Guilleminault & Chowdhuri 2000, Jonczak *et al.* 2009).

Obstructive sleep apnea syndrome

American Academy of Sleep Medicine (AASM) characterizes obstructive sleep apnea (OSA) as recurrent episodes of partial or complete upper airway obstructions during sleep, during which there are attempted but ineffective breathing efforts (The Report of an American Academy of Sleep Medicine Task Force 1999). This includes reduction (hypopnea) or complete cessation (apnea) of airflow for ≥ 10 seconds despite inspiratory efforts and leads to oxygen desaturations (> 3%) and arousals. When daytime symptoms, such as daytime sleepiness, are involved, the state is called obstructive sleep apnea syndrome (OSAS). The respiratory disturbance index (RDI) is the sum of RERA, apnea and hypopnea events per hour.

Daytime sleepiness

The term excessive daytime sleepiness (EDS) is defined as an inability to remain awake or alert in situations where it is required (Ohayon 2008). EDS is always a symptom of a sleep disorder or other disease. There are many different scales and measures for assessing EDS; in this study the term daytime sleepiness (DS) is used to describe them all.

2.1.2 Measures and diagnostic criteria

Habitual Snoring

Different techniques have been used for the measurement and quantifying of snoring, based on the mechanism, loudness, intensity and sites of obstruction in the upper airways (Dalmasso & Prota 1996). However, there is no reference

standard for this, which is why questionnaires are currently recommended for characterizing snoring (Hoffstein 2005). Several different questionnaires have been used.

Obstructive sleep apnea syndrome

The reference standard for the measurement of obstructive sleep apnea is an overnight polysomnography including respiratory monitoring, pulse oximetry, electrocardiogram (ECG) and sleep staging with electroencephalogram (EEG), electromyography (EMG) as well as electrooculography (EOG) for which several techniques and data collection settings (home vs. laboratory) are used. Cardiorespiratory polygraphy is a widely used method, where EEG is not measured. It can be conducted either at home or in a laboratory. The diagnostic criteria for OSAS are listed below. (A person must fulfill either criterion A or B as well as criterion C) (The Report of an American Academy of Sleep Medicine Task Force 1999).

- A) Excessive daytime sleepiness that is not better explained by other factors
- B) Two or more of the following that are not better explained by other factors:
 - choking or gasping during sleep
 - recurrent awakenings from sleep
 - unrefreshing sleep
 - daytime fatigue
 - impaired concentration
- C) Overnight monitoring of 5 or more obstructive breathing events per hour during sleep. These events may include any combination of obstructive apneas/hypopneas or respiratory effort-related arousals.

The severity of OSAS is defined by the severity of daytime sleepiness, AHI and oxygen desaturation. The most severe component of these indicates the severity of OSAS.

For screening purposes of OSAS in the general population, different questionnaires have been used, one of the most well-known being the Berlin questionnaire (Netzer *et al.* 1999). Quite promising results have been reported on its use: in a study by Netzer *et al.* involving 744 primary care patients, the screening with the Berlin questionnaire had a sensitivity of 0.86 and a specificity of 0.77 for respiratory disturbance index (RDI) > 5 (Netzer *et al.* 1999).

Daytime sleepiness

DS can be measured with different self-rating scales, but objective measures have also been used (Littner *et al.* 2005). For the self-rating scales, no reference standard has been defined, and several questionnaires exist for assessing daytime sleepiness.

The reference standard for objective measurement of daytime sleepiness is considered to be the Multiple Sleep Latency Test (MSLT). In MSLT the rapidity of sleep onset is measured over a 20-minute period every 2 hours, 4 or 5 times during the day. The subject lies in bed in a darkened room and is asked to try to go to sleep. Severe daytime sleepiness is defined as an average sleep latency of five minutes or less. The Maintenance of Wakefulness Test (MWT) is another objective measure for daytime sleepiness, the major difference compared to MSLT being that the subject is advised to attempt to stay awake (The Report of an American Academy of Sleep Medicine Task Force 1999). The MSLT is mainly used for diagnosing patients with suspected narcolepsy or idiopathic hypersomnia and MWT for assessing the response to the treatments of these two conditions (Littner *et al.* 2005).

The Stanford Sleepiness Scale (SSS) is one of the best-known self-rating scales. It measures perceived sleepiness on a scale of 1–7, from full alertness to near sleep onset (The Report of an American Academy of Sleep Medicine Task Force 1999). SSS measures the actual state of sleepiness at the time when questionnaire is administered.

The Epworth Sleepiness Scale (ESS) is a widely used questionnaire. It contains eight items on "dozing off" or falling asleep in different situations, which are seen in table 1. The ratings are from 0 (would never doze) to 3 (high chance of dozing) and maximum score is 24 (Johns 1991). ESS reflects the state of sleepiness preceding the administration of the questionnaire. The normal range of ESS was initially placed at 2–10, but as more data have been gathered, there have been suggestions regarding lowering the cut-off point to profound sleepiness to 9 points. In the Sleep Heart Health Study (SHHS), where 1824 subjects were examined, those with RDI 15–30 had mean ESS of 8.3 (Gottlieb *et al.* 1999). On the other hand, ESS has been criticized for lack of validity data and lack of test-retest data in OSA patients (Chervin 2003, Miletin & Hanly 2003). However, so far, ESS is considered one of the best tools available for assessing subjective daytime sleepiness.

Table 1. The Epworth Sleepiness Scale.

No	Situation
1.	Sitting and reading
2.	Watching TV
3.	Sitting, inactive in a public place (e.g. a theatre or a meeting)
4.	As a passenger in a car for an hour without a break
5.	Lying down to rest in the afternoon when circumstances permit
6.	Sitting and talking to someone
7.	Sitting quietly after a lunch without alcohol
8.	In a car, while stopped for a few minutes in the traffic

2.1.3 Etiology and pathophysiology

The upper airways constitute a complex system, in which several muscles and soft tissues are involved. Unlike in other parts of the airways, no cartilage support exists, which allows e.g. vocalization and swallowing and, on the other hand, makes the upper airways collapsible. In inspiration, the muscles of the upper airways, e.g. the genioglossus muscle of the tongue, contract and keep the airway open to effective airflow. The mechanisms behind that are reflex activation to subatmospheric pressure and chemoreceptor stimulation due to hypoxia and hypercapnia (Horner 2008).

In sleep, particularly in rapid eye movement (REM) sleep, the pharyngeal muscle tone decreases, narrowing airways and increasing the resistance to airflow. The neural mechanisms affecting to the muscle tone of the upper airways have been studied mainly in animal models. The role of serotonin and noradrenalin containing neurons as exciting the motoneurons innervating the pharyngeal muscles during daytime and this effect being reduced in REM sleep may affect to airway collapsibility. Furthermore, inhibitory neurotransmitters glycine and γ -aminobutyric acid (GABA) seem to inhibit muscle activity in REM sleep. Glycine and GABA are also inhibitory neurotransmitters in the brain; for example, the neuronal inhibition of benzodiazepines and ethanol acts via interactions with binding sites on GABA_A receptors. As GABA_A receptors are also present in the pharyngeal area, benzodiazepines and ethanol may produce sleep disordered breathing in some individuals (Horner 2008).

The mechanical properties and pharyngeal muscle tone of the upper airways are crucial in sleep disordered breathing, such as habitual snoring and OSAS. Several anatomical factors influence to the size of the upper airways, such as

supine position in sleep, fat deposits around the pharynx, macroglossia, retrognathia, micrognathia, nasal polyps, deviated septa, and hypertrophy of tonsils or adenoids. The decrease of lung volume also decreases the size of the airways. In OSAS patients, compared to control subjects, narrower airspaces behind the tongue and the soft palate have been reported (Horner 2008). Additionally, snoring subjects have been reported to have anatomical and functional abnormalities in upper airways, and as a result flow limitation occurs during sleep (Dalmasso & Prota 1996, Hoffstein *et al.* 1988). Furthermore, when upper airways get narrower, they also become more collapsible.

Snoring is usually an inspiratory sound caused by turbulent airflow, which vibrates the soft structures (e.g. soft palate, uvula and pharyngeal walls) in the upper airways during sleep. In UARS, the subject breathes against a partially closed upper airway, and this may lead to hypopneas or to repeated arousals from sleep due to high subatmospheric inspiratory pressures. In obstructive sleep apnea (OSAS) the pharyngeal airspace collapses, airflow stops (apneas) and this leads to hypoxia and hypercapnia, which usually in turn leads to arousal from sleep. After the obstruction, snoring is usually very loud. Apneas usually last for 25–50 seconds (Horner 2008).

Even though snoring occurs in every sleep stage, it may be more common in sleep stage 2 as well as in slow wave sleep (SWS) (Hoffstein 2005). In the preliminary study by Hoffstein *et al.*, heavy snoring seemed to be presented mostly in the SWS and in REM sleep (Hoffstein *et al.* 1991). In REM sleep, apneas and hypopneas are longer and the oxygen saturation is lower (Horner 2008).

As a consequence of chronic intermittent hypoxia and carbon-dioxide retention, activation of both the sympathetic and parasympathetic nervous systems are present in OSA, which leads to rise in blood pressure and variations in heart rate. This also leads to insufficient inspiratory efforts and the formation of negative intrathoracic pressure against the collapsed upper airways (Bradley & Floras 2009). The cycles of hypoxia and carbon-dioxide retention may also cause oxidative stress, activation of inflammatory pathways, and endothelial dysfunction (Ip *et al.* 2004b, Nieto *et al.* 2004, Ryan *et al.* 2005, Ryan *et al.* 2009).

2.1.4 Occurrence

The prevalence of OSAS and HS according to some population-based studies is presented in Table 2. Both OSAS and HS are reported to be common in middle-aged men (Bixler *et al.* 1998, Young *et al.* 1993). The role of ageing in the prevalence of OSAS is not yet resolved. In many studies OSAS has been found to be highly prevalent after the age of 65 years, but there seems to be a plateau in the prevalence of OSAS at some age point after that (Ancoli-Israel *et al.* 1991). On the other hand, the prevalence of HS has been suggested to increase up to the age of 60 years and to decrease thereafter (Cirignotta 1989, Honsberg *et al.* 1995, Lindberg *et al.* 1998). Ethnic differences in the prevalence of SDB have been very scantily investigated so far (Young *et al.* 2002a).

Table 2. Prevalence of obstructive sleep apnea syndrome (OSAS) and habitual snoring according to adult population studies.

Author(s), year	Area	Age	Study population	Method	Prevalence (%)	
					OSAS	Habitual Snoring
Cirignotta 1989	Italy	30–69	1170 men	Postal questionnaire, tel interview. PSG for 40 patients: AHI > 10 HS: Snoring always	3	10
Stradling & Crosby 1991	UK	35–65	893 men	Ambulatory oximetry at home, ODI4 > 5 Questionnaire, HS: Snoring often	5	17
Young <i>et al.</i> 1993	Wisconsin, USA	30–60	602	Overnight polysomnography: EDS + AHI \geq 5 Questionnaire, HS: snoring, snoring, or breathing pauses every or almost every night or extremely loud snoring	women 2 men 4	women 28 men 44
Bearpark <i>et al.</i> 1995	Australia	40–65	294 men	Ambulatory home sleep recording: EDS + RDI \geq 5	\geq 3	22
Marin <i>et al.</i> 1997	Spain	> 18	1222	HS: Snoring > 50% of the night Nocturnal home oximetry: HS + EDS+ > 10 desaturations/h	women 1 men 2	women 36 men 63
Ohayon <i>et al.</i> 1997	UK	35–64	4972	Interview, Severe snoring: usually or always Tel Interview	women 2 men 4	women 34 men 48
Bixler <i>et al.</i> 1998	Southern Pennsylvania, USA	20–100	4364 men: 741 PSG	In-laboratory PSG: AHI > 10 plus the presence of daytime symptoms	all 3 20–44 y: 1 45–64 y: 5 65–100 y: 2	-
Zielinski <i>et al.</i> 1999	Poland	38–67	1199	Questionnaire, HS: "Often" or "Always"	-	women 27 men 48

Author(s), year	Area	Age	Study population	Method	Prevalence (%)	
					OSAS	Habitual Snoring
Bixler <i>et al.</i> 2001	Southern Pennsylvania, USA	20–100	12 219: 1741 population PSG	In-laboratory PSG: AHI > 10 plus the presence of daytime symptoms	women 1 men 3	-
Duran <i>et al.</i> 2001	Spain	30–70	2148	MESAM IV sleep recording at home: AHI Interview, HS: snoring > 5 times/week	women AHI ≥ 5 28 AHI ≥ 15 7 men	all 35 women 25 men 46
Ip <i>et al.</i> 2001	China	30–60	784 men: 153 PSG	Full PSG in sleep laboratory: AHI ≥ 5 + EDS Questionnaire, HS: snoring ≥ 3 days /week	4	23
Ip <i>et al.</i> 2004a	China	30–60	839 women; 106 PSG	Full PSG in sleep laboratory: AHI ≥ 5 + EDS Questionnaire, HS: snoring ≥ 3 days /week	all 2 30–39 y: 0.5 40–49 y: 1 50–60 y: 6	15
Franklin <i>et al.</i> 2004	Denmark, Estonia, Iceland, Norway, Sweden	25–54	15 555	Postal Questionnaire, HS: loud and disturbing snoring ≥ 3 times per week	-	18
Kim <i>et al.</i> 2004	Korea	40–69	5020: 472 PSG	Interview, 137 home PSG, 335 sleep laboratory PSG: AHI ≥ 5 + EDS, HS definition not told	women 3 men 5	women 13 men 22
Udwadia <i>et al.</i> 2004	India	35–65	658 men: 250 PSG	Home Interview, limited home PSG: AHI ≥ 5 + EDS, HS: snoring > 5 days/week.	8	26
Bouscoulet <i>et al.</i> 2008	Latin America	≥40	4533; 188 polygraphy	Interview, simplified respiratory polygraphy at home: ESS ≥ 11 + RDI ≥ 15/h, HS: snoring all or most nights	10	60

Only few population-based studies are reported about the incidence and natural course of SDB. The incidence of snoring has been studied with varying questionnaires and in wide age ranges, why the comparison of the results is challenging (Honsberg *et al.* 1995, Knuiman *et al.* 2006, Lindberg *et al.* 1998). The incidence of HS in adult populations in 5–14 years has been estimated to be 10–13% (Honsberg *et al.* 1995, Knuiman *et al.* 2006), and it seems that the decrease in the incidence of HS is greatest in age groups over 60 (Honsberg *et al.* 1995, Lindberg *et al.* 1998,). Male gender and obesity or weight gain have been found to predict the incidence of HS (Honsberg *et al.* 1995, Lindberg *et al.* 1998, Knuiman *et al.* 2006). In large population-based longitudinal studies AHI has been suggested to change in time as weight changes: the more weight gain, the higher AHI (Peppard *et al.* 2000, Newman *et al.* 2005). In the Cleveland Family Study, the subjects with normal AHI were studied and the 5-year incidence of moderately severe SDB was found to be 7.5%; the male predominance and the effect of BMI decreased as age increased (Tishler *et al.* 2003).

The prevalence of daytime sleepiness has been estimated either by using the frequency of symptoms or the severity of the symptoms, and the definition of DS varies greatly between different studies. In Table 3, some selected population-based studies of the prevalence of DS are shown. The role of gender in the prevalence of daytime sleepiness is not clear: in some of the studies, there is no gender difference, while in some the occurrence is higher in the women (Bixler *et al.* 2005, Hublin *et al.* 1996, Janson *et al.* 1995, Joo *et al.* 2009, Liu *et al.* 2000, Martikainen *et al.* 1992, Ohayon *et al.* 2002, Ohayon & Vecchierini 2002, Souza *et al.* 2002). The prevalence of DS seems to decrease as age increases (Hublin *et al.* 1996, Liu *et al.* 2000, Souza *et al.* 2002, Joo *et al.* 2009).

Table 3. The prevalence of daytime sleepiness according to population-based studies. Some of the studies classified daytime sleepiness according to the severity of the symptoms and some according to the frequency of the symptoms.

Author(s), year	Area	Age	Study population	Method	Prevalence (%)
Martikainen <i>et al.</i> 1992	Finland	30–65	1190	Frequency	10
Janson <i>et al.</i> 1995	Iceland, Sweden, Belgium	20–45	2202	Frequency	21
Hublin <i>et al.</i> 1996	Finland	33–60	11354	Frequency	9
Zielinski <i>et al.</i> 1999	Poland	38–67	1186	Frequency Severity	26 22
Liu <i>et al.</i> 2000	Japan	≥ 20	3030	Frequency	15
Nugent <i>et al.</i> 2001	Northern Ireland	18–91	3391 men	Severity	20
Ohayon <i>et al.</i> 2002	Germany, Italy, UK, Spain, Portugal	≥ 15	18980	Frequency Severity	15 9
Ohayon & Vecchierini 2002	France	60–101	1026	Severity	14
Souza <i>et al.</i> 2002	Brazil	≥ 18	408	Severity	19
Bixler <i>et al.</i> 2005	USA	20–100	16583	Severity	9
Hiestand <i>et al.</i> 2006	USA	≥ 18	1506	Frequency	26
Joo <i>et al.</i> 2009	Korea	40–69	4405	Severity	12

2.1.5 Factors associated with sleep –disordered breathing

Overweight and obesity

The association between obesity and sleep disorders has been reported in many cross-sectional population-based studies. The definition of obesity varies greatly from different BMI categories to waist circumference and their combinations (Young *et al.* 2002b). High prevalence of obesity has been reported in OSAS patients and high prevalence of SDB (even 50–77%) in obese patients (Young *et al.* 2005). In large longitudinal studies in general populations, weight gain, as well

as weight loss have been reported to effect RDI/AHI (Newman *et al.* 2005, Peppard *et al.* 2000). In a study of 690 subjects, with 8 years' follow-up, 10% weight gain predicted 32% increase in AHI and 10% weight loss predicted 26% decrease in AHI (Peppard *et al.* 2000). The improvement of symptoms and PSG findings during weight loss in obese OSAS patients has also been reported in several small clinical studies (Hakala *et al.* 2000, Kajaste *et al.* 2004, Kansanen *et al.* 1998, Lojander *et al.* 1998). Recently, in a randomized, controlled study on the effects of weight loss in subjects with mild OSAS was conducted. In this study 83 obese patients were treated either with a very low calorie diet (VLCD), supervised lifestyle counselling, or routine lifestyle counselling and followed for one year. In the VLCD group, AHI improved and weight decreased more compared to the control group (Tuomilehto *et al.* 2009, Vgontzas *et al.* 2000).

The location of adipose tissue has been considered to affect the risk of SDB. In the Sleep Heart Health Study (SHHS), BMI, neck circumference and visceral fat were all independently associated with SDB (Newman *et al.* 2005, Vgontzas *et al.* 2000). Excess fat in the neck area may narrow the airways and worsen the upper airway resistance, and abdominal fat raises intra-abdominal pressure, thus lowering functional residual capacity (Leinum *et al.* 2009). The most predictive body habitus for SDB has not yet been identified.

The possible mechanisms between adiposity and SDB has been a target of interest in current research, as adipose tissue is a complex endocrine organ and adipocytes are considered to be a major factor in metabolic and inflammatory regulation. Subjects with SDB have been reported to have elevated leptin levels perhaps as a compensatory mechanism to reduce insulin resistance or indicating leptin resistance. The plasma ghrelin levels are also elevated in patients with SDB suggesting increased caloric intake and weight gain. Nasal continuous positive airway pressure (nCPAP) therapy has been demonstrated to reduce these changes (Leinum *et al.* 2009). Adipose tissue produces inflammatory markers, such as interleukin-6 (IL-6), c-reactive protein (CRP), and tumor necrosis factor- α (TNF α) (Alam *et al.* 2007). These factors have been suggested to associate independently with OSA apart from obesity in many small case-control studies (Alam *et al.* 2007, Ryan *et al.* 2005, Shamsuzzaman *et al.* 2002, Vgontzas *et al.* 2000). There are also several studies in which this association was not seen (Alam *et al.* 2007, Barcelo *et al.* 2004, Taheri *et al.* 2007). In the cross-sectional Wisconsin Sleep Cohort Study, where 907 subjects with SDB were studied, association between SDB and elevated CRP was not found independently from

obesity (Taheri *et al.* 2007). So far it seems that both SDB and obesity are pro-inflammatory conditions.

Cardiovascular diseases

The prevalence of SDB has been reported to be higher in subjects with cardiovascular conditions, such as hypertension, heart failure, ischemic heart disease and stroke, than in the general population (Bradley & Floras 2009).

The cross-sectional independent association between SDB and hypertension has been reported in several population-based studies (Lavie *et al.* 2000, Nieto *et al.* 2000). It has been recommended that SDB should be ruled out as a secondary cause of hypertension (Chobanian *et al.* 2003). It has been estimated that even 50% of OSAS patients are hypertensive and that 30% of hypertensive patients have OSAS (Somers *et al.* 2008). In SHHS, such an association between non-apneic snoring and hypertension was not found (Nieto *et al.* 2000). Growing evidence has also been discovered about the causal relationship between SDB and hypertension (Okcay *et al.* 2008). In a prospective study of 709 subjects, the relative odds ratio (OR) for developing hypertension in 4–8 years in subjects with AHI > 15 vs. 0 was 2.89 (95% CI 1.46–5.64) (Peppard *et al.* 2000). nCPAP treatment has been suggested to reduce the blood pressure at least in hypertensive patients in relatively small case-control studies, but in some studies this effect was not observed (Campos-Rodriguez *et al.* 2006, Dempsey *et al.* 2010, Heitmann *et al.* 2004, Martinez-Garcia *et al.* 2007). In a 24 months' prospective study, where 55 OSAS patients with hypertension were treated with nCPAP, the decrease of blood pressure was associated with the highest blood pressure entry and good compliance to treatment (Campos-Rodriguez *et al.* 2007). The differences in these results may well be due to poor compliance to nCPAP treatment, normotensive patients and small patient samples.

In patients with coronary artery disease (CAD), SDB is two times more common than in subjects without CAD (Somers *et al.* 2008). A cross-sectional association between SDB and CAD has also been reported in large population-based study, even though this association was weak (Shahar *et al.* 2001). OSA patients have also been reported to have more subclinical CAD and family history of premature death from CAD compared to subjects without OSAS (Gami *et al.* 2007, Sorajja *et al.* 2008). In prospective studies, SDB has been reported to be associated with increased mortality, as well as with incidence of myocardial infarction and cerebrovascular events (Marin *et al.* 2005, Moee *et al.* 2001). In a

7-year prospective study of 308 snorers, subjects with OSAS had 4.6 times greater risk of CAD compared to snorers without OSAS. The treatment of OSAS reduced this risk (Peker *et al.* 2006). The treatment of OSAS has also been suggested to diminish the occurrence of new cardiovascular events (Milleron *et al.* 2004).

The prevalence of OSAS has been suggested to be as high as 38% in patients with heart failure (Somers *et al.* 2008). Atrial fibrillation has also been shown to associate with OSAS in subjects under 65 years of age, but prospective evidence is lacking (Bradley & Floras 2009). OSAS has also been reported to independently increase the risk of stroke (Yaggi *et al.* 2005).

In summary, SDB is most likely to increase CVD morbidity, the pathogenesis being most likely multifactorial including increased sympathetic activity, activation of inflammatory pathways, endothelial dysfunction, abnormal blood coagulation and metabolic dysregulation (Nieto *et al.* 2004, Ryan *et al.* 2009, Dempsey *et al.* 2010).

Impaired glucose metabolism

A cross-sectional association between different stages of glucose intolerance and SDB has been reported many times before, and this association has been suggested to be, at least partially, independent of adiposity (Marshall *et al.* 2009, Punjabi *et al.* 2004, Seicean *et al.* 2008, Shin *et al.* 2005, Tuomilehto *et al.* 2008, West *et al.* 2006). It has been estimated that up to 40% of patients with SDB have diabetes and 23% of type 2 diabetics have SDB (Elmasry *et al.* 2001, West *et al.* 2006). In a recent Finnish study of 905 sleep-clinic patients, men with SDB had three times greater prevalence of reimbursed medication for diabetes compared to men without SDB (Anttalainen *et al.* 2010).

Some population based and clinical longitudinal studies also indicate that SDB is a risk factor for developing type 2 diabetes (T2D). However, the interpretation of the results is complex due to many methodological problems such as insufficient sample size, short follow-up time or lack of PSG in defining SDB (Al-Delaimy *et al.* 2002, Botros *et al.* 2009, Elmasry *et al.* 2000, Reichmuth *et al.* 2005). So far the suspected causality has not been fully resolved.

Insulin resistance and hyperinsulinemia have also been suggested to be associated with SDB in several population- and clinical-based cross-sectional studies (Ip *et al.* 2002, Punjabi 2009, Punjabi *et al.* 2004, Punjabi *et al.* 2002, Tiihonen *et al.* 1993). Some case-control studies suggest similar associations, too

(Coughlin *et al.* 2004, Punjabi & Beamer 2009). Coughlin *et al.* studied 61 OSAS patients and 43 controls and found that OSAS was independently associated with higher fasting insulin levels. There was also a trend in higher homeostasis model assessment of insulin resistance (HOMA-IR) (Coughlin *et al.* 2004). In a recent study of newly diagnosed and untreated SDB patients and normal controls, SDB was independently associated with impaired insulin sensitivity, glucose effectiveness and pancreatic β -cell function (Punjabi & Beamer 2009).

The effect of nCPAP treatment on glucose tolerance or insulin resistance has been studied in many though quite small populations, with the follow-up time varying from 2 months to 3 years. The results are still far from conclusive (Punjabi 2009).

The possible mechanisms between SDB and impaired glucose metabolism are shown in Figure 1.

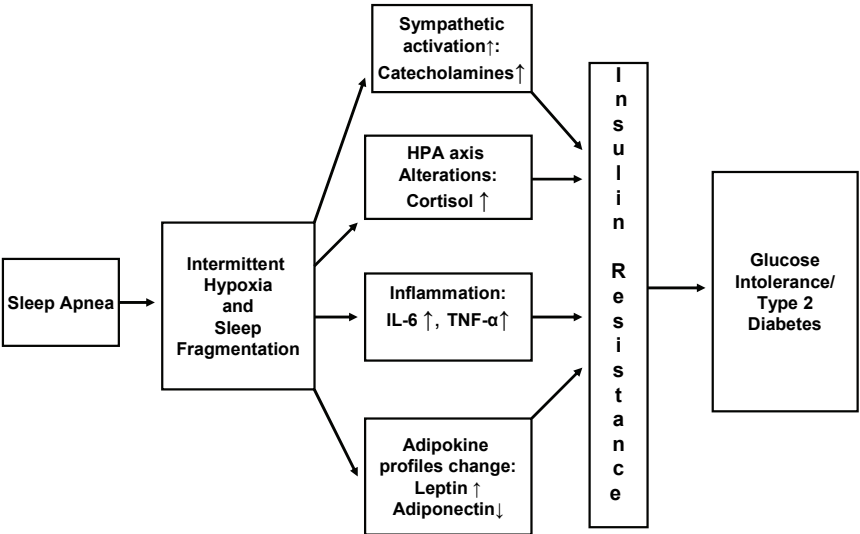


Fig. 1. Potential mechanisms linking sleep apnea to glucose intolerance.

OSA leads to intermittent hypoxia and sleep fragmentation. Hypoxia itself has direct effects on the reduction in insulin sensitivity and it also activates hypothalamic-pituitary-adrenal (HPA) and excessive elevation of cortisol levels, which may lead to reduction in insulin sensitivity and insulin secretion (Shaw *et al.* 2008). The sympathetic nervous system has an important role in the glucose

regulation and fat metabolism. Sleep fragmentation and hypoxia increase sympathetic activation and thus raise the levels of catecholamines, leading to increasing glycogen breakdown and gluconeogenesis (Punjabi & Polotsky 2005). Sympathetic activation may also play a role in higher levels of inflammatory markers in OSA patients. Whether the role of adipokines in the pathophysiology of OSA and impaired glucose is independent of obesity, is not yet fully understood (Shaw *et al.* 2008).

In the SHHS, periodic breathing was found to be more common in subjects with diabetes than in non-diabetics. This could at least partly explain the high prevalence of SDB in diabetes, mediated through autonomic neuropathy, which may alter ventilatory control mechanisms (Resnick *et al.* 2003). The role of autonomic neuropathy in the control of breathing in sleep needs further clarification.

Gender

As mentioned earlier, in many cross-sectional studies SDB has been reported to be more common in men than in women, at least in middle-aged subjects (Table 1). The reason for this has been suggested to involve the activity of the upper airway dilator muscles or the anatomy of oropharynx (Schwab 1999). The anatomy of the upper airways has been studied in different ways, e.g. with MRI. No difference has been found in the anatomy of the oropharynx or in the upper airway fat distribution between men and women, but men seem to have more total neck soft tissue than women (Schwab 1999). Women have been reported to have augmented genioglossal muscle activation in wakefulness, and progesterone has been suspected to have an impact on this (Schwab 1999).

The prevalence of SDB seems to increase in women in the menopausal age (Bixler *et al.* 2001, Duran *et al.* 2001, Kapsimalis & Kryger 2009, Young *et al.* 2003). In a cross-sectional population-based study of 1741 subjects, the prevalence of OSAS increased from 0.6% in premenopause to 1.9% in postmenopause (Bixler *et al.* 2001).

Depression and quality of life

The association between depression and SDB has been investigated in many cross-sectional studies based on clinical and population-based samples (Saunamäki & Jehkonen 2007). In a large cross-sectional population based study

from the Veterans Health Administration database, where over 4 million patient records were examined, the prevalence of depression was high: 22% in OSA patients compared to the non-OSA population, when age, sex and ethnicity were considered as confounding factors and the diagnosis was based on the International Classification of Diseases-Ninth Edition-Clinical Modification (Sharafkhaneh *et al.* 2005). The same phenomenon was also observed in a cross-sectional population-based telephone survey of 18 980 subjects; 18% of those with a DSM-IV breathing-related sleep disorder diagnosis had also been diagnosed with a major depressive disorder. This association remained after adjusting for obesity and hypertension (Ohayon 2003). The quality of the studies on the effect of nCPAP treatment on depressive symptoms in OSA varies greatly. Moreover, in many of these studies the length of the follow-up is quite short, and they often lack a control-group for the treatment (Saunamäki & Jehkonen 2007). So far, the effect of nCPAP on depressive symptoms is far from conclusive.

In spite of persuasive evidence, the independent association of depression with SDB has not yet been conclusively proven and the link between them remains unsolved. It seems that the symptoms of SDB, such as daytime sleepiness, and comorbidities (e.g. obesity, hypertension), could explain their association at least partly (Bardwell *et al.* 1999, Bixler *et al.* 2005, Pillar & Lavie 1998).

In cross-sectional population-based studies the quality of life has been suggested to be inferior in patients with SDB, especially for those with coincident DS (Baldwin *et al.* 2001, Reimer & Flemons 2003). In a 5-year follow-up of SDB in the SHHS, a small increase in RDI was not associated with the worsening of quality of life, which however was associated with DS (Silva *et al.* 2009). The studies on improvement of quality of life during the treatment of OSAS have given varying results; this may be because of small study populations, the wide range of tests used for assessing quality of life, and most importantly, because the quality of life is a subjective assessment in which many areas of life are affected (Reimer & Flemons 2003).

Smoking

A higher prevalence of snoring among smokers and even passive smokers than in non-smokers has been reported in many population based studies (Bloom *et al.* 1988, Franklin *et al.* 2004, Lindberg *et al.* 1997). In a population-based follow-up study of 811 subjects in the USA, smokers were in a higher risk of SDB than

those who had never smoked (Wetter *et al.* 1994). In a population in which the smoking histories of 108 American OSAS patients were compared with those of 106 subjects without OSAS, the prevalence of smoking was nearly two times greater in OSAS patients than in subjects without OSAS (Kashyap *et al.* 2001). Thus, it seems that based on these previous data, smoking is related in SDB. The mechanisms behind these associations still need to be investigated more thoroughly, even though the role of irritation, swelling and inflammatory changes in the upper airways has been suspected (Franklin *et al.* 2004).

Consequences of sleep disordered breathing

Daytime sleepiness is an important symptom of OSAS. Sleepiness is a major risk factor in traffic accidents. The role of OSAS in traffic accidents has been studied in population-based and clinical populations. In a cross-sectional, retrospective population-based study by Young *et al.* the subjects with AHI > 5 had more traffic accidents in the past 5 years than subjects with AHI < 5. They found no association between sleepiness and the risk of traffic accidents (Young *et al.* 1997). It has been shown, that subjective fatigue and cognitive performance are not associated (Van Dongen *et al.* 2011). This association between OSAS and traffic accidents has also been shown in three case-control studies (Barbe *et al.* 1998, Teran-Santos *et al.* 1999, Horstmann *et al.* 2000). Excessive daytime sleepiness caused by OSAS also affects on the ability to work in occupations where absolute vigilance is needed (Hartenbaum *et al.* 2006).

Mortality

In population-based follow-up studies, as well as in clinical studies, the all-cause mortality has been suggested to be greater in subjects with SDB compared to those without SDB, even though cardiovascular deaths are also overrepresented in patients with SDB (Lavie *et al.* 2005, Marin *et al.* 2005, Marshall *et al.* 2008, Marti *et al.* 2002, Young *et al.* 2008). Mortality has been shown to increase as the severity of SDB increases, and the treatment of OSAS seems to decrease it (He *et al.* 1988, Marti *et al.* 2002, Young *et al.* 2008). In men aged < 50 years OSA is associated with early death (He *et al.* 1988, Lavie *et al.* 2005, Marti *et al.* 2002).

2.1.6 Treatment

In obese patients, weight loss, either dietary or surgical, has been reported to decrease AHI and improve daytime sleepiness in the subjects with OSAS (Peppard *et al.* 2000, Shaw *et al.* 2008, Tuomilehto *et al.* 2009). Alcohol and sedatives may worsen the symptoms of OSAS, whereupon avoidance of these may be beneficial (Shaw *et al.* 2008). Exercise has been suggested to improve the symptoms of OSAS independently of body habitus (Giebelhaus *et al.* 2000, Peppard & Young 2004).

Continuous positive airway pressure (CPAP), delivered via a nasal or full-face mask or nasal plugs, forms a pneumatic splint in the upper airways (Sullivan *et al.* 1981). CPAP is used during sleep to prevent an upper airway collapse. It is the best treatment available in moderate or severe OSAS (Shaw *et al.* 2008).

Different oral appliances are used to increase the dimensions of the upper airways, which may be beneficial in mild OSAS (Shaw *et al.* 2008).

Surgical treatment may be effective in the case of large tonsils, adenoids or nasal polyps, and sometimes certain orthodontic or maxillofacial procedures are needed (Shaw *et al.* 2008).

Some preliminary data suggest modanafil to improve daytime sleepiness in OSAS patients (Dinges & Weaver 2003, Kingshott *et al.* 2001).

2.2 Restless legs syndrome

2.2.1 Definition

Restless legs syndrome (RLS) was described for the first time in 1672, but it was not until 1945 when Ekbom named it "restless legs" and defined its clinical features (Ekbom 1945). The main features in RLS are an urge to move the limbs associated with paresthesia/dysesthesia. The symptoms are relieved by activity and they begin or are worst at rest (lying, sitting). Typically, the symptoms worsen in the evening or during the night (Allen *et al.* 2003). RLS can be an idiopathic disorder or a symptomatic syndrome often associated with iron deficiency, pregnancy or end-stage renal disease (Trenkwalder *et al.* 2005). RLS is thought to be a chronic progressive disorder, which needs lifelong treatment (Trenkwalder *et al.* 2005).

2.2.2 Measures and diagnostic criteria

The diagnosis of RLS is based on a clinical interview (Allen *et al.* 2003). The International RLS study group (IRLSSG) defined four clinical characteristics for the diagnosis of RLS in 1995. The criteria were updated at the National Institutes of Health (NIH) RLS workshop in 2002 (Allen *et al.* 2003). These criteria are:

- a) An urge to move the legs, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs
- b) The urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity such as lying or sitting
- c) The urge to move or unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues
- d) The urge to move or unpleasant sensations are worse in the evening or night than during the day or only occur in the evening or the night

There are also supportive criteria, which are not essential to the diagnosis, but may help to arrive at the diagnosis. These include positive family history of RLS, periodic limb movements (during wakefulness or sleep) and positive response to treatment. Associated features also exist, including a certain type of natural clinical course, sleep disturbance and possible disorders found in clinical examination (e.g. iron deficiency) (Allen *et al.* 2003).

Periodic limb movements in sleep (PLMS) are classically described as rhythmic extension of the big toe and dorsiflexion of the ankle, with occasional flexion at the knee and hip. PLMS is measured in a sleep laboratory; the recording and scoring were originally developed by Coleman (Coleman 1982, Montplaisir *et al.* 2005). According to these criteria, the number of PLMS per hour of sleep greater than 5 for the entire night is considered abnormal. Periodic limb movement during sleep or wakefulness has been reported to occur in at least 80% of RLS patients (Allen *et al.* 2003). However, it also occurs often in many other sleep disorders, such as narcolepsy (Montplaisir *et al.* 2000). The suggested immobilisation test (SIT) has been used to measure the connection between RLS and periodic limb movement while awake (PLMW) (Michaud *et al.* 2002). SIT is a 60-minute physiological test, where the subjects remain in bed, reclined at a 45° angle with their legs outstretched. They are instructed to avoid moving voluntarily. Surface EMGs from the right and left anterior tibialis muscles are used to quantify leg movements. In addition, leg discomfort is analysed by a

visual analog scale every 5 min during the test. According to this study, RLS patients often have PLMW. Overall, an elevated PLMS index and the presence of PLMW are supportive to the diagnosis of RLS (Allen *et al.* 2003).

The severity of RLS has been measured with different scales based on the frequency, time of onset and duration of symptoms. The most recent of them is the International Restless Legs Syndrome Study Group Rating Scale (IRLS), which is a 10-point scale and has been compared with independent clinical ratings and with objective parameters, such as the PLMS-index and the SIT-PLMW (Garcia-Borreguero *et al.* 2004, Walters *et al.* 2003). The other well-known scale to assess the severity of RLS is the Johns Hopkins restless legs severity scale (JHRLSS), which is based on the usual onset time of the symptoms. The assumption is that the onset time of the symptoms indicates the length of time that the subject suffers from RLS symptoms per day. This scale has also been shown to correlate well with both PLMS and sleep efficiency (Allen & Earley 2001).

2.2.3 Etiology and pathophysiology

Genetics

The familial component of RLS was described by Ekbom already in 1945. There are many studies concerning the familial forms of the disorder. At least 50% of the RLS subjects have a positive family history (Ekbom & Ulfberg 2009). RLS has also been reported to start earlier with each generation (Ekbom & Ulfberg 2009). In the early-onset form of RLS, an autosomal dominant inheritance model has been suggested (Winkelmann *et al.* 2002). Molecular genetic studies have found several susceptibility gene loci. These loci are on chromosome 12q, 14q, 9p, 2q, 20p, 16p (Ekbom & Ulfberg 2009, Ferini-Strambi *et al.* 2004, Winkelmann *et al.* 2007). RLS is probably a disorder with complex inheritance and genetic heterogeneity.

Neural structures

The localization of neural structures involving the pathophysiology of RLS has been discussed. Some evidence exists about the peripheral origin of RLS (Montplaisir *et al.* 2005).

Patients with a spinal cord injury have been observed to have PLMW and PLMS (Montplaisir *et al.* 2005). Some evidence also exists on the hyperexcitability of motoneurons in primary RLS patients (Bara-Jimenez *et al.* 2000).

The origin of RLS has also been suggested to be in subcortical areas, since functional MRI has shown that leg-related sensory complaints in RLS are associated with thalamic and cerebellar activation (Montplaisir *et al.* 2005). There is also some evidence for the symptoms of RLS being related to cortical sensorimotor dysfunction (Tyvaert *et al.* 2009).

Based on the existing literature, it seems that both the central nervous system and peripheral nervous system are involved in the pathophysiology of RLS.

Neurotransmitter Dysfunctions

Central dopamine has also been one target in the investigation of the pathophysiology of RLS. The possible explanations for RLS have been suggested to be decreased D2 receptor binding, increased intracellular dopamine, and binding for the dopamine transporter in central nervous system (Montplaisir *et al.* 2000, Ruottinen *et al.* 2000, Wetter *et al.* 2004). Dopamine is also an important neurotransmitter in the spinal cord level (Bara-Jimenez *et al.* 2000).

An endogenous opiate system dysfunction has also been suggested as a cause of RLS. This hypothesis has been supported by the fact that opiate receptor blocker naloxone worsens the symptoms of RLS. However, no evidence of the opiate system dysfunction in RLS exists, apart from some pharmacological data (Montplaisir *et al.* 2005).

Iron deficiency

Secondary RLS is present in states which involve iron deficiency, such as end stage renal disease, iron-deficiency anemia, pregnancy, and gastric surgery. That is why the iron levels in blood and cerebrospinal fluid (CSF) have also been addressed in RLS studies. The relation between low ferritin concentrations and symptoms of the RLS has been demonstrated (Earley *et al.* 2004, Kryger *et al.* 2002). Some studies also suggest that in idiopathic RLS, the low brain iron concentration is caused by the dysfunction of iron transportation from serum to the central nervous system (Mizuno *et al.* 2005a). Iron plays an important role in the functioning of postsynaptic D2 receptors and is an important cofactor for tyrosine

hydroxylase, which is the step-limiting enzyme in dopamine synthesis (Allen 2004).

RLS symptoms are known to worsen among as many as one third of women during menstruation. The prevalence of RLS is high during pregnancy, and it has been also suggested that RLS is more common in female blood donors, who are also more iron deficient than women without RLS (Garcia-Borreguero *et al.* 2006, Ulfberg & Nystrom 2004).

2.2.4 Occurrence

RLS is a fairly common but often underdiagnosed state (Table 4). In a large study, conducted in a primary care setting in the UK during 1994–1998, based on the medical records of 1 561 692 persons, the prevalence of clinically diagnosed RLS was only 0.25% (Van, V *et al.* 2004)

Ekbom estimated in 1945 the prevalence of RLS to be 5%. In more recent studies, the prevalence of RLS has ranged from approximately 5% to 15% in Caucasian populations (Table 1) (Hening *et al.* 2004, Zucconi & Ferini-Strambi 2004). In Asian populations, the prevalence of RLS seems to be lower; 1.5% in Japanese population aged 20–80 and 1% in Japanese population aged > 65 (Kageyama *et al.* 2000, Mizuno *et al.* 2005b).

RLS has been suggested in many epidemiological studies to be more common in women (approximately 11–14% in Western populations) than in men (Bjorvatn *et al.* 2005, Phillips *et al.* 2006, Rothdach *et al.* 2000, Ulfberg *et al.* 2001b, Wenning *et al.* 2005).

The occurrence of RLS in adult populations seems to be lowest in the age group 18–29 years, approximately 5% (Bjorvatn *et al.* 2005, Phillips *et al.* 2000). According to cross-sectional population-based studies, the prevalence of RLS seems to increase up to age group 50–60 years (Berger *et al.* 2004, Broman *et al.* 2008, Nichols *et al.* 2003, Phillips *et al.* 2000). A decrease of prevalence between ages 60–79 has also been reported in some population-based studies (Phillips *et al.* 2000, Nichols *et al.* 2003, Tison *et al.* 2005). In some studies, no change in the prevalence of RLS has been observed after the age of 50 years (Bjorvatn *et al.* 2005, Hogl *et al.* 2005).

Table 4. Prevalence of restless legs syndrome (RLS) according to population studies.

Author(s), year	Area	Age	Study population	Method	Prevalence (%)
Ekbom 1945	Sweden	Retired Militaires	503	Interview	5*
Kageyama <i>et al.</i> 2000	Japan	> 20	4612	Questionnaire	1.5 *
Phillips <i>et al.</i> 2000	Kentucky (USA)	> 18	1803	Tel. Interview	10 women men 10
Rothdach <i>et al.</i> 2000	Germany	65–83	369	Interview	All 10 women 14 men 6
Ulfberg <i>et al.</i> 2001	Sweden	18–64	4000 men	Postal questionnaire	men 6
Ohayon & Roth 2002	Europe (UK, Spain, Germany, Italy)	15–100	18 980	Tel Interview	All 6 women 7 men 4
Nichols <i>et al.</i> 2003	USA	18–93	2099	Self-administered Questionnaire	All 24 women 28 men 20
Berger <i>et al.</i> 2004	Germany	20–79	4310	Interview	All 11 women 13 men 8
Hening <i>et al.</i> 2004	USA, UK, France, Germany, Spain	mean 51.4, SD 17.6	23052	Questionnaire	11*
Rijsman <i>et al.</i> 2004	Netherlands	≥ 50	1683	Postal Questionnaire	All 7 women 8 men 6
Sevim <i>et al.</i> 2004	Turkey	18–79	3234	Face-to-face interview	All 3 women 4 men 3
Allen <i>et al.</i> 2005	Europe and USA	≥ 18	15 391	Interview	All 3 women 4 men 2
Bjornvatn <i>et al.</i> 2005	Norway and Denmark	18–99	2005	Tel Interview	All 12 women 13 men 9
Hogl <i>et al.</i> 2005	Italy	50–89	701	Interview	All 11 women 14 men 7

Author(s), year	Area	Age	Study population	Method	Prevalence (%)
Kim <i>et al.</i> 2005	Korea	40–69	9939	Interview	All 12 women 15 men 9
Mizuno <i>et al.</i> 2005	Japan	> 65	8900	Postal Questionnaire + Interview	All 1 women 1.5 men 0.5
Tison <i>et al.</i> 2005	France	≥ 18	10263	Face-to-face Interview	All 9 women 10 men 5
Wenning <i>et al.</i> 2005	Italy	50–89	706	Interview	All 11 women 14 men 7
Phillips <i>et al.</i> 2006	USA	mean age 49	1506	Tel Interview	All 10 women 11 men 8
Winkelman <i>et al.</i> 2006	USA	30–60	2821	Postal Questionnaire	All 11 women 11 men 10
Ulfberg <i>et al.</i> 2007	Sweden	18–90	1000	Tel Interview	All 5 women 6 men 4
Broman <i>et al.</i> 2008	Sweden	20–59	1962	Postal Questionnaire	All 19 women 22 men 15
Winkelman <i>et al.</i> 2008	USA	44–98	5307	self-administered questionnaire	All 5 women 7 men 3

*The proportions were not given by gender

2.2.5 Factors associated with restless legs syndrome

Female gender

As mentioned earlier, RLS is observed to be more prevalent in women than in men in many population based cross-sectional studies (Table 4). The increased prevalence of RLS during pregnancy, even as high as 19%, suggests an association between RLS and sex hormones. The symptoms seem to be worst in the third semester, when estrogens, progesterone and prolactin levels are at their

highest (Manconi *et al.* 2004b). In a population of 642 Italian pregnant women, RLS was related to the third semester of pregnancy, and the symptoms often disappeared after the delivery (Manconi *et al.* 2004a, Manconi *et al.* 2004b). In cross-sectional studies, parity has been suggested to be an independent risk factor for RLS (Berger *et al.* 2004). The causes and mechanisms behind this gender difference in RLS are not yet fully understood. In addition to sex hormones, iron status changes due to reproductive cycle, patterns of inheritance, co-morbidities with RLS, and women's different experience of the symptoms have been suggested as possible explanations.

The connection between sex hormones and RLS has been investigated from both a pre- and postmenopausal point of view. In a recent Swedish study, 5000 women aged 18–64 years were studied, and no relationship between RLS and use of hormone replacement therapy or postmenopausal state was found, while there was an association between RLS and vasomotor symptoms (night sweats) during the menopausal transition (Wesstrom *et al.* 2008). In a French study, Ghorayeb *et al.* studied 536 female RLS patients and found no association between hormonal changes and RLS (Ghorayeb *et al.* 2008). Thus, iron deficiency may well be a likely cause of female overrepresentation in RLS.

Depression

An association between RLS and depression has been found in many cross-sectional population based studies (Phillips *et al.* 2006, Sevim *et al.* 2004, Ulfberg *et al.* 2007, Ulfberg *et al.* 2001a, Winkelmann *et al.* 2006). In most of them, the diagnosis of RLS and depression has been made by either telephone interview (Phillips *et al.* 2006, Ulfberg *et al.* 2007) or postal questionnaire (Ulfberg *et al.* 2001a, Winkelmann *et al.* 2006). Only in the study of Sevim *et al.* face-to-face interviews were used, which may have significantly reduced the proportion of false diagnoses (Sevim *et al.* 2004). A connection between RLS and depression has also been found in case-control studies (Banno *et al.* 2000, Krishnan *et al.* 2003, Winkelmann *et al.* 2005). Winkelmann *et al.* (2005) compared 130 middle-aged RLS patients with 2265 healthy controls and found that RLS patients suffered from anxiety- and depressive disorders more often than the healthy controls. However, the number of RLS patients was rather small. A similar result was also found in the work of Banno *et al.* comparing RLS patients to healthy controls (2000). In subjects with Parkinson's disease, Krishnan *et al.* (2003) found

that the subjects who also had RLS suffered from depressive symptoms more often than those Parkinson's disease patients who did not have RLS.

The mechanism of the connection between RLS and depression still remains unclear, but poor sleep quality and fractional sleep may well be factors that at least worsen depressive symptoms. In fact, in one small, cross-sectional study in which geriatric RLS patients were studied, the subjects generally complained of poor sleep quality, but not depressive symptoms at all. The writers assume that this could be due to the fact that people aged over 65 are often retired and may freely take naps in the daytime. They also assumed that another reason for the result may have been the questionnaire used to assess depressive symptoms; it was not specially designed for the elderly. This report was, however, small and cross-sectional, so no definite conclusions can be made (Cuellar *et al.* 2007). The role of the dopaminergic system in depression has also been investigated. The deficiency of dopamine transmission and decrease in D2/D3 receptor binding are suggested to be possible mechanisms in some forms of depression (Dailly *et al.* 2004).

The use of antidepressants, especially selective serotonin reuptake inhibitors (SSRI) and tricyclic antidepressants, has also been studied in relation to causing or worsening RLS symptoms. In epidemiological studies where a possible association between these two has been found, the results have been controversial (Ohayon & Roth 2002). In a case-control study, RLS patients used more medications overall than controls. The same tendency was observed in the use of antidepressants (Pearson *et al.* 2008). In a retrospective study of sleep clinic patients suffering from insomnia, no conclusive evidence of any associations between RLS and antidepressants could be observed (Brown *et al.* 2005). The greater use of antidepressants may well have been due to a greater proportion of depression in RLS patients. However, the question whether antidepressants worsen RLS symptoms is more complex, and no simple answers to this arise from the literature. Hornyak *et al.* concluded that if patients are treated properly for RLS before starting antidepressive medication, the negative influence of the antidepressants to RLS is not observed (Hornyak *et al.* 2006).

Obesity

The association between RLS and obesity, especially central adiposity, has been discovered only recently. In a large study of over 100 000 subjects, abdominal and overall adiposity were observed to increase the likelihood of RLS (Gao *et al.*

2009). The role of the dopaminergic system in the association between obesity and RLS has also been discussed. In a small case control study the availability of dopamine D2 receptor was found to be decreased in obese subjects, and the number of dopamine receptors was inversely correlated with BMI (Wang *et al.* 2001). As dopamine is a factor that modulates motivation and reward circuits, overeating may be a way to compensate for the decreased activation of these circuits. The mechanism between obesity and RLS is, however, likely multifactorial: cardiovascular diseases are associated with both obesity and RLS, and there may also be vascular pathology involved in RLS (Winkelman *et al.* 2008).

Daytime sleepiness and sleep disturbances

It is well-known that subjects suffering from RLS are often sleepy during daytime. This has come up in many epidemiological studies (Bjorvatn *et al.* 2005, Kim *et al.* 2005, Rijsman *et al.* 2004, Winkelman *et al.* 2006). It has been estimated that 20–25% of untreated, idiopathic RLS patients are at an increased risk for daytime sleepiness (Fulda & Wetter 2007).

Cardiovascular risk factors

The association between RLS and cardiovascular disease has only quite recently become a target of interest in clinical studies. In epidemiological studies, this association has been noticed earlier (Ulfberg *et al.* 2001a, Ohayon *et al.* 2002, Winkelman *et al.* 2006), but it was the Sleep Heart Health Study (SHHS) that focused on this question (Winkelman *et al.* 2008). In SHHS, RLS was associated with CVD and CAD. The association was stronger in subjects older than 65 years. After adjustment for CVD risk factors the relation was not diminished. (Winkelman *et al.* 2008).

The mechanisms behind this relationship still remain unclear, but increases in heart rate and blood pressure during periodic leg movements in sleep have been suspected to be one reason (Gosselin *et al.* 2003, Siddiqui *et al.* 2007). Even though the association between hypertension and RLS has not been observed in all previous studies, it might have become more evident if blood pressure was measured in a 24-hour period instead of one measurement (Winkelman *et al.* 2008). Another reason for the connection of RLS and cardiovascular disease may be loss of sleep; short sleep duration has been shown to be associated with

modestly increased risk of coronary events in the Nurses' Health Study (Ayas *et al.* 2003). Some medication used for the treatment of RLS may also expose to CVD; in one cohort study ergot-derived dopamine agonists pergolide and cabergoline associated with increased risk of newly diagnosed valvular heart disease (Schade *et al.* 2007). RLS and CVD may also share some mutual background factors which may explain their connection, even though in the Sleep Heart Health Study the relationship was found to be independent (Winkelman *et al.* 2008).

Impaired glucose metabolism

As different stages of glucose intolerance are associated with sleep disorders, the association between RLS and T2D has roused interest (Shaw *et al.* 2008). In population-based studies, the connection between RLS and T2D remains unclear (Kim *et al.* 2005, Winkelman *et al.* 2008). These different results may be due to several factors: diabetes may be assessed either according to self-reporting or based on OGTT, the diabetes types may vary, the ages of populations are different. The studies also differ in design: some are telephone interviews, some clinical interviews.

The possible association between RLS and diabetes may be approached from two points of views: from patients with diabetes and from those with RLS. In studies conducted in diabetes clinic studies, the prevalence of RLS in T2D patients has been found to be much higher than in non-diabetic subjects: 18–33% (Gemignani *et al.* 2007, Lopes *et al.* 2005, Merlino *et al.* 2007, Skomro *et al.* 2001). The simplest answer would be diabetic neuropathy, as RLS and peripheral neuropathy have been shown to be independently associated in diabetic patients (Lopes *et al.* 2005, Merlino *et al.* 2007). Gemignani *et al.* (2007) studied 99 patients with polyneuropathy or mononeuropathy multiplex caused by diabetes, IGT or IFG. They found that RLS was associated mostly with small fibre sensory neuropathy and symptoms of burning feet. They concluded that RLS is a relevant feature and likely to be linked with small fibre involvement in diabetic neuropathy. The limitations of this study were the small sample and retrospective design, so no causal conclusions can be made. In another investigation, 124 type 2 diabetics and 87 controls were studied, and the presence of polyneuropathy was found to be an independent risk factor for RLS in diabetics. In this study, 27% of the RLS patients had polyneuropathy (Merlino *et al.* 2007). Cuellar and Ratcliffe wanted to investigate the impact of RLS on diabetics' glycemic control,

sleepiness, sleep problems and depression in a small, descriptive, comparative, case-control study. They found that RLS affected sleep quality, sleepiness and depression in type 2 diabetic patients, but not glycemic control (Cuellar & Ratcliffe 2008).

From the RLS point of view, there are few case-control studies on the association between RLS and diabetes. In a study by Banno *et al.* (2000), no association between diabetes and RLS could be found. However, in their study, the diabetes diagnosis was taken from patient records, and the milder forms of glucose intolerance or new diagnoses of diabetes were not detected due to OGTT's not being used.

The relationship of diabetes and RLS is not yet resolved. It seems that diabetic neuropathy partially explains the association between RLS and diabetes, but not all of it. In fact, based on the current literature, we do not even know which comes first, RLS or diabetes. The increased sympathetic activation caused by fragmented sleep and sleep deprivation could cause insulin resistance and, consequently, type 2 diabetes. Longitudinal studies could clarify this association further.

2.2.6 Treatment

RLS has traditionally been mainly treated by drugs. Nowadays, nonpharmacological treatments have also attracted interest. The aim of the treatment is to decrease discomfort and to enhance quality of life (Trenkwalder *et al.* 2008).

Only few studies exist on the nonpharmacological treatments of RLS. In one small study the effects of exercise were investigated. The result was promising, suggesting that exercise would alleviate the symptoms of RLS. However, the first nonpharmacological treatment to take into consideration is good sleep hygiene, which should be taken care of before medication (Oertel *et al.* 2007).

The secondary causes of RLS as well as associated disorders should, of course, be treated when possible; e.g. if a patient has a low level of ferritin, oral iron treatment is indicated (Montplaisir *et al.* 2005).

A dopaminergic agent levodopa has been shown to produce a significant reduction of RLS symptoms (Trenkwalder *et al.* 2008). However, adverse effects are numerous. The most difficult adverse effects in RLS patients are morning rebound and RLS augmentation (Montplaisir *et al.* 2005). Nonergot-derived dopaminergic agonists, such as pramipexole and ropinirole, are now

recommended as the first-line treatment of RLS, because they are more effective and they produce less adverse effects than levodopa (Trenkwalder *et al.* 2008). Ergot-derived dopamine agonists, such as bromocriptine, pergolide, cabergoline may be effective treatments, but they are not recommended as the first choice, since the risks of cardiac valvular fibrosis and other fibrotic side effects are increased (Trenkwalder *et al.* 2008).

Opioids are very efficient in treating RLS, but the possibility of misuse and addictive effects significantly limits their use. Therefore, their use is recommended to be restricted only to severe cases, especially those unresponsive to other treatments (Trenkwalder *et al.* 2008).

Anticonvulsants, gabapentin being the most studied one, have been shown to improve RLS symptoms, and the adverse effects are also rare. Gabapentin is not as effective as dopaminergic agents, but may be useful in mild cases of RLS or in patients who have experienced adverse effects with dopaminergic medications. Carbamazepine, topiramate, and valproic acid have also been investigated in the treatment of RLS, and they are likely to be efficacious, but side effects should be taken into consideration (Trenkwalder *et al.* 2008).

Benzodiazepines, such as clonazepam, have been shown to improve sleep continuity in RLS patients, but the effects on RLS symptoms are modest. Daytime somnolence is also a major side effect, which can even worsen the RLS symptoms (Trenkwalder *et al.* 2008).

Clonidine is also likely to be efficacious in the treatment of RLS, the most common side effects being daytime somnolence, headaches, orthostatic hypotension and even mental changes (Trenkwalder *et al.* 2008).

Magnesium and folic acid may as well be used in the treatment of RLS, but there are no well-designed randomized, controlled trials of them (Trenkwalder *et al.* 2008).

3 The aims of the study

The broad aims of this study were to estimate the occurrence of sleep-disordered breathing, daytime sleepiness and RLS, as well as their associations with cardiovascular risk factors and depressive symptoms in the urban population in Northern Finland.

More specifically, the aims of the study were:

1. To produce valid and comparable information about the occurrence of snoring, self-reported sleep apnea, daytime sleepiness and RLS in populations aged 56–57, 61–63 and 72–73 years (I-IV).
2. To find out the natural course of habitual snoring and RLS in 61–73 year-old subjects. (IV)
3. To find out if there are associations between glucose tolerance, insulin sensitivity as well as other cardiovascular risk factors with sleep disorders and RLS in our study populations (I-IV)
4. To resolve possible associations between depressive symptoms and sleep disorders and RLS in cross-sectional and longitudinal study populations (I-IV)

Additionally, some unpublished data are presented.

4 Subjects and methods

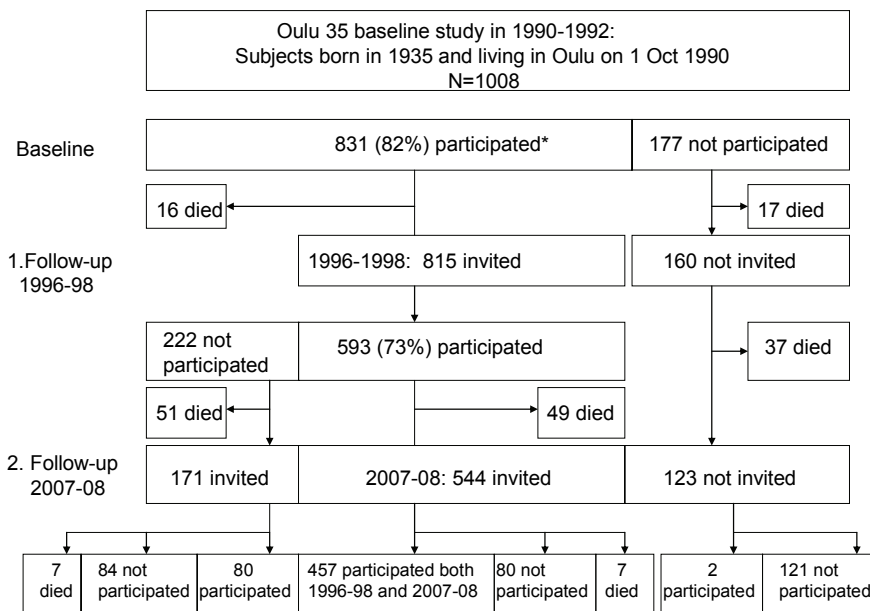
The present work was based on material from two separate studies. The Oulu 35 longitudinal research programme (Oulu35) was initially started in 1990, and follow-up studies in this population were conducted in 1996–1998 and in 2007–2008 when the subjects were 61–63 and 72–73 years, respectively (Figure 2). The Oulu 45 cross-sectional study population (Oulu45) was examined in 2001–2002 (56–57 years old subjects).

4.1 Subjects and design

The prevalence of sleep apnea, habitual snoring, restless legs syndrome and excessive daytime sleepiness and their possible associations with cardiovascular risk factors and depression were examined in both of the study populations. Additionally, the natural course of habitual snoring and RLS and their risk factors were examined among the subjects participating in the Oulu35 longitudinal study.

4.1.1 Oulu 35 longitudinal study

A population-based longitudinal research programme was initiated in 1990 covering all persons born in 1935 and living in the city of Oulu in Northern Finland. So far, three phases of the study have been conducted. The baseline study was performed in 1990–1992 (N = 1008). The subjects who participated at baseline (N = 831) and were still alive in 1996 were invited to the first follow-up in 1996–1998, and 593 (73%) of them participated in the pertinent examinations (Rajala *et al.* 1995, Rajala *et al.* 2001). The second follow-up survey was conducted in 2007–2008, inviting all the eligible subjects from the original cohort still alive and living in the city of Oulu on 21st of March 2007 (N = 838). The present study covers all those subjects who participated both in 1996–1998 and in 2007–2008 (N = 457), because sleep disorders were not addressed in the baseline phase in 1990. Subjects who had moved out of the city of Oulu before the clinical examinations were not invited (Figure 2). The background characteristics of the study populations are presented in Table 5.



*51 had only laboratory measurements

Fig. 2. Flow chart of the Oulu 35 research programme: the baseline study in 1990–1992, first follow-up on 1996–1998 and second follow-up on 2007–2008.

4.1.2 Oulu 45 cohort study

The Oulu 45 study consisted of subjects born in 1945 and living in Oulu in 2001. The original study population comprised 1 332 subjects, 995 (75%) of whom participated in the examinations. The background characteristics of the study populations are presented in Table 3.

4.2 Methods

The participants were invited to attend laboratory measurements and clinical examinations by a letter. A structured questionnaire that contained items on sleeping and snoring as well as other background variables, including e.g. smoking, depressive symptoms and use of any medication, was sent alongside the letter. The questionnaires were completed with assistance of the research nurse at

the clinical examination visits, if needed. In all the study populations, nearly the same measurements were used.

Table 5. Background characteristics of the Study populations.

Variables	Oulu 35 1996–1998 (%)		Oulu 35 2007–2008 (%)		Oulu 45 (%)	
	Men	Women	Men	Women	Men	Women
	n = 245	n = 348	n = 218	n = 321	n = 438	n = 555
Marital status						
Married	88	66	83	54	75	63
Unmarried	4	8	6	9	13	15
Divorced	6	14	5	13	11	16
Widow	2	13	6	24	1	6
Education						
Primary school	49	62	50	59	16	14
Vocational courses/school	31	22	31	22	44	48
Vocational college	12	9	13	10	19	25
University	7	7	7	8	21	13
Known diabetes	8	4	16	11	4	3
Depression ¹	5	8	9	13	10	12

¹Zung sum score ≥ 45

4.3 Self-administered questionnaires

Sleeping and snoring

Sleeping and snoring were assessed by five questions. The probability of dozing off was assessed by the Epworth sleepiness scale (ESS) (Johns 1991). A cut-off point of eight or ten points was used to define daytime sleepy persons (Kumar *et al.* 2003). Habitual snoring was defined based on the question “Do you snore while sleeping? (Ask other people if you don’t know.)”. Those who reported snoring every or almost every night were classified as habitual snorers based on the BNSQ (Partinen & Gislason 1995). The classification of OSAS is shown in Table 6. The cutoff point for ESS in the classification of sleep apnea was placed at a mean score of eight points, to include subjects with mild obstructive sleep apnea with a respiratory disturbance index (RDI) of 15 to 29 (Gottlieb *et al.* 1999).

Table 6. The criteria of obstructive sleep apnea syndrome (OSAS).

A subject was classified to have OSAS if the following criteria were fulfilled:

ESS	(1) a sum score of 8 or more
Snoring	(2) every or almost every night
Quality of snoring and breathing pauses	(3) "I snore very loudly (other people hear my snoring in the adjacent room)" or "I snore very loudly and intermittently (there are silent breathing pauses when snoring is not heard and at times very loud snorts with gasping" or breathing pauses (apneas) 3–7 nights per week

Restless legs syndrome

The symptoms of RLS were assessed by one question: "Have you ever suffered from restless legs? By restless legs we mean unpleasant feelings (often hard to describe) in the legs at rest (such as lying or sitting), especially when going to bed, which urge you to move your legs or walk." The alternative responses were: Never, less than once a year, less than once a month, less than once a week, 1–2 days/evenings/nights per week, 3–5 days/evenings/nights per week, every or almost every day/evening/night. The subject was defined to have RLS if he/she indicated suffering from restless legs 1–7 days/ evenings/nights/week (Articles III and IV).

Other questionnaires and instruments

The Zung self-rated depression scale (ZSDS) was used to assess depressive symptoms (Zung 1965). The raw sum score varies from 20 to 80. Participants who score 45 raw points or more have traditionally been defined as suffering from depression (Zung 1965). There were questions determining the use of sleep medication and psychotropic medication.

Smoking was assessed by two questions: "Have you ever smoked?" with response alternatives: 1) never, 2) yes and "Do you smoke nowadays?" with response alternatives: 1) 7 days per week, 2) 5–6 days per week, 3) 2–4 days per week, 4) 1 day per week, 5) occasionally and 6) I don't smoke. Those who had never smoked or had stopped smoking were classified as non-smokers. Those who smoked regularly (1–7 days per week) or occasionally were classified as current smokers.

Physical activity was measured with a question "How often do you exercise at least half an hour in your leisure time?" The answers were then divided into

three categories: 1 = never or less than once in month, 2 = 1–4 times per month, 3 = 2–7 times per week (Article III). There were questions to determine the presence of rheumatoid arthritis and other arthropathy. (Articles III and IV).

In the 1996–1998 survey and in the Oulu 45 study, a subject was considered as having history of coronary heart disease (CHD) if he/she had had a history of myocardial infarction (MI) or angina pectoris (diagnosed by a physician) or had been hospitalized because of a MI, had had a diagnosis of CHD, or used nitroglycerin medication (Articles I-III). In the follow-up study in 2007–2008, history of CHD was recorded in any subject who reported having CHD or used nitro-glycerine medication (Article IV).

4.4 Clinical examinations

The anthropometric measures (height, weight, waist circumference, hip circumference) and neck circumference were measured in light clothing by a trained nurse. Waist circumference was measured midway between the lowest ribs and the iliac crest during expiration and hip circumference two fingers above the pubic bone. Neck circumference was measured with a flexible tape in a standardized manner horizontally above the cricothyroid cartilage to 1 mm accuracy. The waist-hip circumference ratio (WHR) and body mass index were calculated (BMI = weight divided by height squared; kg/m²).

Blood pressure was measured twice by the research nurse with an automatic device (Omron®, Omron Healthcare Inc, Japan) in a sitting position, and the means of these two measurements of systolic and diastolic pressures, respectively, were calculated. The subject was considered as having hypertension, if diastolic blood pressure was ≥ 90 mmHg or systolic blood pressure ≥ 160 mmHg or if the person reported a previously diagnosed hypertension/previously treated hypertension or antihypertensive medication.

4.5 Laboratory measurements

All the subjects who did not have previously diagnosed any type of diabetes mellitus were invited to participate in a 2 h oral glucose tolerance test after a 10 h fast. Blood samples were obtained before (fasting blood glucose value) and 120 min after a 75 g glucose load. The results of the OGTT test were classified according to the WHO criteria 1998 for diabetes mellitus (Alberti & Zimmet

1998). The IGT and IFG groups were then combined as impaired glucose regulation (IGR) (Alberti & Zimmet 1998).

The serum immunoreactive insulin concentration was determined by RIA using the Phadeseph RIA 100 kit (Pharmacia diagnostics AB, Uppsala, Sweden). Insulin sensitivity was measured by QUICKI, which was calculated as $Q = 1/(\log \text{FPI} + \log \text{FBG})$, where fasting plasma insulin (FPI) is expressed as mU/l and fasting glucose (FBG) is expressed as mg/dl (Katz *et al.* 2000).

Plasma CRP was determined by fully automated immunoanalyzer Innotrac Aio! (Innotrac Diagnostics Oy, Turku, Finland) (Hedberg *et al.* 2004). For statistical analyses, cutpoints of < 1.0 mg/L, 1.0–3.0 mg/L and > 3.0 mg/L were used (Pearson *et al.* 2003) (Article II).

Microalbuminuria was defined by calculating the urinary albumin-to-creatinine ratio. Urine albumin and creatinine concentrations were measured from an overnight spot urine sample. The highest deciles of the urinary albumin-to-creatinine ratio (≥ 2.5 mg/mmol) were used as a measure of microalbuminuria (Article I).

4.6 Ethical aspects

A written consent was obtained from all subjects after the purpose of the study was explained to them. The voluntary participation as well as the subjects' right to withdraw from the study at any time was outlined in a consent form. No potentially harmful procedures were conducted, and if a medical condition needing treatment was found, the subject was guided to medical care. The study protocols were approved by the Ethical committee of the Northern Ostrobothnia Hospital District. The data are stored on the researcher's personal computer and on the server of the Institute of Health Sciences of the University of Oulu. The computers and server are behind locked doors, and a personal username and password are required to view them. The questionnaires are stored and the data protection of them is guaranteed by the institute of Health Sciences in University of Oulu.

4.7 Statistical analyses

The prevalences of sleep-disordered breathing, daytime sleepiness and RLS defined by glucose tolerance status as well as by other covariates, are presented as percentages. To assess the independent associations between the cardiovascular

risk factors, glucose intolerance, depressive symptoms as well as other covariates with sleep disordered breathing, daytime sleepiness and RLS, a multiple logistic regression model including these covariates was fitted.

In the longitudinal study, the proportions describing the overall permanence or change of the initial status in the two target conditions were described in pertinent transition tables. The prognostic roles of the various background and clinical characteristics in the prevalence, permanence, and incidence of HS and RLS (at least once a week), respectively, were analysed in a series of logistic regression models, in which these characteristics were included as explanatory variables. In models 1A and 1B the presence of HS and RLS, respectively, in the first survey in 1996–98 was the outcome variable, and the values of the explanatory variables were also as recorded at the same time. Models 2A and 2B were similar to the previous ones, but now the presence of HS and RLS as well as the explanatory variables were taken from the survey in 2007–8. Models 3A and 3B addressed the permanence of HS and RLS, respectively. Model 3A covered only those subjects who had HS in 1996–98, and the outcome was the presence of HS in 2007–8. The values of the explanatory variables were as in 2007–8. Similarly, Model 3B covered only those subjects who had RLS in 1996–98, and the outcome was the presence of RLS in 2007–8. Finally, in Models 4A and 4B the outcomes were the occurrences of new cases of HS and RLS, respectively, in 2007–8 among those subjects free from the pertinent condition in 1996–98. Again, the explanatory variables were reflecting the situation in 2007–8.

For the statistical analyses, SPSS (Statistical Package for Social Science, Inc., Chicago, IL) for Windows versions 8.0–16.0. and the R environment of statistical computing and graphics were used, and particularly the function `glm()` was used to fit the logistic model (R Development Core Team 2010 <http://www.R-project.org>).

5 Results

5.1 The occurrence of sleep disorders and daytime sleepiness

The prevalence of sleep disorders, DS and RLS in the various cross-sectional studies are jointly reported in Table 7. In the Oulu45 study, the prevalences of self-reported OSA, HS and DS were higher compared to the Oulu35 population in 1996–1998 or 2007–2008. In addition, RLS was more prevalent in women than in men in the Oulu45 population, which was not observed in Oulu35 population aged 61–63 or 72–73 years. HS and self-reported OSAS seemed to be more common in men than in women in all the studies (Table 7).

Table 7. Prevalence % (N) of self-reported obstructive sleep apnea syndrome (OSAS), habitual snoring, daytime sleepiness and restless legs syndrome (RLS) in the cross-sectional study populations.

	Population	Age	All	Men	Women
Self-reported OSAS	Oulu45	56–57 years	8 (66)	11 (42)	5 (24)
	Oulu35	61–63 years	4 (23)	6 (14)	3 (9)
	Oulu35	72–73 years	3 (12)	6 (10)	1(2)
Habitual snoring	Oulu45	56–57 years	31 (295)	38 (161)	26 (134)
	Oulu35	61–63 years	26 (143)	30 (68)	23 (75)
	Oulu35	72–73 years	19 (82)	23 (41)	16 (41)
Daytime sleepiness ESS ≥ 8	Oulu45	56–57 years	27 (246)	26 (108)	27 (138)
	Oulu35	61–63 years	20 (109)	22 (50)	18 (59)
	Oulu35	72–73 years	19 (90)	24 (40)	15 (34)
Daytime sleepiness ESS ≥ 10	Oulu45	56–57 years	16 (149)	16 (67)	16 (82)
	Oulu35	61–63 years	9 (53)	10 (22)	9 (31)
	Oulu35	72–73 years	11 (51)	13 (26)	9 (25)
RLS 1–7 times/week	Oulu45	56–57 years	18 (169)	15 (63)	20 (106)
	Oulu35	61–63 years	21 (122)	22 (52)	21 (70)
	Oulu35	72–73 years	15 (65)	14 (26)	15 (39)
RLS 3–7 times/week	Oulu45	56–57 years	12 (112)	10 (43)	13 (69)
	Oulu35	61–63 years	14 (81)	15 (34)	14 (47)
	Oulu35	72–73 years	9 (38)	9 (16)	8 (22)

ESS = Epworth Sleepiness Scale

5.2 Factors associated with sleep disorders and daytime sleepiness in cross-sectional populations

The cross-sectional associations between HS, OSAS, DS and some other selected variables were studied in the Oulu35 population both at the age of 61–63 years (I) and 72–73 years (IV) and in the Oulu45 population at the age of 56–57 years (II, III).

5.2.1 Daytime sleepiness, habitual snoring and obstructive sleep apnea syndrome (I,II)

Obesity

In an unadjusted analysis, DS and HS were associated with waist circumference and BMI in the subjects born in 1935. Self-reported OSAS was also associated with elevated waist circumference in both the Oulu 35 subjects aged 61–63 and the Oulu 45 populations. Independent associations were also observed in logistic regression model in both populations. In the Oulu 35 study, BMI was associated with DS, HS and OSAS while in Oulu 45 population waist circumference was associated with OSAS (Tables 8 and 9). When BMI was added to the model for the Oulu 45, the results were similar: waist circumference was still independently predictive of OSAS, whereas BMI was not (data not shown).

Table 8. Adjusted Odds ratios (OR) and 95 per cent confidence intervals (95% CI) between daytime sleepiness (DS), habitual snoring (HS) and self-reported obstructive sleep apnea (OSAS) (as dependent variables) and type 2 diabetes (T2D), impaired glucose regulation (IGR), insulin sensitivity (QUICKI), body mass index (BMI), male gender, smoking, using of sleep medication, depression as well as neck circumference (Neck) (as explanatory variables) in Oulu35 study population, aged 61–63 years.

Explanatory variable	Daytime sleepiness	Habitual Snoring	OSAS
	OR 95% CI	OR 95% CI	OR 95% CI
T2D	0.79 0.39–1.62	1.93 1.04–3.57	- - *
IGR	0.75 0.43–1.32	0.82 0.48–1.39	- - *
QUICKI	0.96 0.86–1.07	0.97 0.89–1.07	0.98 0.79–1.22
BMI	1.06 1.00–1.12	1.05 0.99–1.11	1.20 1.09–1.34
Male gender	1.32 0.85–2.06	1.31 0.87–1.97	2.61 1.01–6.72
Smoking	0.80 0.43–1.49	1.69 1.00–2.84	0.68 0.18–2.59
Sleep medication	0.33 0.10–1.14	1.20 0.54–2.69	0.00 0.00–0.00
Depression	3.00 1.40–6.46	1.75 0.82–3.74	2.57 0.64–10.22
Neck	1.00 1.00–1.01	1.01 1.00–1.02	1.02 1.01–1.04

* Due to small number of cases, the independent relation between sleep apnea and T2D could not be studied

Table 9. Adjusted odds ratios (OR) and 95 per cent confidence intervals (95% CI) between self-reported obstructive sleep apnoea syndrome (OSAS) and glucose tolerance status, gender, smoking, high sensitivity CRP level (hsCRP), physical activity as well as waist circumference (waist) as explanatory variables in a logistic model in Oulu 45 study population, aged 56–57 years.

Explanatory variable	OR 95% CI
Baseline odds* (per 100)	1.7 0.4–6.3
Male gender	1.68 0.86–3.29
Glucose tolerance status (vs NGT)	
Impaired glucose regulation	0.91 0.43–1.93
Type 2 diabetes	2.56 1.20–5.47
Smoking	1.34 0.73–2.46
Hypertension	1.14 0.61–2.14
hs-CRP 1–3 mg/L (vs < 1)	1.28 0.57–2.86
hs-CRP > 3 mg/L	1.33 0.55–3.20
Physical activity 2–7/week (vs less)	0.71 0.33–1.54
Waist (per 10 cm)	1.41 1.10–1.82
Zung 31–45	3.44 1.55–7.63
Zung 46–65	4.60 1.73–12.27

* Male non-smoker with NGT, hs-CRP < 1, physical activity < 2 times/week, waist circumference = 90 cm, Zung = 0–30.

Impaired glucose metabolism

HS was more common in the diabetic subjects aged 61–63 years in the Oulu 35 study than in those with IGR or NGT (42% vs. 22% or 24%, respectively). T2D was also independently associated with HS (Table 8). In another model, with T2D as the outcome variable, HS was independently associated with T2D (OR 2.79, 95% CI 1.50–5.19). No difference was found in the prevalence of DS in diabetic patients compared to non-diabetic subjects (Table 8).

In the Oulu 45 subjects, a greater proportion of type 2 diabetics had OSAS than of the subjects in the other glucose tolerance groups (22% of previously diagnosed diabetes, 21% of newly diagnosed diabetes vs. 10% of IGT, 7% of IGF and 6% of NGT patients). The association between OSAS and T2D was also seen in the logistic regression model, but the evidence of such an association between OSAS and IGR was inconclusive due to the estimate having a wide error margin (Table 9). In another model with a more refined classification of glucose tolerance, the following odds ratio (OR) estimates (and 95% confidence intervals, CIs) were obtained for the four categories of elevated vs. normal glucose tolerance: previous T2D 2.85 (0.91–8.92), newly diagnosed T2D 2.42 (1.01–5.82), IGT 0.92 (0.39–2.15), and IFG 0.88 (0.24–3.20), respectively, while the estimates for the other covariates remained unchanged. Hence, the modelling of the effect of glucose tolerance based on only three categories was well justified.

Hs-CRP

In the Oulu 45 study, OSAS seemed to be more prevalent in those whose hs-CRP level was > 3.0 mg/L compared to those with $hs-CRP \leq 3$ mg/L, but this association vanished in the logistic regression model.

Smoking

Smoking was more common among the HS subjects than among the non-snorers in the Oulu 35 population (37% vs. 24%), but this was not the case in the subjects with DS or OSAS. In the logistic regression analysis, smoking was independently associated with HS, but the evidence of this association in subjects with DS or OSAS was inconclusive (Table 8).

In the Oulu 45 population, OSAS appeared to be more prevalent among current smokers (11% vs 7%) than non-smokers, but in the multiple regression

model the evidence of this association was unclear; the confidence interval being wide and around 1.0 (Table 9).

Coronary heart disease and hypertension

In the Oulu 35 population no association between sleep disorders and hypertension or coronary heart disease was found (data not shown).

OSAS was more common in hypertensive subjects (10% vs. 5%) in the Oulu 45 population, but no clear independent association was found in the fitted logistic regression model (Table 9).

Depressive symptoms

Depressive symptoms were more prevalent in all sleep disorder-categories in the Oulu 35 subjects, the figures being 10% in subjects with HS vs. 5% in non-snorers, 13% in subjects with OSAS vs. 6% in the subjects without OSAS, 12% in the subjects with DS vs. 5% in the non-sleepy ones. In the fitted logistic regression model, depressive symptoms were most pronounced with DS, but the evidence of this association with HS or OSAS was inconclusive because of the wide error margins (Table 8). The use of sleep medication did not differ between the subjects with DS and the non-sleepy persons, or the subjects with HS compared to the non-snorers (data not shown). No one in the OSAS group reported using sleep medication. Only one person reported using psychotropic medication.

Among the Oulu 45 subjects, OSAS was more prevalent in subjects with depressive symptoms: in those who had a moderately elevated (31–45) or high (46–65) Zung sum score the prevalence of sleep apnea was 10% and 14%, respectively, in comparison to 4% among those who had a Zung sum score of 20–30. Zung sum score was also strongly associated with sleep apnea in the fitted logistic regression model (Table 9). The use of hypnotic medication had no effect on the result.

5.2.2 Restless legs syndrome (III)

In the Oulu 45 subjects, RLS was associated with DS, HS, waist circumference CHD, and depressive symptoms as well as with the use of hypnotic medication and antidepressants CHD, but weakly if at all with type 2 diabetes (III, Table 2).

In subjects with rheumatoid arthritis or other arthropathy, RLS was also more common than among those who did not have these conditions (III, Table 2).

In the fitted multiple logistic model RLS was independently associated with a Zung sum score of 30–45 and 45–65, female gender, CHD, DS and arthropathy (Table 10). Weak associations were also found between smoking, waist circumference and RLS (Table 10). The evidence of association between T2D, IGR, HS, hypnotic medication and RLS was inconclusive (Table 10).

Table 10. Adjusted odds ratios (OR) and 95 percent confidence intervals (95% CI) between restless legs syndrome and glucose tolerance status, gender, smoking, coronary heart disease (CHD), waist circumference (waist), Zung self-rated depression scale, use of antidepressant medication, daytime sleepiness, habitual snoring, use of hypnotic medication, as well as the presence of any arthropathy (including rheumatoid arthritis and other arthropathies) as explanatory variables in a logistic model in Oulu45 study population, aged 56–57.

Explanatory variable	OR	95% CI
Baseline odds*	0.05	0.03–0.09
Female gender	1.64	0.98–2.72
Glucose tolerance status (vs. NGT)		
IGR	1.18	0.70–2.00
T2D	0.67	0.31–1.47
Smoking	1.49	0.92–2.39
CHD	2.92	1.18–7.23
Waist/10cm	1.15	0.95–1.39
Hypertension	0.88	0.56–1.40
Zung (30–45)	1.95	1.09–3.48
Zung (45–65)	3.67	1.71–7.90
Antidepressant medication	2.10	1.06–4.19
Daytime sleepiness	2.12	1.32–3.41
Habitual snoring	1.42	0.90–2.25
Hypnotic medication	0.74	0.35–1.57
Arthropathy	1.69	1.04–2.72

* refers to a male, with NGT, non-smoker, no CHD, waist circumference = 90 cm, no hypertension, Zung = 0–30, ESS < 10, non-snorer, no sleep medication in use, no arthropathy

5.3 The occurrence of habitual snoring and restless legs syndrome during 10 years (IV)

In a 10-year period, the overall prevalence of both HS and RLS ≥ 1 times/week decreased: from 26% to 19% and from 20% to 15%, respectively. The direction

and magnitude of the change was similar in both genders. Half of those who snored in 1996–1998, stopped snoring in the 10 years, and half of those who suffered from restless legs 3–7 times/ week in 1996–1998, suffered from this syndrome less than once a week in 2007–2008 (Tables 11 and 12). The incidence of HS and RLS ≥ 1 times/week was 7%. The same phenomenon was also seen among those who initially had RLS 1–2 nights/week: 2/3 of them had RLS less than once per week in 2006–2008 (Table 12).

Table 11. The prevalence (%), permanence (%) and incidence of new cases (%) of habitual snoring (HS) during 1996–2008 (numbers of subjects in parentheses).

HS 1996–1998	HS 2007–2008		
	No	Yes	Total (N) %
No	93 (295)	7 (24)	100 (319) 74
Yes	50 (57)	50 (57)	100 (114) 26
Total	81 (352)	19 (81)	100 (433) 100

Table 12. The prevalence (%), permanence (%) and incidence of new cases (%) of restless legs syndrome (RLS) during 1996–2008 (numbers of subjects in parentheses).

RLS 1996 -1998	RLS 2007–2008			Total (N) %
	Less than once a week	1–2 times per week	3–7 times per week	
Less than once a week	93 (329)	4 (16)	3 (9)	100 (354) 80
1–2 times per week	68 (21)	19 (6)	13 (4)	100 (31) 7
3–7 times per week	50 (30)	8 (5)	42 (25)	100 (60) 13
Total	85 (380)	6 (27)	9 (38)	100 (445) 100

5.4 Risk factors and factors associated with habitual snoring and restless legs syndrome in the 10 years' follow-up (IV)

In the follow-up study, we first examined the associations between the prevalence of HS or RLS and several previously known risk factors in 1996–1998 and 2007–2008. The included factors examined were gender, glucose tolerance, Zung sum score, ESS, smoking, waist circumference, hypertension and coronary artery disease (data not shown; IV, Table 1). A high Zung sum score was the only factor, which was associated with both HS and RLS. The use of antidepressants or hypnotic medication could not be shown to have an effect on the course of RLS or HS (data not shown).

Male gender predicted the incidence of new HS cases, even though error margins were wide due to relatively small number of cases (IV, Table 5). The same phenomenon was discovered in other factors previously reported to be associated with habitual snoring. The Zung sum score in 2007–2008 was associated with HS in 2007–2008, and a trend in the association between the Zung sum score and HS in 1996–1998 as well as with the incidence of new cases of HS was also found. ESS was also associated with HS in 1996–1998 and 2007–2008, but for the permanence and incidence of HS, the pertinent confidence intervals were wide. Waist circumference was associated most pronouncedly with the prevalence of HS in 2007–2008, but with weaker evidence with the prevalence HS in 1996–1998, and in the permanence and the incidence of new HS cases. T2D and smoking were associated with the prevalence of HS in 1996–1998, but the roles of these factors were unclear in the prevalence of HS in 2007–2008, or the permanence and incidence of HS.

The prevalence of RLS in both 1996–1998 and 2007–2008 were associated with the Zung sum score, which was also predictive of a risk for the permanence and the incidence of new RLS cases. ESS was associated with the prevalence of RLS in 1996–1998, but the evidence of this association in the other RLS outcomes was inconclusive due to the wide error margins. Waist circumference predicted new cases of RLS in 2007–2008 and was associated weakly with the prevalence of RLS in 1996–1998 and 2007–2008. When the risk factors in 1996–1998 were used (data not shown), the results were similar for the permanence and the incidence of new cases for both HS and RLS.

6 Discussion

6.1 Rationale for the study

Sleep disorders, daytime sleepiness and RLS have all been reported to be fairly common states. Our study contributes information about the prevalence and associated factors of these states in three different age groups in Northern Finland. Little is previously known about the natural course and predictive factors of these states in subjects from their sixties to seventies, about which our study also contributes information.

6.2 Methodological issues

6.2.1 Study populations

The study populations were unselected collections of urban subjects in Finland aged 56–57, 61–63 and 72–73 years. The results obtained may, with due cautions, be generalized at least to sufficiently similar Nordic populations. The response rates were quite high in Oulu35 and Oulu45 cross-sectional studies; 73% and 75%.

In the Oulu35 second follow-up study conducted during 2007–2008, the major shortcoming was the rather small size of the study population. The response rate in the follow-up was also quite low, 55% of the original cohort, since only those subjects who had participated both in 1996–1998 and 2007–2008 were included. This could lead to selection bias due to non-response. The small size of the population also contributed to the wide error margins. Based on some available information on the non-respondents, no differences in sex, baseline glucose status, anthropometric measurements, blood pressure, or lipid profile were found between the participants and non-participants. However, there were more current smokers among the non-participants than among the participants (29% vs. 14%) (Cederberg *et al.* 2010).

In 1990, 51 subjects participated only in laboratory measurements. A majority of them were men but no other significant differences were found compared to other study subjects. 26 of them participated in 1996–1998, and 13 in the 2007–2008. Due to the small number of cases, further comparison between these subjects could not be made.

6.2.2 Questionnaires

The major limitation in the study was the use of self-administered questionnaires in the assessment of OSAS and RLS. Unfortunately, for logistic reasons, the use of PSG in a study population of this size was not feasible, and financial constraints prevented its use for a validation study even in a small sub-sample. Therefore, it was not possible to estimate the sensitivity and specificity of the screening tool for OSAS or RLS. Reported sensitivities and specificities of similar instruments for screening OSAS have varied from 0.78 to 0.99, and 0.45 to 0.91, respectively, but these have mainly been estimated in selected clinical populations (Chervin 2005). As for RLS, a single standard question almost similar to the present study in a clinic-based population was estimated to have a sensitivity of 100% and a specificity of 97% for diagnosing RLS (Ferri *et al.* 2007). Because of the highly selective clinical study population, the results of Ferri *et al.* should be very cautiously generalized to population-based studies such as the present one.

The use of imperfect questionnaires leads to the possibility of a misclassification bias in the results obtained. In a low-prevalence population, specificity typically has a more significant impact on misclassification bias than does sensitivity. However, even if the absolute prevalence were overestimated because of a lowered specificity, there is no reason to presume that the misclassification was differential with respect to any covariate, except perhaps gender. Therefore, the likely direction of the bias in the relative odds estimates for associations with potential explanatory factors would be towards the null value (OR = 1); thus our OR estimates and their error margins are probably conservative. We were also able to adjust for confounding factors due to several known determinants of OSAS, HS, DS and RLS by using a multiple logistic regression model.

Habitual snoring

HS has been assessed in many different ways in the literature. Here HS was defined as in the Basic Nordic Sleep Questionnaire (BNSQ), which is a well-known and widely used tool for classifying HS (Partinen & Gislason 1995). In fact, the questionnaire is nowadays recommended for assessment of HS (Hoffstein 2005).

Daytime sleepiness

In this study, ESS was used for assessing DS. It has been suggested to correlate well with MSLT (Johns 1991). The cut-off points for excessive daytime sleepiness were originally placed at 10 points in severe OSA, but a great variety in the sum score has been reported in general populations (Johns 1993, Sanford *et al.* 2006). ESS has been criticized for the lack of test-retest data in subjects with OSA and for the lack of adequate construct validity as well as responsiveness data (Miletin & Hanly 2003). In SHHS, however, ESS score correlated well with different stages of SDB (Gottlieb *et al.* 1999).

Obstructive sleep apnea syndrome

Self-reported snoring has been evaluated to be a rather good tool for screening OSAS, even though when the age of subjects increases (> 70 years), the role of snoring as a screening tool for OSAS seems to decrease (Kapuniai *et al.* 1988, Telakivi *et al.* 1987). The same concerns subjects with mild OSAS, and this motivated to use a sum score variable in this study, too (Kapuniai *et al.* 1988). The questionnaire items on the basis of which OSAS was assessed were very similar to those previously used in other studies, e.g. the Berlin questionnaire, including questions about snoring, breathing pauses and daytime sleepiness (Table 4, Hiestand *et al.* 2006, Netzer *et al.* 1999). As for the association between ESS and RDI, in SHHS the mean ESS score was 8.3 in patients with RDI of 15 to < 30, which is why the cut-off point of 8 was chosen: to include the subjects with mild OSA (Gottlieb *et al.* 1999). Even though ESS alone does not correlate with the severity of OSAS, the data from a large primary care population in the USA suggest that the probability of finding OSAS would be higher if both DS and HS were present (Netzer *et al.* 2003).

Restless legs syndrome

One question was used to assess RLS, including all four criteria defined by the IRLSSG (Allen *et al.* 2003). The lack of interviews to supplement this question probably leads to the inclusion of subjects with other states, such as leg cramps, diabetic neuropathy or anaemia. Unfortunately, because of the rather small numbers of cases, it was not possible to properly estimate the effect of all conditions and diseases or any secondary form of RLS. However, the subjects

with arthropathy had more RLS symptoms than those with no arthropathy, suggesting that the secondary form of RLS could at least partly explain the rather high prevalence of RLS in this study. One reason for this may also be the use of anti-inflammatory analgetics in patients with arthropathy leading to anemia. Unfortunately, our study did not allow us to study this possibility.

6.2.3 Laboratory measurements

The laboratory measurements were performed according to the state of the art, and had adequate quality.

6.3 Occurrence of sleep disorders and daytime sleepiness

Comparison of the present results with previous studies based on questionnaires is challenging due to several factors, e.g. different classifications of HS, DS and RLS, the wording of the questions, and different response categories in them.

6.3.1 Habitual snoring

The prevalence of HS was observed to be highest in the 56–57 year-old population, and the prevalence decreased thereafter (Table 5). The same phenomenon was seen in both genders. Half of the self-reported HS symptoms also vanished in 10 years' time. This supports earlier observations in both cross-sectional and longitudinal studies: the prevalence of HS seems to decrease after the age of 60–65 (Honsberg *et al.* 1995, Lindberg *et al.* 1998, Marin *et al.* 1997, Ohayon *et al.* 1997, Zielinski *et al.* 1999). One reason for this might be weight loss, but at least in our populations, the mean BMI, waist circumference or weight did not change dramatically in the 10-year period. Sleep architecture could also explain this decrease: snoring is suggested to be most intense in slow-wave sleep, and the proportion of slow wave-sleep decreases with age (Redline *et al.* 2004). Other masking disorders or conditions common at older ages that could lessen attention to sleep disorders may also contribute to these results. Social and psychological factors, such as the possible loss of a bed partner upon ageing could diminish awareness of snoring: in our study, the proportion of widows doubled in 10 years and the prevalence of snoring decreased among them slightly, but not significantly more compared to those with bed partner.

6.3.2 Daytime sleepiness

The observed prevalence of DS was highest in the population aged 56–57 years, and in the 10 years' follow-up study, there was no difference in the occurrence of DS in subjects aged 61–63 or 72–73 years. The definition of DS varies in different studies: it has been assessed in terms of frequency, number of days per week or ESS (Ohayon 2008). In studies in which ESS was used, the prevalence of EDS was similar to ours, and seemed to decrease after the age of 60 (Joo *et al.* 2009, Souza *et al.* 2002).

6.3.3 Obstructive sleep apnea syndrome

The prevalence of OSAS has varied from 1–14% in population-based studies (Table 1). OSAS has been reported to be approximately three times more prevalent in subjects > 65 years old compared to middle-aged subjects (Young *et al.* 2002a). In this study, the highest prevalence of OSAS was observed among the subjects 56–57 years old. During the 10-years' follow-up of persons initially in their sixties until their seventies, the occurrence of OSAS remained the same (Table 5). The role of aging in the occurrence of OSA has been discussed widely, especially when HS has been reported to decrease during ageing, and possible reasons for this have been thought to be loss of bed partners or loss of hearing (Young *et al.* 2002a). The older adults may also suffer more from central than obstructive sleep apnea, which could explain the vanishing of habitual snoring (as a sign of obstructive sleep apnea) during ageing (Bixler *et al.* 1998). In this study, however, the number of subjects suspected with OSAS was very small in the follow-up, so any conclusions can not be drawn from it.

6.3.4 Restless legs syndrome

In this study, the prevalence of RLS was highest in the subjects in their late fifties and early sixties, and the occurrence of RLS seemed to decrease with ageing. Half of the self-reported RLS symptoms also improved in 10 years' time. In earlier cross-sectional studies, the prevalence of RLS has either remained the same or decreased after 60 years of age (Rothdach *et al.* 2000, Bjornvatn *et al.* 2005, Tison *et al.* 2005, Garcia-Borreguero *et al.* 2006). Compared with these cross-sectional studies, the longitudinal design here allowed evaluation of the natural

course of RLS, even though the questionnaire used was self-administered and somewhat incomplete.

Many population-based cross-sectional studies have observed RLS to be more prevalent in women than in men (Garcia-Borreguero *et al.* 2006). In the current populations, the 56–57 year-old women had more RLS than men, whereas no gender difference was found in the follow-up study. This may partly have been due to a greater proportion of postmenopausal women in the follow-up study: if iron deficiency is a cause of RLS, the prevalence would naturally decrease after menopause (Garcia-Borreguero *et al.* 2006).

6.4 Factors associated with sleep disorders and daytime sleepiness

6.4.1 Habitual snoring, obstructive sleep apnea syndrome and daytime sleepiness

In this study, the different components of metabolic syndrome (METS) (T2D, central obesity, smoking) were observed to be associated with HS and OSAS in cross-sectional analyses of subjects aged 56–57 and 61–63 years. However, in these populations, the associations seemed to lose their significance along with ageing, leaving only male gender and DS to predict new cases of HS in subjects in their seventies. The association between HS/OSAS and the components metabolic syndrome is well-known, but the lack of proper prospective studies has made it difficult to judge (Tasali & Ip 2008). Chronic intermittent hypoxia and sleep fragmentation causing or maintaining inflammation have been suggested to be key factors between OSAS, obesity and metabolic changes (Punjabi *et al.* 2004, Tasali & Ip 2008). In a recent population-based study, where 812 subjects (230 had AHI measured) without METS were examined, loud snoring was an independent risk factor for developing METS in 3 years' time, and it also independently predicted hyperglycaemia (Troxel *et al.* 2010).

In line with several previous studies, male gender predicted best the incidence of habitual snoring in our study, too. The explanation for this is still quite obscure; the present data does not allow any further conclusions on the possible causalities (Cirignotta 1989, Honsberg *et al.* 1995, Lindberg *et al.* 1998).

Daytime sleepiness is a part of the OSAS, but also an independent association between DS and HS has been reported earlier. A possible mechanism behind this

has suggested to be sleep fragmentation (Gottlieb *et al.* 2000, Young *et al.* 1993). Unfortunately, this study could not have revealed such an association, even if it existed, because PSG was not available.

The connection between depressive symptoms and SDB is still under discussion; it may associate independently with SDB or the connection may be due to other SDB symptoms or comorbidities (Bixler *et al.* 2005, Saunamäki & Jehkonen 2007). In the Oulu35 longitudinal study, Zung sum score associated with the prevalence of HS in 1996–1998 and 2007–2008 and also predicted the permanence of HS and incidence of new HS cases in 10 years. There was also an independent association between Zung sum score and DS in the Oulu35 cross-sectional study in 1996–1998. The role of depressive symptoms in sleep disorders still needs further prospective studies revealing possible associations, which probably are multifactorial.

6.4.2 Restless legs syndrome

In the 56–57 year-old-population, CHD associated independently with RLS, which association was not seen in the Oulu35 longitudinal study, probably due to the small number of cases. This association has also been suggested in other epidemiological studies, e.g. in the SHHS, where it was stronger in the subjects older than 65 years than in younger ones (Ohayon *et al.* 2001, Winkelman *et al.* 2008). Possible reasons can only be speculated; sleep loss, mutual background factors, heart rate or blood pressure variability may well be involved (Ayas *et al.* 2003, Winkelman *et al.* 2008). In this study, hypertension was not, however, associated with RLS, but the lack nocturnal blood pressure measurements may for its part have had an effect on this result.

In this study, both depression and obesity predicted the incidence of RLS. Even though vascular pathology could explain the association between obesity, CVD and RLS, other mechanisms have been introduced, too (Winkelman *et al.* 2008). The association between depression and RLS and obesity and RLS have both been suggested to lie in some changes in dopaminergic system in preliminary studies (Wang *et al.* 2001, Dailly *et al.* 2004, Gao *et al.* 2009). For depression and RLS, decreased D2 receptor binding has been studied, and overeating might be a way to compensate for the decreased activation of these circuits. Due to the epidemiological nature of the present work, we could not examine these possible mechanisms.

6.5 Conclusions and implications

This descriptive study included two different, geographically defined populations aged 56–57 and 61–63 years and living in Northern Finland, in the city of Oulu. The first study population born in 1935, was examined twice, at baseline and after a ten-year follow-up (allowing both cross-sectional baseline analyses and ten-year follow-up analyses). The second study population, born in 1945, was examined in a cross-sectional manner. The participation rates in both the cross-sectional as well as in the follow-up study were reasonably high. As the same definitions and study tools were used in all of these four studies, the results are well comparable with each other.

As for the prevalence of sleep disorders, the findings of these studies are mainly similar to those of most earlier studies: habitual snoring, obstructive sleep apnea and restless legs syndrome are common in 56–57, 61–63 and 72–73 year-old subjects. The prevalences of habitual snoring as well as that of RLS also seem to diminish during ageing.

The features of metabolic syndrome are common in subjects with habitual snoring and OSAS in their fifties and sixties, but these associations seem to lose their importance as subjects get older.

In older adults, the possibility of depressive symptoms should be considered as a risk factor for RLS.

This study contributes information especially on the natural course of sleep disorders, which is lacking not only in Northern Finland but is scarce overall. Even though these results are not as such applicable to clinical work, they should be kept in mind, as the symptoms and risk factors of HS and RLS are possibly treatable or at least relievable.

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Original articles

- I Renko A-K, Hiltunen L, Laakso M, Rajala U & Keinänen-Kiukaanniemi S (2005) The relationship of glucose tolerance to sleep disorders and daytime sleepiness. *Diabetes Research and Clinical Practice* 67: 84–91.
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- III Juuti A-K, Läärä E, Rajala U, Laakso M, Härkönen P, Keinänen-Kiukaanniemi S & Hiltunen L (2010). Prevalence and associated factors of restless legs in a 57-year-old urban population in northern Finland. *Acta Neurologica Scandinavica* 122: 63–9.
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