Snoring and Sleep Apnea in Women

Risk Factors, Signs and Consequences

MALIN SVENSSON
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Abstract

Obstructive sleep apnea syndrome (OSAS) is characterized by snoring, apneas and excessive daytime sleepiness (EDS). Obesity is a risk factor for snoring and sleep apnea, but data on other factors in relation to obesity are ambiguous. Symptoms of sleep apnea in women have not been fully elucidated. OSAS is an important risk factor for cardiovascular disease (CVD). A common feature in patients with CVD and sleep apnea is an increase in systemic inflammation.

From the general population 7,051 women ≥ 20 years answered a questionnaire on snoring and sleep disturbances. Habitual snoring was found in 8% of the total population, and influenced by age, obesity and smoking. The highest prevalence (14%) was found in women 50-59 years. In lean women, alcohol dependence was associated with snoring, while physical inactivity was a risk factor for snoring in obese women.

Further, 230 snoring women and 170 women regardless of snoring status were investigated with polysomnography, blood sampling and anthropometric measurements. Of these, 132 participants underwent an ocular and endoscopic examination of their upper airways. Several findings in the upper airways characterised normal-weight women with an apnea-hypopnea index (AHI) ≥ 10. In women with BMI of > 25, no pharyngeal characteristics predicted sleep apnea.

When adjusting for age, obesity, smoking, AHI and sleep parameters, several aspects of daytime sleepiness correlated to snoring independently of AHI (EDS, falling asleep involuntarily during day, waking up unrefreshed and fatigue). No symptoms correlated to AHI independently of snoring.

Blood samples were analysed for systemic inflammation (CRP, TNFα, IL-6, myeloperoxidase (MPO) and lysozyme). Strong correlations were found between obesity and inflammatory markers. AHI and nocturnal hypoxia correlated to all markers except MPO. When adjusting for age, obesity and smoking, only IL-6 and TNFα were independently associated with nocturnal hypoxia.

In conclusion, age and obesity influence the prevalence of snoring and sleep apnea in women from the general population. Other risk factors differ according to BMI. Daytime symptoms are independently related to snoring per se. Despite a strong correlation between obesity and inflammation, an independent relationship between sleep apnea and inflammatory markers was found.

Keywords: snoring, sleep apnea, women, general population, risk factors, daytime sleepiness, inflammation, pharynx

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urn:nbn:se:uu:diva-9515 (http://urn.kb.se/resolve?urn=urn:nbn:se:uu:diva-9515)
And if tonight my soul may find her peace
in sleep, and sink in good oblivion,
and in the morning wake like a new-opened flower
then I have been dipped again in God, and new-created.

D.H. Lawrence (1885-1930)

To my children, Hanna and Max
List of Papers

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


IV Svensson M, Venge P, Janson C, Lindberg E. Relationship between sleep apnea and markers of systemic inflammation in women from the general population (manuscript).

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<td>AI</td>
<td>Apnea Index (number of apneas per hour sleep)</td>
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<td>BMI</td>
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<td>CI</td>
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<td>Continuous Positive Airway Pressure</td>
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<td>Interleukin-6</td>
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<td>Tumor Necrosis Factor α</td>
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<td>Upper Airway Resistance Syndrome</td>
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Introduction

Background

Sleep-disordered breathing

The realization that snoring might be more than a mere nuisance dates back to the late 1970s. It was found that obstructive sleep apnea is almost inevitably observed together with snoring (1, 2) and that sleep-disordered breathing (SDB) could be regarded as a continuous spectrum from occasional snoring to sleep apnea (Figure 1). However, a progression from snoring to sleep apnea does not occur invariably in the particular individual, as a remission in snoring frequency over time has been reported (3, 4).

Figure 1. The spectrum of sleep disordered breathing. Printed with permission from Elsevier Saunders, Principles and Practice of Sleep Medicine, 4th edition, 2005, p 1109, eds Kryger M, Roth T, Dement W
The consequences of SDB have been found to consist of two basically different entities: excessive daytime sleepiness and negative long-term effects on the cardiovascular and metabolic profile. Historically, snoring in combination with excessive sleepiness has been described in the literature (5) and in medical reviews of case studies (6, 7). The connection between SDB and daytime sleepiness has since been confirmed in large epidemiological studies (8-10). Further, an increased risk of occupational accidents (11) and traffic accidents (12, 13) has been found in persons with SDB, probably attributable to the increased daytime sleepiness.

Negative long-term consequences of untreated sleep apnea have been shown in the form of an increased risk of hypertension (14-16), stroke (17, 18) and death (19-21), independent of other risk factors, and a dose-response relationship between SDB severity and the risk of cardiovascular events has been implied (18). Further, the treatment of sleep apnea has been shown to reduce cardiovascular morbidity without changing other risk factors (18). An increasing amount of data also indicates an independent negative influence by SDB on glucose metabolism (22-26).

The treatment of sleep-disordered breathing is designed to lower or eliminate the risk of pharyngeal collapse during sleep. Even a moderate weight loss has been shown to reduce the AHI (27), as has a large weight loss after bariatric surgery (28).

The most common surgical procedure in the pharynx is uvulopalatopharyngoplasty (UPPP) (29). However, it has been found to be effective in treating fewer than 50% of patients with OSAS (30). Tracheotomy abolishes the obstructive events, as respiration through the stoma by-passes the site(s) of obstruction. It is, however, coupled by a not negligible amount of morbidity for the patient.

A mandibular advancement splint advances the mandible during sleep, which increases the retropharyngeal area and also increases muscular tone in the pharynx, to avoid pharyngeal collapse. This leads to an improvement in daytime symptoms and the AHI (31, 32).

Continuous Positive Airway Pressure (CPAP) applied via an (oro-) nasal mask acts like a pneumatic splint, preventing the upper airways from collapsing, and is effective in relieving daytime symptoms and reducing obstructive events, and blood pressure and cardiovascular morbidity (18, 33-35). In their 18-year mortality follow-up of the Wisconsin Sleep Cohort (n=1,522), Young et al. found that the adjusted all-cause mortality hazard ratio for SDB was 3.0. When people who had used CPAP were excluded it increased to 3.8, indicating that CPAP treatment of sleep apnea can also reduce the mortality risk (20).

So far, most knowledge about SDB is based on studies of men, or studies including both genders. However, some data point to differences between the genders in terms of symptoms at presentation at the sleep clinic (36-39). Women have been found to have more unspecific symptoms at presentation.
(i.e. difficulty inducing sleep, depression, fatigue) than men. On the other hand, some data point in the other direction (40). Symptoms of sleep apnea are also reported to occur at lower AHI in women than in men (40). This proposed difference has been discussed as an explanation of why women are proportionally under-represented at sleep clinics, with referral rates ranging from 1.25:1 (10) to 8:1 (41). Gender-specific clinical findings in the pharynx (the site of obstruction) have also been found in some studies (42-45) and this could be another possible explanation for the under-diagnosis of women.

Definitions

Snoring
Snoring is a sound that is generated by the vibration of tissues in the unstable oropharynx-pharynx during sleep. So far, no widely accepted measurement of snoring has been put forward, i.e. it is unclear whether the sound frequency, the sound level or the actual presence of snoring is the important feature. In scientific work, as well as clinically, the tool that is most frequently used to assess snoring is questionnaires. One problem with questionnaires, however, is the lack of validation (46). Questionnaires rely on self-reported data which are likely to vary as a result of demographic, psychosocial and other factors and may be coloured by recall bias.

Obstructive apnea/hypopnea
An obstructive hypopnea/apnea is characterized by a transient reduction in, or complete cessation of, breathing due to upper airway occlusion. According to a task force of the American Academy of Sleep Medicine, an apnea is defined as a > 50% decrease in breathing from baseline lasting for ≥ 10 seconds, while a hypopnea is a clear decrease in breathing associated with either an oxyhaemoglobin desaturation of > 3% or an arousal, which lasts for at least 10 seconds (47). In the clinical situation, however, an apnea is most commonly defined as a complete cession of airflow lasting 10 seconds or more (8).

Sleep-Disordered Breathing
SDB is a term that is not well defined in the literature. According to one textbook of sleep medicine, it encompasses respiratory disturbances during sleep: snoring, asymptomatic apneas and full-blown sleep apnea (48). In the following text, SDB will be equated with snoring and/or sleep apnea regardless of symptoms.
Apnea-hypopnea index

The apnea-hypopnea index (AHI) is the mean number of apneas/hypopneas per hour of sleep recorded during an overnight monitoring. A small number of apneas is considered to be a normal finding and the widely accepted limit for abnormality is an AHI of $> 5$ (47, 49). However, since a high prevalence (9-24%) of $\text{AHI} \geq 5$ has been found in population-based studies (8, 50), higher cut-off points are often used in studies. Moreover, no safe lower limit for the AHI has been possible to establish.

Obstructive Sleep Apnea Syndrome

According to the American Academy of Sleep Medicine, the diagnostic criteria for the Obstructive Sleep Apnea-Hypopnea syndrome (in the following text called Obstructive Sleep Apnea Syndrome, OSAS) are: I) five or more obstructive breathing events per hour of sleep during overnight monitoring and II) excessive daytime sleepiness not better explained by other factors, or III) at least two of the following: choking or gasping during sleep; recurrent awakenings during sleep; unrefreshing sleep; daytime fatigue; impaired concentration (47).

In clinical, as well as scientific, practice, a simplified definition of OSAS is often used: an AHI of $\geq 5$ in combination with daytime hypsomnolence (8). Moreover, an AHI of $\geq 15$ without excessive daytime sleepiness has been proposed by The American Academy of Sleep Medicine in the ICSD-2 (International Classification of Sleep Disorders 2) as a sufficient diagnostic criterion for obstructive sleep apnea (51).

Excessive daytime sleepiness

Excessive daytime sleepiness (EDS) is a state in which the person experiences unwanted sleepiness or involuntary sleep episodes during the day. Attempts have been made to objectify this state by laboratory measurements. The Multiple Sleep Latency Test (MSLT) (52), and the Maintenance of Wakefulness Test (MWT) (53) are the most widely accepted in-laboratory tests, but they are not considered suitable as screening tools (54) and the results of studies relating to the correlation between sleep apnea and these measures have been divergent. Instead, in many studies, questionnaires have been used to assess EDS. One validated, and frequently used, questionnaire is the Epworth Sleepiness Scale (ESS). On this scale, the risk of dozing off in different situations during the day is investigated by eight questions (55). The daytime sleepiness is evaluated on a 24-point scale, where a higher score indicates a higher level of daytime sleepiness. A cut-off point of 10 to indicate EDS is widely used in studies. This and other questionnaires are,
however, subjective assessments of a state that is difficult to define, leaving several sources of misinterpretation in studies.

Pathogenesis

Snoring and hypopneas-apneas

The obstruction (partial or total) of airflow that occurs during snoring or a hypopnea-apnea is situated in the upper airways. This consists of the airway from the nose to the larynx. Unlike the nose, the larynx and the trachea, the naso-oro and hypopharynx lack the support of bone and cartilaginous tissues and is therefore the only collapsible segment of the upper airways. The patency of this part of the airway depends on activity in the approximately 20 muscles surrounding the pharynx, together with a complex interaction between the velocity of the air passing the segment, the lumen of the segment and gravity (56).

During sleep, a decrease in motor output to the pharyngeal muscles, in combination with the supine position where gravity contributes to a narrowing of the airway, may promote the collapse of the airway. A decrease in the cross-sectional area may further compromise the airway via the Bernoulli effect, where the acceleration of the air through the smaller lumen reduces the lateral wall pressure, thus facilitating a collapse. Attempts to breathe against a (partly) closed airway increase the suction pressure, causing progressively increasing negative intrathoracic pressure and an arousal (a brief change in EEG pattern without awakening).

Excessive daytime sleepiness

The exact cause of the excessive daytime sleepiness in patients with snoring and/or OSAS is not clear. Hypotheses include sleep fragmentation by arousals occurring due to an abnormal increase in respiratory effort (57, 58) and lower sleep efficiency due to snoring (59). However, even though frequent arousals are a common finding in patients with severe OSAS, several studies have failed to find an association between the level of AHI and daytime sleepiness (8, 60, 61).

Nycturia, voluntary voiding at night, is associated with sleep apnea, especially in patients with severe disease (58, 62). This repeated interruption of sleep may further contribute to daytime sleepiness.

Inflammatory cytokines (tumour necrosis factor-α, TNFα, and interleukin-6, IL-6) have been found to be elevated in sleep apnea patients independently of obesity and correlated to sleepiness and fatigue (24). These cytokines are somnogenic and also involved in sleep regulation. The
treatment of sleep apnea has been shown to reduce the levels of inflammatory markers, as well as symptoms of excessive daytime sleepiness (63, 64).

Increased risk of cardiovascular morbidity in sleep-disordered breathing

Respiration during sleep is mainly controlled by an automatic control system consisting of chemoreceptors in the carotid body and medulla. During an obstructive apnea, hypoxia and a rise in CO2 occurs, the latter being the primary stimulus to ventilation (65). Increasing respiratory effort increases the negative intrathoracic pressure, which, in turn, increases cardiac pre-load. At the end of an apnea the heart rate and blood pressure rise in conjunction with an arousal.

Normally, the blood pressure declines during sleep, but a ‘non-dipping’ pattern has been shown in patients with sleep apnea (66, 67), as well as an abnormal nocturnal variation in blood pressure and heart rate (68). An arousal is associated with increased sympathetic activation and peripheral vasoconstriction which can be measured by peripheral arterial tonometry (PAT) (69) or indirectly by finger plethysmography (70).

Sleep-disordered breathing and inflammation

More and more data confirm that atherothrombosis is partly an inflammatory disease (71, 72) and that CRP and IL-6 are risk markers of cardiovascular morbidity (73-75). Elevated levels of myeloperoxidase (MPO) are seen in patients with the acute coronary syndrome and are independent predictors of mortality in these patients (76, 77). One possible link between SDB and cardiovascular morbidity is that the oxidative stress that occurs due to the apneas leads to an inflammatory and immunologic reaction (78). In clinical patients with full-blown OSAS there is an association between sleep apnea and inflammatory markers independent of obesity (79-82). In these patients, the treatment of sleep apnea is also followed by a significant reduction in CRP and plasma cytokines (63, 64).

CRP is an acute-phase reactant released from the liver in response to an elevated level of cytokines (such as IL-6 and TNFα) produced by monocytes/macrophages due to tissue damage. Lysozyme (muramidase) measured in the blood derives mostly from monocytes/macrophages and has the enzymatic ability to break down bacterial cell wall peptidoglycans generating somnogenic and pyrogenic muramyl peptides. The muramyl peptides in turn activate monocytes to release various cytokines such as IL-1, IL-6 and TNFα, which are also involved in sleep regulation. MPO is mainly found in
monocytes/macrophages and its enzymatic activity has been implicated in lipid peroxidation and NO conversion, which are critical steps in the development in atherosclerosis (83). Taken together, these mechanisms may contribute to the increased risk of cardiovascular morbidity in SDB.

Prevalence of sleep-disordered breathing

In studies of both genders, SDB has been found to be twice as common in men as in women. Self-reported habitual snoring has been found in 11-15% of women and 20-28% of men in the general population in epidemiological studies (3, 84, 85), with a clear age dependence. Peak incidences at 50-59 years of age in men and at 60-64 years in women, with a decline at higher ages, have been demonstrated (10, 86).

In their study, Young and co-workers estimated the prevalence of an AHI of ≥ 5 as 9% in a cohort of middle-aged working women, with the highest prevalence (16%) among women aged 50 to 60 years (8). Two per cent of the women and 4% of the men were estimated to suffer from both an AHI of ≥ 5 and hypersomnolence, thereby meeting the minimum criteria for OSAS. This is in accordance with another study in which the lower limit of OSAS was estimated as 2.5% in women 40 to 60 years of age (85).

Risk factors for sleep-disordered breathing

A close relationship has been shown between obesity and snoring/sleep apnea in both genders (8, 85, 87, 88), possibly due in part to a narrowing of the pharynx by parapharyngeal fat deposits. On the other hand, waist circumference has been found to be equally predictive of snoring as neck circumference (89) and a better predictor of sleep apnea than BMI or neck circumference (90), indicating that local obesity is not the sole explanation of this link. Some data show that it is the presence of central obesity that constitutes the elevated risk for sleep apnea (24, 90).

Age has a clear influence on the prevalence of SDB in both genders. This influence on snoring does not appear to be linear, however, since a decline in prevalence from a peak at 50-64 years has been shown in some studies (10, 86). The nature of the connection between age and SDB is not entirely clear. A decline in muscular tone (91, 92), and respiratory effort during apneas (93), with age have been shown. Further, a reduction in the sensitivity of ventilatory responses with age has been suggested (94, 95). In females, some studies have shown an increase of SDB in postmenopausal women compared with premenopausal women (41, 96, 97) and a clear decrease in prevalence among postmenopausal women receiving hormone replacement therapy.
(96), implying a hormonal influence on the patency of the upper airway. However, the underlying mechanisms explaining the gender difference in the prevalence of SDB cannot solely be explained by this difference in hormonal state.

A correlation between smoking and an increased risk of SDB has been demonstrated (85, 98-101). Proposed mechanisms include the effect of nicotine withdrawal and local oedema in mucous membranes causing a narrowing of the upper airways (99, 102-104).

The use of alcohol has been associated with the prevalence of snoring in men only (105), in men and women (106) and an association with AHI was found in both genders (100) but only in men in one study (107), while other studies have failed to find this correlation (84). Varying methods to determine alcohol use may partly explain these divergent results.

Structural predisposing factors for pharyngeal narrowing causing snoring and/or apneas include tonsillar and uvular hypertrophy, retrognathia (45, 108) and hyperplasia, oedema or fat deposits in the upper airway soft tissues (109). In addition, nasal obstruction of different genesis can result in an airway collapse due to a change in up-stream airflow velocity.

Patophysiological changes, such as oedema and neurogenic lesions, in the parapharyngeal soft tissues have also been shown in snorers and individuals with OSAS compared with controls (110-113). Whether these changes are a primary cause of the collapsibility of the upper airway, or secondary to trauma caused by vibrations remains unclear.

Consequences

The most common symptom of untreated snoring and/or sleep apnea is excessive daytime sleepiness which can impair work and social activities and increase the risk of accidents (114). Health consequences include hypertension (16, 86, 115-117), diabetes (117), heart failure and stroke (118) and death (119).
Aims

The aims of the work in this thesis were to study a population-based sample of women and:

1. To analyze risk factors associated with snoring in women, with special emphasis on factors associated with snoring in women with different BMI levels
2. To identify findings in the upper airways that could serve as predictors of SDB in women
3. To investigate the relationship between symptoms and the level of SDB
4. To explore whether there is an association between SDB and systemic inflammation
Methods

Population
For phase I of the study a random sample of 10,000 women aged ≥ 20 years was drawn from the population registry at the Municipality of Uppsala, Sweden. They were all sent a postal questionnaire in April 2000. Of these, 158 were returned unopened due to an incorrect address. As a reminder, all the women were sent a postcard after one week and the non-responders were sent two more questionnaires at the most. The total response rate was 71.6%, leaving a total of 7,051 questionnaires to be analyzed for Paper I.

According to answers to the question about snoring in the initial questionnaire, the subjects were defined as either habitual snorers or non-snorers (see below). In Phase II, a random sample of 230 habitual snorers and 170 randomly selected subjects from the whole cohort, aged < 70 years, took part in further investigations. This oversampling of participants with suspected SDB was made to yield a cohort with adequate variance in nocturnal breathing disturbances. Investigations included full-night polysomnography (PSG), a physical examination and blood sampling. A new questionnaire was completed in conjunction with the PSG.

In Paper II, a nose and throat examination including fiberoptic evaluation of the upper airway was performed in 132 women randomly selected from the 400 subjects who underwent a PSG.

In Paper III, the answers from the second questionnaire on potential symptoms of snoring and sleep apnea were compared with the results of the 400 polysomnographies.

Analyses of blood samples were made for markers of systemic inflammation (i.e. C-reactive protein, CRP; interleukin-6, IL-6; tumour necrosis factor alpha, TNFa; myeloperoxidase, MPO, and lysozyme). Comparisons were made between the level of inflammation and indices of sleep apnea in Paper IV.

Questionnaires
The initial questionnaire for Paper I comprised 109 questions, including questions on snoring and potential risk factors for snoring. The subjects stated their height and weight and the body mass index (BMI, expressed in
kilograms per square meter) was calculated. They were also asked to measure their neck and waist circumferences using a tape measure that was included with the questionnaire. Instructions requested the participants to measure the neck circumference at the level with the smallest diameter, and the waist circumference at the level of the navel.

Snoring habits were evaluated according to a five-point scale. Subjects reporting loud and disturbing snoring ‘often’ or ‘very often’ were characterized as habitual snorers, whereas non-habitual snorers reported loud and disturbing snoring ‘never’, ‘seldom’ or ‘sometimes’. Smoking habits were assessed using six questions. The subjects were categorized as either non-smokers (i.e. never smoked), previous smokers (quit smoking at least six months prior to answering the questionnaire), current smokers of < 10 cigarettes a day, or current smokers of ≥ 10 cigarettes a day.

Alcohol dependence was evaluated according to the CAGE (cut down, annoyed by criticism, guilty about drinking, eye-opener drinks) alcohol screening questionnaire (120, 121). Confirmation of two or more of the four questions classified the subject as being alcohol dependent.

The subjects were asked about current, regular medication, including hormone replacement therapy and sedatives.

The level of the subject’s physical activity was assessed. It was considered to be normal to high physical activity when the women spent at least four hours a week on activities such as gardening, cycling or more intensive physical work, while the women in the low-activity group spent most of their leisure time on sedentary activities (122).

The questionnaire contained 15 questions relating to menopausal and hormonal status. Two different approaches to assign menopausal status to the subjects were used. According to the strict approach, women who had regular menstrual periods, were not receiving hormone replacement therapy and stated that they had not passed into menopause were considered to be premenopausal. Women who answered that they had passed into menopause, had had their last menstrual period at least 12 months ago and were not receiving hormone replacement therapy were assigned to the postmenopausal group. In the age-based approach, the women were assigned to menopause group according to age: women ≤ 46 years were considered premenopausal and women 53 years or older as postmenopausal. Women 47 to 52 years of age constituted a group with uncertain menopausal status.

For Papers II- IV, a new questionnaire comprising 55 questions was completed and the subjects were classified as habitual snorers, or non-habitual snorers, according to the same classification as above.

Smoking habits were assessed by six questions and the subjects were categorized as current smokers or non-smokers in Papers II-IV.

The subjects were asked about symptoms of nasal obstruction during the day and night.
Seven questions were used to assess symptoms of snoring and/or sleep apnea in Paper III. Daytime sleepiness was assessed by four different questions and the Epworth Sleepiness Scale (ESS) was also used (55), where a value of 10 or more was regarded as excessive daytime sleepiness.

Examinations

The BMI in Paper I was calculated from self-reported data relating to the subjects’ height and weight.

For Papers II-IV, all the subjects underwent a full-night PSG (see below). Their height, weight, neck, hip and waist circumferences were measured by a research nurse. The neck circumference was measured at the level of the cricothyroid membrane and the waist circumference midway between the lower rib margin and the superior iliac spine. There was a reasonably close correlation between the BMI calculated from self-reported data and that calculated from measured data \((r = 0.86, p < 0.0001)\), as well as between self-measured and true neck circumference \((r = 0.86, p < 0.0001)\) and self-measured and true waist circumference \((r = 0.8, p < 0.0001)\).

In Paper II, 132 randomly selected women were examined by an otorhinolaryngologist (M.S or M.H) before undergoing the PSG. A number of clinical features in the nose and pharynx were classified. Fiberoptic nasopharyngoscopy was performed with the subject in the supine position. To evaluate upper airway patency, the subject was instructed to perform a Muller Manoeuvre (MM) (123). This consists of a maximum inspiration effort against a closed mouth and sealed nose, while the examiner observes the collapse at the level of the soft palate and at the level of the tongue base. Peak nasal inspiratory flow (PNIF) was measured with a peak inspiratory flow meter. The PNIF rate (l/min) was recorded by forced inspiration through the nose.

Laboratory analyses

Blood samples were obtained (between 7 and 9 am from the fasting subjects) for plasma CRP, IL-6, TNFα, MPO and lysozyme. CRP, IL-6 and TNFα were assayed at the routine department of Clinical Chemistry at Akademiska Sjukhuset, Uppsala, on the Architect (Abbott Diagnostics, Abbott Park, IL, USA) and Immulite 2500 (Siemens Healthcare Diagnostics, Deerfield, IL, USA) instruments, respectively, according to the instructions of the manufacturer. Myeloperoxidase was assayed by an ELISA assay from Diagnostics Development (Uppsala, Sweden) according to the instructions of the manufacturer. Lysozyme was assayed by an in-house radio-immunoassay as de-
scribed before (124). The within-assay and between assay variations were < 10% CV for all assays.

**Polysomnography**

Studies were conducted as home-based, full-night polysomnographies (PSG) (Flaga hf, Iceland). They included continuous recordings of electroencephalograms (C3-A2, C4-A1), electrooculograms, electromyograms (submental and bilateral anterior tibialis muscles), airflow (oronasal thermistor and nasal flow pressure sensor), respiratory effort from piezo-electric belts (thoracic and abdominal), electrocardiograms, pharyngeal sounds from a piezo vibration sensor and body position. The data were downloaded to the Somnologica reviewing analysis software (Version 2.0, Flaga hf). Sleep was scored manually according to standard criteria (125) by a specially trained nurse.

An apnea was defined as the complete cessation of nasal and oral airflow for at least 10 seconds, while a hypopnea was a 50% or more reduction in airflow, accompanied by an arousal or an oxygen desaturation of 3% or more. An apnea-hypopnea index (AHI) was calculated as the mean number of apneas and hypopneas per hour of sleep. A decrease of 3% or more from baseline SaO2 defined desaturation and an oxygen-desaturation index (ODI 3%, the number of 3% or higher desaturations per hour of sleep) was calculated. The lowest SaO2 during the recording was noted, as well as the percentage of total sleep time spent with a SaO2 below 90% (% TST with SaO2 < 90%).

**Statistics**

Normal distribution data are presented as the mean ± standard deviation (SD) and prevalence (%). The chi square test was used to compare categorical variables between groups of women. The means of continuous variables in different groups were compared using the unpaired t-test, ANOVA test of variances, or the Mann-Whitney non-parametric test, as appropriate.

Multiple logistic regression analyses were performed to study the influence of several possible explanatory variables on a dependent variable and associations are presented as odds ratios (OR) with 95% confidence intervals (95% CI).

Levels of non-normally distributed variables were logarithmically normalised to allow for parametric analysis. Geometric means were then calculated and reported. Linear regression models to account for multiple variables were created to assess independent relationships between clinical pa-
rameters and logarithmically transformed variables. The critical statistical confidence level selected for all analyses was $p < 0.05$.

Ethics
The informed consent of all participants was obtained and the studies were approved by the Ethics Committee at the Medical Faculty at Uppsala University, Uppsala, Sweden.
Random selection: 10,000 women, 20 years and older, in Uppsala, Sweden

- Questionnaire, response rate 71.6%, n= 7,051
  - Loud and disturbing snoring 'sometimes', 'seldom' or 'never', n= 6,299
  - Loud and disturbing snoring 'often' or 'very often', n= 518

  Paper I: Responders to snoring question, n= 6,817
  Random selection < 70 years
  - n= 170
  - n= 230

  Polysomnography, questionnaire, blood sampling, n= 400

  Paper II: Nose- and throat investigation, n= 132
  Random selection
  Paper IV: Responders to snoring question, n= 395

  Paper III

Figure 2. Study design
Results

Response rate

Of the 7,051 women answering the initial questionnaire in Phase I, 6,817 women (96.7%) had answered the question about snoring and comprised the final study population in Paper I. When comparing the response rate for each 10-year stratum, there were no significant differences within the 20- to 69-year-old age groups (9.2 to 10% of the total female population in the actual area participated in the actual study), while the rates in the older age groups were somewhat lower. Of the women 70-79 years, and over 80 years in the population, 7.8 and 4.4% of the women answered the questionnaire respectively.

Of the 401 women categorized as habitual snorers in Phase I who were invited to participate in Phase II of the study, 230 agreed to participate (57.4%). The 230 subjects included in Phase II were somewhat older than those who declined (49 ± 10 years compared to 47 ± 13 years). The number of women who were invited regardless of snoring status in Phase I was 406. Of these, 170 chose to participate in further investigations (41.9%). The subjects declining participation in Phase II were younger than the women agreeing to undergo further investigations (39 ± 14 years compared to 44 ± 12 years, p<0.0001). However, no significant difference of reported snoring in Phase I existed between the two groups (1.8 vs. 3.6%, p=0.3).

All the 132 subjects who were asked to undergo a clinical nose and throat examination in Paper II agreed to participate.

Of the 400 participants in Phase II, five had not answered the question on snoring. The 395 subjects with a complete questionnaire and PSG comprised the study population in Paper III.

Paper I

Of the 6,817 women answering the initial questionnaire including the question on habitual snoring in Paper I, 518 (7.6%) reported habitual snoring. The snorers were significantly older, had a higher mean BMI and had larger neck and waist circumferences, compared with the non-snorers. Habitually snoring women were more often smokers and were less physically active than the non-snoring women.
The prevalence of habitual snoring was highly age dependent. The prevalence was 2.5% in the group aged 20 to 29 years, with a peak prevalence of 14% in the 50-59 year age group, followed by a decline at higher ages (Figure 3).

![Figure 3. Prevalence of self-reported habitual snoring by age](image)

There was a strong linear correlation between BMI and the prevalence of habitual snoring, where the prevalence was 5.4% in subjects with a BMI of 20 to less than 25 kg/m² and 19.7% in obese subjects (BMI 30 kg/m² and above). A similar correlation was seen between the prevalence of habitual snoring and neck and waist circumference. Of the women with a neck circumference of 34-35 cm, 8.5% reported habitual snoring, while the prevalence was almost twice as high in women with a neck circumference of 36 cm or more (15.8%).

Since both age and anthropometric variables had a strong influence on the risk of self-reported habitual snoring, logistic regressions adjusting for these confounders were performed for each BMI group separately. Due to the strong correlation between neck and waist circumferences (r = 0.62; p < 0.0001), only neck circumference was included in the multivariate analyses (Table 1).
Table 1. Risk factors Associated with Self-Reported Habitual Snoring in a Random Sample of Women in Different BMI Groups.

<table>
<thead>
<tr>
<th></th>
<th>BMI &lt; 20 kg/m² (n=680)</th>
<th>BMI 20-&lt;25 kg/m² (n=3439)</th>
<th>BMI 25-&lt;30 kg/m² (n=1437)</th>
<th>BMI ≥ 30 kg/m² (n=486)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neck circumference</td>
<td>0.88 (0.68-1.14)</td>
<td>1.04 (0.97-1.11)</td>
<td>1.12 (1.05-1.20)</td>
<td>1.15 (1.06-1.25)</td>
</tr>
<tr>
<td>Waist circumference</td>
<td>1.04 (0.96-1.13)</td>
<td>1.03 (1.01-1.04)</td>
<td>1.03 (1.01-1.05)</td>
<td>1.01 (0.99-1.04)</td>
</tr>
<tr>
<td>Non smoker</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Previous smoker</td>
<td>0.94 (0.17-5.14)</td>
<td>1.55 (1.07-2.45)</td>
<td>1.07 (0.72-1.60)</td>
<td>0.85 (0.48-1.51)</td>
</tr>
<tr>
<td>Smoker &lt; 10cig./day</td>
<td>1.17 (0.22-6.38)</td>
<td>2.05 (1.29-3.26)</td>
<td>1.38 (0.78-2.43)</td>
<td>0.66 (0.25-1.74)</td>
</tr>
<tr>
<td>Smoker &gt;= 10cig./day</td>
<td>1.63 (0.30-8.99)</td>
<td>3.42 (2.12-5.51)</td>
<td>1.60 (0.90-2.84)</td>
<td>1.56 (0.69-3.55)</td>
</tr>
<tr>
<td>Physical activity: high</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Physical activity: low</td>
<td>0.73 (0.15-3.50)</td>
<td>0.96 (0.62-1.49)</td>
<td>1.15 (0.77-1.72)</td>
<td>1.73 (1.02-2.93)</td>
</tr>
<tr>
<td>Alcohol dependence</td>
<td>6.64 (1.17-37.8)</td>
<td>1.09 (0.57-2.10)</td>
<td>0.82 (0.35-1.93)</td>
<td>0.29 (0.04-2.34)</td>
</tr>
<tr>
<td>Use of benzodiazepines</td>
<td>0.74 (0.04-14.57)</td>
<td>0.74 (0.17-3.22)</td>
<td>1.91 (0.58-6.28)</td>
<td>1.41 (0.28-7.01)</td>
</tr>
</tbody>
</table>

Values are given as the adjusted OR for snoring (95% CI) (adjusted for age and all risk factors presented in the table). The OR was calculated for an increase of 1 cm in neck and waist circumference. The OR for waist circumference was calculated with waist as the only anthropometric value, whereas all the other calculations use neck circumference as the only anthropometric value.

The influence of neck circumference and low physical activity on the risk of being a habitual snorer increased with increasing BMI. In contrast, the influence of alcohol dependence on the risk of reporting habitual snoring decreased with increasing BMI. A relationship between smoking and snoring was only found in women considered to be of normal weight (BMI 20 - < 25 kg/m²).

No significant correlation was found between menopausal status and habitual snoring in the logistic regressions, regardless of whether the strict or
age-based criteria for menopausal status were applied. Adding the use of hormone replacement therapy did not affect these results.

**Paper II**

In Paper II, 56 (42%) of the 132 examined women reported habitual snoring, and 76 subjects were categorized as non-snorers. PSG showed that 68 women (52%) had sleep apnea defined as an AHI of $\geq 10$. There was no significant difference in the prevalence of smoking, nasal congestion stated by the subject, PNIF scores or alcohol consumption between habitual and non-habitual snorers, or between women with and without sleep apnea. Only a collapse of 75% or more at the level of the soft palate during the Muller Manoeuvre (MM) significantly distinguished women with sleep apnea from women with an AHI of $< 10$ ($p = 0.047$, OR 2.20 (1.0004-4.68), when analyzing the total cohort.

When dichotomizing for overweight (BMI $\geq 25$ kg/m²), findings during the nose and throat examination that significantly distinguished subjects with an AHI of $\geq 10$ from subjects without sleep apnea were only found in the normal weight group (Figure 4).
Figure 4. Prevalence (%) of anatomical and functional features in women with and without sleep apnea (n=132). AHI = apnea-hypopnea index, BMI = body mass index, MM = Muller Manoeuvre.

Low soft palate

![Bar chart showing prevalence of low soft palate for AHI < 10 and AHI ≥ 10. BMI < 25 kg/m², p = 0.03 and BMI ≥ 25 kg/m², p = 0.99.]

collapse =>75% at soft palate

![Bar chart showing prevalence of soft palate collapse greater than or equal to 75%. BMI < 25 kg/m², p = 0.03 and BMI ≥ 25 kg/m², p = 0.73.]

In women with BMI < 25 kg/m², the presence of a low soft palate (p = 0.03, OR 3.50, (95% CI 1.08-11.29)); a ≥ 75% collapse at the soft palate during the MM (p = 0.03, OR 4.04 (95% CI 1.10-14.88)); retrognathia (p = 0.01, OR 5.17 (95% CI 1.31-20.39)) and uvula on posterior pharyngeal wall in the supine position (p = 0.002, OR 8.62 (95% CI 1.96-37.95)); were significantly more common in women with sleep apnea than in normal subjects.

Paper III

The 395 women with polysomnography and a complete questionnaire were 50 ± 11 years old with a mean BMI of 26.6 ± 4.8 kg/m². Of the total population, 152 (38.5%) were classified as habitual snorers and about one third of the population fitted in each of the three AHI categories (AHI < 5, AHI 5 - <
15, AHI ≥ 15) respectively. Since there was a close correlation between age, BMI, AHI level and the prevalence of habitual snoring, logistic regressions adjusting for these possible confounders were performed, analyzing possible symptoms of snoring and sleep apnea.

Snoring was related to four different measures of daytime sleepiness independently of age, BMI and AHI (Figure 5).

Figure 5. Habitual snoring as a risk factor for different symptoms, after adjustments for AHI, age, and BMI; log ORs and 95% CI

Further adjustment for smoking, total sleep time, percentage of slow wave sleep and percentage of REM sleep confirmed the independent relationship between snoring and reports of excessive daytime sleepiness (OR 2.28 (1.31-3.99 95% CI)); falling asleep involuntarily during the day (2.11 (1.06-4.21)); waking up unrefreshed in the morning (2.14 (1.30-3.52)); and daytime fatigue (2.77 (1.54-4.99)).
Sleep apnea (i.e. an AHI of 5-<15, or ≥15) was not related to fatigue or any of the measures of daytime sleepiness, either in univariate or in multivariate analyses (Figure 6). Waking up with a dry mouth in the morning was independently related to both snoring (2.00 (1.22-3.27)) and an AHI of ≥15 (2.24 (1.14-4.40)) Nycturia was not independently related to either snoring or sleep apnea.

![Figure 6. AHI ≥15 as a risk factor for different symptoms, after adjustments for snoring, age, and BMI; log ORs and 95% CI.](image)

To further evaluate the relationship between snoring, sleep apnea and daytime sleepiness, four exclusive groups were constructed in which the presence of snoring and apneas in combination was analyzed in relation to EDS (Table 2). In this case, the association between snoring and EDS irrespective of AHI was confirmed, as only the groups with snorers showed an increased risk of excessive daytime sleepiness.
Table 2. *Relative risk for symptoms according to snoring- and apnea status.*

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Non-snoring, AHI &lt; 15</th>
<th>Snoring, AHI &lt; 15</th>
<th>Non-snoring, AHI ≥ 15</th>
<th>Snoring, AHI ≥ 15</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=183)</td>
<td>(n=78)</td>
<td>(n=60)</td>
<td>(n=74)</td>
</tr>
<tr>
<td>ESS ≥ 10</td>
<td>1</td>
<td>2.50 (1.24-4.09)</td>
<td>2.23 (1.12-4.43)</td>
<td>1.79 (0.95-3.39)</td>
</tr>
<tr>
<td>Waking up unrefreshed</td>
<td>1</td>
<td>2.69 (1.44-5.05)</td>
<td>1.41 (0.64-3.10)</td>
<td>2.33 (1.17-4.61)</td>
</tr>
<tr>
<td>Excessive daytime sleepiness</td>
<td>1</td>
<td>3.11 (1.56-6.23)</td>
<td>1.88 (0.79-4.47)</td>
<td>2.47 (1.14-5.36)</td>
</tr>
<tr>
<td>Falling asleep involuntarily during day</td>
<td>1</td>
<td>4.0 (1.64-9.72)</td>
<td>2.51 (0.84-7.44)</td>
<td>3.04 (1.13-8.21)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1</td>
<td>2.85 (1.42-5.72)</td>
<td>1.15 (0.45-2.93)</td>
<td>2.14 (0.98-4.67)</td>
</tr>
<tr>
<td>Dry mouth on awakening</td>
<td>1</td>
<td>2.77 (1.46-5.26)</td>
<td>2.40 (1.14-5.06)</td>
<td>4.26 (2.17-8.36)</td>
</tr>
<tr>
<td>Nycturia</td>
<td>1</td>
<td>0.93 (0.51-1.70)</td>
<td>1.22 (0.60-2.50)</td>
<td>1.82 (0.97-3.42)</td>
</tr>
</tbody>
</table>

Odds ratios (OR) and 95% CI adjusted for age and body mass index are presented. ESS = Epworth Sleepiness Scale
Paper IV

Due to data loss from blood samples, two participants had to be excluded, leaving data from 398 subjects to be analyzed. The results from PSG, anthropometric values and analyses of inflammatory markers (logarithmically normalized) were compared. Women with sleep apnea (AHI ≥ 15) had higher levels of CRP, IL-6 and lysozyme and these subjects were generally older and more obese than non-apnoic subjects (Table 3).

Table 3. Characteristics, baseline and according to AHI, for study population

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>AHI&lt;15</th>
<th>AHI≥15</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=398)</td>
<td>(n=262)</td>
<td>(n=136)</td>
<td></td>
</tr>
<tr>
<td>CRP</td>
<td>1.50</td>
<td>1.34</td>
<td>1.86</td>
<td>0.005</td>
</tr>
<tr>
<td>IL-6</td>
<td>0.88</td>
<td>0.81</td>
<td>1.04</td>
<td>0.04</td>
</tr>
<tr>
<td>MPO</td>
<td>177.2</td>
<td>187.0</td>
<td>159.7</td>
<td>0.1</td>
</tr>
<tr>
<td>TNFα</td>
<td>2.0</td>
<td>2.0</td>
<td>2.04</td>
<td>0.7</td>
</tr>
<tr>
<td>lysozyme</td>
<td>998.1</td>
<td>973.4</td>
<td>1047.1</td>
<td>0.008</td>
</tr>
<tr>
<td>age</td>
<td>50 (11)</td>
<td>47 (11)</td>
<td>56 (9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>AHI</td>
<td>14 (16)</td>
<td>5 (4)</td>
<td>30 (17)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BMI</td>
<td>27 (5)</td>
<td>26 (4)</td>
<td>29 (5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>waist circumference</td>
<td>88.5 (12.6)</td>
<td>85.8 (11.8)</td>
<td>93.9 (12.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>smoking</td>
<td>21 (82)</td>
<td>20 (51)</td>
<td>24 (31)</td>
<td>0.4</td>
</tr>
</tbody>
</table>

Geometrical means are presented for non-parametrical variables (CRP, IL-6, MPO, TNFα and lysozyme). Means and standard deviations are presented for normally distributed variables. % (n) are presented for nominal variables. BMI = body mass index, AHI = apnea-hypopnea index (events/hour)

In univariate analyses, a close relationship between obesity and increased levels of all inflammatory markers was found, as well as a correlation between CRP/cytokines (except MPO) and AHI and/or hypoxic indices. Age correlated significantly to the level of CRP, MPO and lysozyme, while MPO was associated with smoking. To adjust for these confounders, multiple linear regressions adjusting for obesity (waist circumference), age and smoking...
were made. In these analyses, only IL-6 and TNFα showed an independent relationship with hypoxia (% total sleep time spent with oxygen saturation below 90% and ODI 3% respectively). No independent relationship was found between markers of systemic inflammation and the apnea-hypopnea index (Table 4).
Table 4. *Independent influence of obstructive events on inflammatory markers*

<table>
<thead>
<tr>
<th></th>
<th>CRP</th>
<th>IL-6</th>
<th>MPO</th>
<th>TNFα</th>
<th>Lysozyme</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>beta-koeff</td>
<td>p-value</td>
<td>beta-koeff</td>
<td>p-value</td>
<td>beta-koeff</td>
</tr>
<tr>
<td>AHI</td>
<td>0.001</td>
<td>0.7</td>
<td>0.003</td>
<td>0.2</td>
<td>0.0003</td>
</tr>
<tr>
<td>ODI 3%</td>
<td>0.002</td>
<td>0.4</td>
<td>0.003</td>
<td>0.1</td>
<td>0.001</td>
</tr>
<tr>
<td>% TST with saturation &lt;90%</td>
<td>0.003</td>
<td>0.4</td>
<td>0.009</td>
<td><strong>0.03</strong></td>
<td>0.003</td>
</tr>
<tr>
<td>lowest O2 saturation</td>
<td>0.001</td>
<td>0.7</td>
<td>-0.005</td>
<td>0.2</td>
<td>0.0003</td>
</tr>
</tbody>
</table>

Adjusted for waist circumference, age and smoking. AHI = apnea-hypopnea index (events/hour), ODI = oxygen desaturation index, % TST = % total sleep time.
Conclusions

The main findings in this study are that the prevalence of self-reported habitual snoring in women is strongly age dependent and that risk factors associated with snoring and the importance of explanatory factors in the pharynx vary with the level of BMI. Further, we found that one of the main symptoms attributed to sleep-disordered breathing, daytime sleepiness, appears to be correlated to the snoring *per se* and not to the presence of apneas. Moreover, women with sleep apnea have higher levels of inflammatory markers than women without sleep apnea. Most of this association is related to obesity. The levels of IL-6 and TNFα were, however, independently associated with indexes of nocturnal hypoxia even after adjusting for obesity.
Discussion

Prevalence of self-reported snoring

In this study, the peak prevalence of snoring occurred between 50 and 59 years of age. In an epidemiological survey of middle-aged women, the prevalence of habitual snoring increased until the age range of 55 to 59 years, but older women were not investigated (85). Further, in a prospective study, an age of 65 years and older was associated with a remission in reported snoring in women (4). Similar findings have been made in men (3, 4). The reason for this decline in self-reported snoring prevalence is unclear, as is the question of whether there is a true decline in snoring, or just more unreliable self-reports with higher age. However, in an age-stratified sample of men, Lindberg et al. failed to show a significant difference in the specificity and sensitivity of self-reported snoring compared with measured snoring between younger and older age groups (126) indicating that there is a true difference in the prevalence of snoring in different ages. One possible explanation for this could be a decrease in respiratory effort due to a lower muscle tone in older ages, thus creating a less negative intrathoracic pressure and a slower passage of air through the upper airways preventing an airway collapse.

Moreover, in the actual study, no significant difference in the prevalence of self-reported snoring was found between subjects who shared a bedroom with another person and those who did not, implying that the prevalence of self-reported snoring in this cohort is not to a great extent influenced by the presence of informants, a known source of bias for self-reported snoring.

Risk factors for sleep-disordered breathing

Several previous studies have found that the prevalence of habitual snoring and sleep apnea increases with increasing BMI, waist and neck circumferences (90, 99, 106), in accordance with the present study. This effect is thought to be due in part to fat deposits in the neck, impeding the pharyngeal airway size, and possibly also to the weight of the fatty tissue in the neck causing a dynamic loading of the airway (127). However, some data show that the main pathological feature in SDB is central obesity (24, 90), implying another underlying mechanism rather than just mass loading. Women
have been found to have a higher BMI than men at the corresponding level of AHI (41). However, when using the waist-hip ratio (a better measure of central obesity) instead of BMI in the Wisconsin Sleep Cohort Study, the association between SDB and obesity was equalized between genders (128), thereby strengthening the importance of central obesity as a risk factor. This fact could provide a link between SDB and cardiovascular morbidity.

Experimental studies have demonstrated an increasing frequency and duration of upper airway occlusion after alcohol ingestion (129, 130). It has been suggested that this is due to induced oropharyngeal muscle hypotonia and the depression of arousal mechanisms.

A correlation between smoking and habitual snoring has been previously demonstrated (84, 85), with a dose-response relationship in some studies (99, 103). The effect of smoking on the patency of the upper airway might be twofold. An irritant effect of the smoke on the mucosa in the nose and pharynx may induce oedema, resulting in a narrowing of the upper airway (99). Moreover, a positive effect of nicotine on the upper airway musculature in animals has been shown (104), as well as a decrease in the number of apneas occurring two hours after the administration of nicotine to eight patients with sleep apnea (102). This might suggest that the withdrawal of nicotine during the night could increase the resistance in the upper airway. In the present study, a dose-response relationship between smoking and habitual snoring was only found in women of normal weight, while alcohol dependence was only correlated to snoring in lean women. It is possible that the mechanisms mentioned above are proportionally more important in women without overweight, while in obese women the presence of excess fat tissue overshadows the influence of these factors.

A low level of physical activity was associated with a higher risk of habitual snoring in obese women in our population. The same association has been indicated in a previous study of men, even when adjusting for age and obesity (131). Whether physical inactivity truly is a risk factor that is associated with snoring or is instead a consequence of daytime sleepiness and fatigue remains unclear.

Sleep apnea and clinical features in the upper airway

Factors influencing the static area in the pharynx (i.e. tonsil, uvula and tongue size, lateral narrowing of the pharyngeal walls, mandibular retrognathia) and the dynamic area (level and degree of pharyngeal collapse during the Muller Manoeuvre) have been found to correlate with sleep apnea (44, 45, 87, 108).

In this study, clinical findings in the upper airway associated with sleep apnea were only found in women of normal weight. In a study using cephalometry during the Muller Manoeuvre, the authors found that AHI correlated
to different anatomical features in the pharynx in obese versus non-obese subjects (132). As this is the only study in which subjects were analyzed separately according to BMI to our knowledge, it is possible to speculate that, in overweight and obese subjects, it is the overall impingement of the redundancy of soft tissues (i.e. fat deposits) that causes the upper airway obstruction, while in normal-weight women specific anatomical features in the upper airway are more important. However, when using BMI in attempts to predict outcome of pharyngeal surgery (UPPP), varying results have been found. Some studies have found preoperative BMI to be predictive of treatment success (133, 134), while other authors have failed to find this connection (135, 136). This further emphasizes the complex association between SDB and obesity.

Symptoms of snoring and sleep apnea

Excessive daytime sleepiness (EDS) has previously been regarded as the main symptom of sleep apnea and snoring as the main sign and studies have shown a correlation between AHI and excessive daytime sleepiness (137). However, Young et al. found that habitually snoring men and women with an AHI of less than five and subjects with an AHI of ≥ 5 more frequently reported symptoms of hypersomnolence compared with non-snoring controls (8). Moreover, in the Sleep Heart Health Study comprising some 5,700 community-dwelling subjects (3,040 women), Gottlieb and colleagues found that snoring was related to an Epworth Sleepiness Scale score of more than 11, independently of the apnea frequency (138). Further, no significant interaction was found between snoring and AHI as predictors of excessive daytime sleepiness (138). One possible explanation of snoring-related daytime sleepiness is the upper airway resistance syndrome (UARS) described by Guilleminault et al. (57, 139). It is characterized by episodes of increased respiratory effort due to the partial collapse of the upper airway, followed by arousals causing daytime sleepiness. Whether UARS constitutes a separate entity or can be regarded as an intermediate phase between snoring and sleep apnea remains unclear.

In our study, we found a clear correlation between EDS and snoring, but no correlation was found with sleep apnea when adjusting for snoring. As this is the first study to our knowledge to show that snoring per se can be an underlying cause of daytime sleepiness in women, it is possible to speculate that these women from the general population are found in the milder part of the sleep-disordered breathing spectrum than most clinical populations.

A dry mouth on awakening is a known symptom of sleep apnea and snoring and is likely to be due to increased breathing through an open mouth (140). When comparing patients with sleep apnea with healthy controls, patients were found to spend significantly more time with their mouths open.
during sleep compared with controls (141). Opening of the mouth was associated with an inferior-posterior movement of the mandible, which reduces the diameter of the pharynx (142) and increases the upper airway collapsibility and respiratory resistance in healthy volunteers (143). This is in accordance with the present study in which a dry mouth on awakening was the only symptom found in both snorers and subjects with sleep apnea.

Systemic inflammation and sleep apnea

Snoring-induced vibrations in the pharynx, and their consequences, are one possible explanation of daytime sleepiness. An increase in interleukin-8 after 12 and 24 hours of vibration applied to cell cultures of human bronchial cells has been shown, indicating that vibrations from the snoring could induce airway inflammation (144).

Obesity, especially visceral/central obesity, increases systemic inflammation (24). However, TNFα and IL-6 have been shown to be elevated in clinical sleep apnea independently of obesity (24), as has the level of CRP (63, 80, 82). Cytokines are involved in sleep regulation and have been shown to be associated with sleepiness and fatigue in men (79). Further, treatment with a TNFα antagonist reduced sleepiness, the level of TNFα and IL-6, as well as the AHI (145). Reducing the number of apneas-hypopneas by means of surgery (64), or CPAP (63, 146, 147) has been shown to lower systemic inflammation, even though this was not found in one study of obese men (148).

In our study, we found an independent correlation between IL-6 and TNFα and markers of hypoxia (% sleep time with an oxygen saturation below 90% and ODI 3% respectively) and not the AHI. This is in line with a study by Yokoe et al. in which IL-6 correlated to the percentage of sleep time with SaO2 < 90% and lowest nocturnal SaO2 but not to apneas (63). It is possible to speculate that this constitutes one of the links between untreated SDB and cardiovascular morbidity, since it has been proposed that intermittent hypoxia during the night gives rise to a reperfusion injury involved in myocardial infarction and stroke (149).

In addition, epidemiological studies have shown an independent relationship between CRP and cardiovascular morbidity. In an eight-year follow-up of 14,700 initially healthy women, CRP added independent prognostic information about the risk of cardiovascular events in addition to characteristics of the metabolic syndrome (74). Further, in 543 healthy men an elevated CRP level predicted cardiovascular disease during an eight-year follow-up when adjusting for known risk factors (not sleep apnea, however) (73).
In the present cohort, daytime sleepiness was related to snoring but not to the AHI. This link does not appear to be the result of an elevation of inflammatory markers since we found no correlation between snoring and inflammation, or between different measures of excessive daytime sleepiness and inflammation when adjusting for confounders (data not shown). It is possible to speculate that there is a dose-response correlation between these entities and that women in our sample constitute a healthier cohort than those found at sleep clinics.
Overall discussion and future work

Who to treat, and why?

In the population, SDB could be regarded as a continuum ranging from snoring without any sleep disturbance, through intermittent airway occlusions causing arousals, to nocturnal apneas causing circulatory, inflammatory, and hormonal disturbances, as well as disturbed sleep (Figure 1).

That patients with apneas during the night causing intermittent hypoxia and fluctuations in blood pressure, and disturbed sleep giving consequences on daytime performance and well-being, should be treated is not controversial. However, when moving along the axis of sleep-disturbed breathing, the cut-off for who to treat, and who not to treat, is not evident. For example, in large epidemiological studies associations between snoring and development of hypertension has been found in both men and women (3, 150). In these studies, the investigated parameter was self-reported snoring and no information was available on the eventual presence of apneas. Further studies with nocturnal PSG have shown that the apnea index is an independent risk factor for hypertension (14, 16, 115, 116). However, no account was taken for if the subjects were habitual snorers or not in these studies. The upper airway resistance syndrome (UARS) where increased respiratory effort due to partial occlusion of the airway causes arousals (without giving rise to apneas), has been shown to cause intermittent elevations of blood pressure (151). Lindberg et al found that sleepy snorers had an increased risk of developing hypertension as apposed to non-sleepy snorers (117, 152), and that excessive daytime sleepiness with or without snoring was a risk factor for diabetes in women (117). This could be interpreted as an indication that the presence of excessive daytime sleepiness is involved in the pathological process. Few studies have investigated the effect of treating sleepy snorers without apneas, but in those who have, a significant improvement in daytime sleepiness after treatment in both genders has been shown (57, 153).

In Paper III we found that self-reported habitual snoring was associated with excessive daytime sleepiness, even when adjusting for AHI. To our knowledge this is the only study where snoring per se is shown to be associated with excessive daytime sleepiness, independent of apneas or hypopneas. In Paper IV we found a correlation between the somnogenic, inflammatory markers IL-6 and TNF$\alpha$ and hypoxic indices of sleep apnea. We failed, however, to find a significant association between signs of systemic inflamma-
tion and snoring without apneas. It is possible to speculate that there is a dose-response relationship between the levels of systemic markers and level of SDB, explaining that in this cohort from the general population no correlation between snoring and inflammation was found.

The future

The complexity of the intricate correlation between (central) obesity, snoring, apneas and desaturations, arousals, excessive daytime sleepiness, inflammation, hypertension, stroke, diabetes and so forth warrants further investigations. Is the correlation of snoring to excessive daytime sleepiness independent of apneas existent in men? In long-time follow up, will sleepy snorers experience an elevated risk for hypertension, diabetes and so forth, independent of the AHI? Will we find elevated levels of inflammatory markers including MPO and lysozyme in clinical populations at sleep laboratories?

Figure 7. Correlation between snoring, apnea-hypopnea index (AHI) and excessive daytime sleepiness (EDS)

The answer to all these questions could help us in evaluating who should be treated for their sleep-disordered breathing, and who does not need any spe-
cial treatment. This is important as we could expect that the increasing prevalence of obesity in the western world increases the prevalence of sleep-disordered breathing in the future.
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References


Frågeformulär inför sömnregistrering

Datum: ........................................... Namn: ..........................................................
Individnr: ........................................... Ålder: ...........................................
Vikt: ........................................... Längd: ...........................................
Civilstånd: ❑ Gift/Sambo ❑ Fränskild ❑ Ensamstående

Ålder: ........................................... Vikt: ...........................................
Längd: ...........................................

Yrke: ........................................... Arbetsuppgifter: ...........................................

Arbetstider: ❑ Bekväma (mån-fre) ❑ Skift/obekväma arbetstider

OM ATT SOMNA OCH ATT SOVA

1. Jag tror att jag behöver sova ca. ............... timmar och ............... minuter per natt.
2. Nu sover jag ungefär ............... timmar och ............... minuter per natt
3. Har Du sömnbesvär? ❑ Ja ❑ Nej

Om ja: Vad tror Du Dina sömnbesvär beror på?:

Inte alls Litet En hel del Mycket Väldigt mycket

a. Värk i kroppen ........................................... 1 2 3 4 5
b. Annan sjukdom ........................................... 1 2 3 4 5
c. Att jag är spänd ........................................... 1 2 3 4 5
d. Oregelbundna tider ........................................... 1 2 3 4 5
e. Stress på jobbet ........................................... 1 2 3 4 5
f. Problem i familjen ........................................... 1 2 3 4 5
g. Nedstämdhet ........................................... 1 2 3 4 5
h. För mycket kaffe ........................................... 1 2 3 4 5
i. För mycket alkohol ........................................... 1 2 3 4 5
j. Medicinffekter ........................................... 1 2 3 4 5
k. Dålig sovrummiljö ........................................... 1 2 3 4 5
l. Att jag snarkar ........................................... 1 2 3 4 5
m. Småbarn ........................................... 1 2 3 4 5

4. Hur ofta:

Aldrig Sällan Ibland Ofta Mycket

a. Snarkar Du högt och störande? .................. 1 2 3 4 5
b. Har Du halsbränna eller sura uppstötningar när Du gått och lagt Dig? .................. 1 2 3 4 5
c. Har Du besvär med krypningar i benen när Du skall somna? .................. 1 2 3 4 5
d. Har Du nästäppa som gör att det är svårt att somna? .. 1 2 3 4 5
e. Använder Du sömmmedicin? .................. 1 2 3 4 5
f. Har personer i Din omgivning påpekat att Du har andningsuppehåll under sömn? .................. 1 2 3 4 5
g. Kastar Du Dig av och an i sängen? .................. 1 2 3 4 5
h. Svettas Du nattetid? .................. 1 2 3 4 5
i. Besväras Du av nästäppa nattetid? .................. 1 2 3 4 5
j. Vaknar Du upp hastigt med en känsla av att inte kunna andas? .................. 1 2 3 4 5
k. Vaknar Du och behöver gå på toaletten för att kissa?. 1 2 3 4 5

(Antal toalettbesök per natt: ..................)

1
5. Hur stora besvär har du med:

<table>
<thead>
<tr>
<th>Besvär</th>
<th>Inga</th>
<th>Små</th>
<th>Måttliga</th>
<th>Stora</th>
<th>Mycket stora</th>
</tr>
</thead>
<tbody>
<tr>
<td>a- att somna på kvällen?</td>
<td>1</td>
<td>2</td>
<td>3</td>
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<td>5</td>
</tr>
<tr>
<td>b- att Du vaknar under natten upprepade gånger?</td>
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<td>2</td>
<td>3</td>
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<tr>
<td>c- att Du vaknar för tidigt och inte kan somna om?</td>
<td>1</td>
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<td>3</td>
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<td>5</td>
</tr>
<tr>
<td>d- sömnen inte gör Dig utvilad?</td>
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<td>2</td>
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<td>4</td>
<td>5</td>
</tr>
<tr>
<td>e- att Du känner Dig sömnig under dagen?</td>
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<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>f- att Du känner Dig trött i kroppen under dagen?</td>
<td>1</td>
<td>2</td>
<td>3</td>
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<td>5</td>
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<tr>
<td>g- koncentrationssvårigheter?</td>
<td>1</td>
<td>2</td>
<td>3</td>
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<td>5</td>
</tr>
<tr>
<td>h- minnessvårigheter?</td>
<td>1</td>
<td>2</td>
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<td>5</td>
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</tbody>
</table>

OM ATT VAKNA

6. Hur ofta:

<table>
<thead>
<tr>
<th>Besvär</th>
<th>Aldrig</th>
<th>Sällan</th>
<th>Ibland</th>
<th>Ofta</th>
<th>Mycket ofta</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Känner Du Dig utvilad när Du vaknar?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
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<tr>
<td>b. Vaknar Du med huvudvärk?</td>
<td>1</td>
<td>2</td>
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<td>5</td>
</tr>
<tr>
<td>c. Vaknar Du och är torr i munnen?</td>
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<td>2</td>
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<td>5</td>
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<tr>
<td>d. Känner Du Dig kraftlös så att Du inte kan röra Dig när Du nyss har vaknat?</td>
<td>1</td>
<td>2</td>
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</table>

OM HUR DU FUNGERAR PÅ DAGEN

7. Hur ofta:

<table>
<thead>
<tr>
<th>Besvär</th>
<th>Aldrig</th>
<th>Sällan</th>
<th>Ibland</th>
<th>Ofta</th>
<th>Mycket ofta</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Somnar Du till ofrivilligt under dagen,</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>t ex vid en paus i arbetet?..................</td>
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<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>b. Somnar Du till när Du kopplar av under</td>
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<tr>
<td>dagen/kvällen, t ex framför TV:n?..........</td>
<td>1</td>
<td>2</td>
<td>3</td>
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<td>5</td>
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<tr>
<td>c. Tappar Du under en kort tid, kraften i</td>
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<td></td>
<td></td>
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<tr>
<td>musklerna i samband med starka känslor?</td>
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<tr>
<td>(gläde, sorg, ilska...)..</td>
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<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>d. Har Du besvär av nästäppa dagtid?.........</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>e. Känner Du Dig lättirriterad?...............</td>
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<tr>
<td>f. Om Du kör bil: Har Du någon gång somnat</td>
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<tr>
<td>eller varit nära att somna när Du kört bil?</td>
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<td>5</td>
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</tbody>
</table>

8. Anser Du att Du pga dagsömnighet:

<table>
<thead>
<tr>
<th>Besvär</th>
<th>Vardag</th>
<th>Helger/Ledighet</th>
</tr>
</thead>
<tbody>
<tr>
<td>a - har svårt att sköta arbetet tillfredsställande?</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>b - att Du undviker att gå bio, teater etc?</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>c - har svårt att umgås med folk?</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

9. Hur mycket av nedanstående dricker Du?

<table>
<thead>
<tr>
<th>Drink</th>
<th>Vardag</th>
<th>Helger/Ledighet</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Kaffe</td>
<td>....... koppar</td>
<td>b. ......... koppar</td>
</tr>
<tr>
<td>c. Te</td>
<td>......... koppar</td>
<td>d. ......... koppar</td>
</tr>
</tbody>
</table>

- $0 = \text{aldrig slumra}$
- $1 = \text{liten risk att slumra}$
- $2 = \text{måttlig risk att slumra}$
- $3 = \text{stor risk att slumra}$

<table>
<thead>
<tr>
<th>Situation</th>
<th>0</th>
<th>1</th>
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<th>3</th>
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</thead>
<tbody>
<tr>
<td>a. Sitter och läser</td>
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<tr>
<td>b. Tittar på TV</td>
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<tr>
<td>c. Sitter överksam på allmän plats (t ex teater eller ett möte)</td>
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<tr>
<td>d. Som passagerare i en bil i en timme utan paus</td>
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<tr>
<td>e. Ligger ner och vilar på eftermiddagen om omständigheterna tillåter...</td>
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<tr>
<td>f. Sitter och pratar med någon</td>
<td></td>
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<tr>
<td>g. Sitter stilla efter att ha ätit lunch (utan alkohol)</td>
<td></td>
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</tr>
<tr>
<td>h. I en bil som stannat några minuter i trafiken</td>
<td></td>
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</tr>
</tbody>
</table>

11a. Har Du periodvis upplevt behov av att röra på ena/bägge benen pga. spontant uppkomen obehagskänsla i benet/benen? 
- a. Aldrig eller mindre än en gång per månad
- b. Mindre än en gång i veckan
- c. Under 1-2 nätter per vecka
- d. Under 3-5 nätter per vecka
- e. Varje natt eller nästan varje natt

11b. Har Du svårt att vara helt stilla med benet/benen när besvären uppstår? ..
- a. Förvärras eller uppstår dessa symtom enbart i vila, medan aktivitet ger åtminstone delvis eller tillfällig lindring? ..
- b. Förvärras dessa symtom kvälls- och nattetid? ..
- c. Har Du några problem med värk och stelhet i leder och muskulatur som stör sömnen?

12. Snarkar Du när Du sover (fråga andra personer om Du inte är säker)?
- a. Aldrig eller mindre än en gång per månad
- b. Mindre än en gång i veckan
- c. Under 1-2 nätter per vecka
- d. Under 3-5 nätter per vecka
- e. Varje natt eller nästan varje natt

13. Hur snarkar Du (fråga andra personer om kvalitén på Din snarkning)?
- a. Jag snarkar inte
- b. Min snarkning låter regelbunden och den är av låg volym
- c. Det låter regelbundet men ganska högt
- d. Det låter regelbundet men det är väldigt högt (andra människor hör min snarkning i nästa rum)
- e. Jag snarkar väldigt högt och oregelbundet (det är tysta andningspauser då snarkning ej hörs och stundvis väldigt höga frustningar med häftiga andetag)
14. Har Du haft andningsuppehåll (sömnapné) under sömn (har andra människor lagt märke till att Du har pauser i andningen när Du sover)?
   □ a Aldrig eller mindre än en gång per månad
   □ b Mindre än en gång i veckan
   □ c Under 1-2 nätter per vecka
   □ d Under 3-5 nätter per vecka
   □ e Varje natt eller nästan varje natt

15. Om Du snarkar minst 1-2 gånger per vecka, hur många år har Du snarkat?
   a) Jag har snarkat i ungefär _______år. b) Jag var omkring _______ år gammal när jag började snarka.

16. Hur dags går Du vanligtvis och lägger Dig (för att sova)?
   a. under arbetsvecka: kl_______
   b. under lediga dagar: kl_______

17. Hur dags vaknar Du vanligtvis?
   a. under arbetsvecka: kl_______
   b. under lediga dagar: kl_______

18. Har Du upplevt att Du fått för lite sömn under de senaste tre månaderna?
   □ a Aldrig eller mindre än en gång i månaden
   □ b Mindre än en gång i veckan
   □ c Under 1-2 dagar per vecka
   □ d Under 3-5 dagar per vecka
   □ e Dagligen eller nästan dagligen

19. Hur ofta tar Du en tupplur under dagtid?
   □ a Aldrig eller mindre än en gång per månad
   □ b Mindre än en gång i veckan
   □ c Under 1-2 dagar per vecka
   □ d Under 3-5 dagar per vecka
   □ e Dagligen eller nästan dagligen

20. Om Du tar en tupplur, hur lång brukar den vanligtvis vara?
   Mina tupplurar varar vanligtvis omkring (a)______ timmar (b)______ minuter

21. Hur många timmars sömn behöver Du per natt (hur många timmar skulle Du sova om Du hade möjlighet att sova så länge Du behöver)?
   Jag behöver (a)______ timmar och (b)______ minuter sömn per natt.

22a. Har Du någonsin sökt läkare pga snarkningar eller dagsömnighet?  Ja □ Nej □
22b. Om ja: När?____________________________________________________________
22c. Vilken undersökning/utredning gjordes? _______________________________
   __________________________________________________________
22d. Var gjordes detta?_________________________________________________
22e. Fick Du någon behandling?  Ja □ Nej □
22f. Om ja, vilken behandling? 

22g. Blev Du bättre av behandlingen? 

Ja ☐ Nej ☐

Tack för din medverkan!
Frågeformulär Luftvägssjukdomar

1. Har Du haft pip eller väsningar i bröstet vid något tillfälle under de senaste 12 månaderna? Ja □ Nej □

OM "NEJ" HOPPA TILL FRÅGA 2, OM "JA":

1.1 Har Du överhuvudtaget varit det minsta andfådd när Du haft pip eller väsningar i bröstet? Ja □ Nej □

1.2 Har Du haft detta pip eller väsande i bröstet när Du inte samtidigt varit förkyld? Ja □ Nej □

2. Har Du vaknat med en trånghetskänsla i bröstet vid något tillfälle under de senaste 12 månaderna? Ja □ Nej □

3. Har Du vaknat av anfall av andnöd vid något tillfälle under de senaste 12 månaderna? Ja □ Nej □

4. Har Du vaknat av en hostattack vid något tillfälle under de senaste 12 månaderna? Ja □ Nej □

5. Har Du haft något astma-anfall under de senaste 12 månaderna? Ja □ Nej □

6. Använder Du för närvarande någon medicin (spray, inhalationspulver eller tabletter) mot astma? Ja □ Nej □

7. Har Du under de senaste åren besvärats av långvarig hosta? Ja □ Nej □

8. Brukar Du hosta upp slem, eller har Du slem i bröstet som Du har svårt att få upp Ja □ Nej □

OM "NEJ" HOPPA TILL FRÅGA 9, OM "JA":

8.1. Får Du upp slem på det här viset nästan varje dag under åtminstone tre månader varje år? Ja □ Nej □

8.2. Om ja hur gammal var Du när dessa besvär började __________ år

8.3. Har Du haft sådana perioder under minst två år i följd? Ja □ Nej □

9. Har Du eller har Du haft astma? Ja □ Nej □

10. Har Du av läkare fått diagnosen astma? Ja □ Nej □

11. Hur gammal var du när du första gången hade astmabesvär? ________________ år

12. Vilket år hade Du senast astmabesvär? År _____________

13. Har Du hösnuva eller någon annan allergisk snuva? Ja □ Nej □

**OM "NEJ" HOPPA TILL FRÅGA 15, OM "JA":**

14.1 Vilken typ av näsbesvär har Du?

- Nästäppa ☐ Ja ☐ Nej ☐
- Snuva ☐ Ja ☐ Nej ☐
- Nysningar ☐ Ja ☐ Nej ☐
- Klåda ☐ Ja ☐ Nej ☐
- Nedsatt luktsinne ☐ Ja ☐ Nej ☐

14.2 Om JA hur gammal var Du när Du märkte det första gången? _________ år


- Vår ☐
- Sommar ☐
- Höst ☐
- Vinter ☐
- Alltid ☐
- Vet ej ☐

14.4 Vilket år hade Du senast näsbesvär? År__________

14.5 Hur ofta har Du haft näsbesvär under de senaste 12 månaderna?

- Dagligen/flera gånger per vecka ☐
- Några gånger per vecka ☐
- Några gånger per månad ☐
- Mera sällan ☐
- Inga besvär sista 12 månader ☐

15. Får Du näsbesvär (nästäppa, nysningar eller dylikt) vid exponering för

- Damm ☐ Ja ☐ Nej ☐
- Rödvin/alkohol ☐ Ja ☐ Nej ☐
- Kyla ☐ Ja ☐ Nej ☐
- Blåst ☐ Ja ☐ Nej ☐
- Starka dofter ☐ Ja ☐ Nej ☐
- Viss mat ☐ Ja ☐ Nej ☐
- Tobaksrök ☐ Ja ☐ Nej ☐
- Acetylsalicylsyra ☐ Ja ☐ Nej ☐

16. Är Du opererad i näsan för

- Sned nässkiljevägg/näsbrosk ☐ Ja ☐ Nej ☐
- Polyper i näsan (i vuxen ålder) ☐ Ja ☐ Nej ☐
- Annan näsoperation ☐ Ja ☐ Nej ☐

17. Använder Du någon medicin för näsbesvär? Ja ☐ Nej ☐

17.1 Om JA; vilken medicin? (namn):____________________________________________

**TACK FÖR DIN MEDVERKAN!**
FRÅGOR OM HORMONBEHANDLING, MENSTRUATION MM

1. Behandlas Du med kvinnligt könshormon (östrogen-behandling)  □ Ja  □ Nej

   Om ja:
   1a) Hur länge hade mensliknande blödningar varit borta när Du började med
       östrogen/hormonbehandling? ____________________ månader.

   1b) När startade Du med hormonbehandlingen?
       År:_________ Mån:_________

   1c) Vad heter hormonpreparatet?______________________________________

   1d) Vilken dosering tar Du? (Styrka på medicinen och hur ofta den tas)

________________________________________________________________________

2. Har Du tidigare haft östrogenbehandling?  □ Ja  □ Nej

   Om ja:
   2a) Vad hette preparatet?_________________________________________

   2b) Hur länge behandlades Du?_____________________________________

   2c) När slutade Du med behandlingen?
       År:_________ Mån:_________

Om Du EJ har hormonbehandling:

3. När hade Du senaste mensliknande blödning? År:_______ Mån:_______ Dag:_______

4. Ungefär hur många gånger har Du haft mens senaste halvåret? ____________ gånger

5. Ungefär hur många gånger har Du haft mens senaste året? _________________gånger.

6. Har Du besvär av typ ”övergångsbesvär?”  □ Ja  □ Nej

   Om ja; Vilken typ av besvär? (Ange med ett kryss på skalan hur stora besvär Du
   har av respektive symtom:

   6a) Blodvallningar  □ Ja  □ Nej

       __________ ggr/dygn

       Mycket
       lindriga
       besvär

       |-----------------|-----------------|
       Mycket
       svåra
       besvär
6b) Svettningar

☐ Ja  ☐ Nej

________ ggr/dygn

Mycket lindriga besvär

______________

Mycket svåra besvär

6c) Irritabilitet

☐ Ja  ☐ Nej

Mycket lindriga besvär

______________

Mycket svåra besvär
Individnr: __________________

FRÅGEFORMULÄR VID SÖMNUNDELSÖKNING

Namn: ________________________________________ Datum nattreg: ________________

Födelseland: _________________________________________________________________

Födelseland mor: _________________________ Födelseland far: _________________________

1a. Går Du på läkarkontroller pga högt blodtryck? Ja ☐ Nej ☐

1b. Om ja: För hur många år sedan fick Du första gången veta att Du har högt blodtryck?

1c. I hur många år har Du ätit medicin för högt blodtryck? ____________ år.

1d. Om nej: Har Du någonsin haft högt blodtryck? Ja ☐ Nej ☐

2a. Har Du någonsin haft hjärtinfarkt? Ja ☐ Nej ☐

2b. Om ja: Vilket/vilka år?___________________________________________________

2c. Var Du inlagd på sjukhus? Ja ☐ Nej ☐

2d. Vilket sjukhus?___________________________________________________

3a. Har Du hjärtsvikt? Ja ☐ Nej ☐

3b. Om nej: Har Du någonsin haft hjärtsvikt? Ja ☐ Nej ☐

3c. Om ja: När?___________________________________________________________

3d. Vårdades Du på sjukhus? Ja ☐ Nej ☐

3e. Vilket sjukhus/Vilken vårdcentral?____________________________________

4a. Har Du någonsin haft kärlkramp i bröstet? Ja ☐ Nej ☐

4b. Om ja: Har Du kärlkramp? Ja ☐ Nej ☐

4c. Om ja: Hur ofta har Du besvär? (Kan kryssas i flera alternativ)

☐ Vid tyngre ansträngning som joggning eller snöskottning.

☐ Vid gång i trappor och uppförsbackar.

☐ Vid gång på plan mark.

☐ I vila, t.ex. när ser på TV.

☐ Har även besvär nattetid.

4d. Har Du genomgått kärlkramsooperation (by-pass-operation)? Ja ☐ År _______ Nej ☐

4f. Har Du genomgått "ballongsprängning" av kranskärl (PTCA)? Ja ☐ År _______ Nej ☐

5a. Har Du någon lungsjukdom? Ja ☐ Nej ☐

5b. Om ja: Vilken?_______________________________________________________

1
6a. Har Du haft stroke (Hjärnblödning/propp i hjärnan)?  
Ja ☐  Nej ☐

6b. Om ja:  
Vilket/vilka år?

6c. Var Du inlagd på sjukhus?  
Ja ☐  Nej ☐

6d. Vilket/vilka sjukhus?

6e. Restsymtom?

7a. Har Du diabetes (sockersjuka)?  
Ja ☐  Nej ☐

7b. Om ja:  
Hur gammal var Du när Du fick diabetes?  
__________________________ år.

7c. Vilken behandling har Du mot diabetes?  
☐ Endast kostbehandling  
☐ Tablettbehandling  
☐ Insulinbehandling  
☐ Både tablett- och insulinbehandling

7d. Om Du inte har diabetes, har Du tidigare vid något tillfälle haft förhöjt blodsocker som krävt extra läkarkontroller (t.ex. i samband med graviditet eller kortisonbehandling)?  
Ja ☐  Nej ☐

8a-g. Går Du på regelbundna läkarkontroller pga några andra sjukdomar, i så fall vilka?

9. Vilka mediciner tar Du för närvarande?

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<thead>
<tr>
<th>Medicin</th>
<th>Styrka</th>
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<th>Sen år</th>
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2
10a. Har Du någonsin rökt dagligen under minst 6 månader?  
   JA □  NEJ □

10b. **Om ja:** Hur gammal var Du när Du började röka?  
    ____________ år.

10c. Röker Du för närvarande? 
    JA □  NEJ □

10d. **Om nej, när slutade Du?**  
    År ____________

10e. Om Du röker cigaretter, eller om Du rökte cigaretter innan Du slutade röka,  
    hur många cigaretter röker/rökte Du per dag?  
    CA__________ cig/dag.

10f. Om Du röker/rökte pipa, hur många dagar räcker/räckte ett 50-grams tobakspaket?  
    ______________ dagar.

11a. Har Du någonsin snusat dagligen under minst 6 månader?  
    JA □  NEJ □

11b. **Om ja:** Snusar Du fortfarande?  
    JA □  NEJ □

11c. Om Du fortfarande snusar, ungefär hur länge räcker en 50 g -dosa?  
    ______________ dagar.

12. **Använder Du tuggtobak, nikotinplåster eller nikotintuggummi?**  
    JA □  NEJ □


☐ Du ägnar Dig mestadels åt läsning, TV, bio eller annan stillasittande sysselsättning på fritiden.

☐ Du promenerar, cyklar eller rör Dig på annat sätt under minst fyra timmar i veckan. I detta räknas också gång eller cykling till eller från arbetet samt söndagspromenader, ordinärt trädgårdsarbete, fiske, bordtennis, bowling.

☐ Du ägnar Dig åt t.ex. löpning, simning, tennis, badminton, morgongymnastik eller liknande, som motionssport. Tyngre trädgårdsarbete och liknande räknas till denna grupp. Observera att det skall vara i genomsnitt minst tre timmar i veckan.

☐ Du ägnar Dig år hård träning och tävling i löpning, orientering, skidåkning, simning, fotboll, handboll etc. regelbundet och flera gånger i veckan.

14. Om det skulle behövas för undersökningen, får vi lov att beställa journalkopior från sjukhus och eller vårdcentral för de vårdtillfällen Du angivit i Dina svar här?  
    JA □  NEJ □

Namnunderskrift:_____________________________________________________________________________
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