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Snoring and Sleep Apnea

A Study of Evolution and Consequences in a Male Population

Minireview based on a doctoral thesis

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INTRODUCTION

Historical aspects

Interest in sleep and dreams has existed since the dawn of history. Aristotle, Hippocrates, Freud and Pavlov all attempted to explain the physiological and psychological bases of sleep and dreaming. In spite of this, until this century and with few exceptions, sleep was universally regarded as an inactive state of the brain. This can be exemplified by the definition of sleep from 1834, "Sleep is the intermediate state between wakefulness and death; wakefulness being regarded as the active state of all the animal and intellectual functions, and death as that of their total suspension" (1).

One of the most critical turning points in sleep research took place in 1928 when the German psychiatrist Hans Berger recorded electrical activity of the human brain and discovered differences in these rhythms when subjects were awake or asleep (2). During the 1950s, rapid eye movement (REM) sleep, or dream sleep, was described. When convincing evidence was provided that the brain is very active during REM sleep, certain areas being even more active than during wakefulness, the notion of sleep as a passive process was totally abolished (3).

In the early 1970s some sleep disorder clinics started to use respiratory and cardiac sensors routinely in their all-night sleep studies. This gave rise to new possibilities to study sleep and sleep disorders and since then the all-night diagnostic test has been known as polysomnography. Polysomnography is now the golden standard test for quantifying sleep and for assessing abnormal physiological events in sleep - such as sleep apnea, periodic movements, electroencephalographic abnormalities and arousals.

Inadequate or poor sleep can result in drowsiness and impaired alertness and cognitive ability, reducing productivity on the job and increasing the opportunity for human error and fatigue-related accidents (4-6). During the last decade, there has been an increasing awareness of the

health and economic consequences of sleep deprivation and poor sleep quality (7-9).

Obstructive sleep apnea syndrome (OSAS) is sometimes called the leading sleep disorder of the twentieth century. It was discovered independently by a French and a German group in 1965 (10, 11). In retrospect, however, there are other descriptions in the literature in which the characters have probably suffered from OSAS (12, 13). The most well-known of them is perhaps Joe, a fat boy with loud snoring, excessive sleepiness and probably right-sided heart failure, described by Charles Dickens in the novel *The Posthumous Papers of the Pickwick Club* in 1837 (14).

Even though it was described far earlier, it was not until the last 20 years that interest in OSAS as an important medical disorder increased markedly. This was a result of the development of more simple and sophisticated instruments for diagnosing OSAS and more effective and well-tolerated treatments. The recently discovered high prevalence of OSAS in the population, actually reaching the prevalences of diseases such as diabetes and asthma among middle-aged people, further accelerated the intensity of research within this field. As a consequence, snoring has achieved a totally new status, being elevated from a harmless social nuisance to an important clinical symptom (Figure 1).

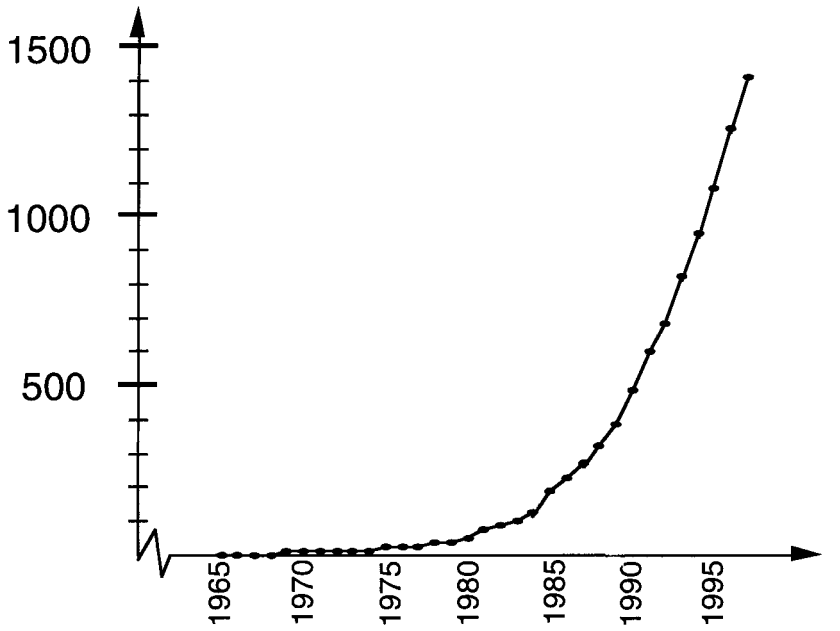


Figure 1.
Cumulative number of medical journal articles on "snoring". Result of computerised search of Medline for the period 1965 - 1997.

Our knowledge of the impact of snoring and OSAS on public health is, however, still limited. This is an issue which is currently being discussed, where opinions range from an impact on the health and welfare of our society which rivals that of smoking (15) to no effect (apart from sleepiness) when age and obesity are taken into account (16).

Sleep-disordered breathing

Sleep-disordered breathing includes a wide range of conditions linked by narrow upper airways and the loss of normal respiration patterns during sleep. At one end of the spectrum, there are subjects with intermittent partial obstruction of the upper airways giving rise to snoring without fragmentation of sleep and no daytime symptoms ("simple snorers"). In more advanced cases, the condition is characterized by repetitive airflow cessations leading to hypoxemia, frequent arousals and fragmented sleep (OSAS). The most severe form is a condition previously often referred to as the Pickwickian syndrome, with obesity and frequent apneas during sleep separated only by short periods of effective ventilation with loud snoring. In these severe cases, the sleep is dramatically fragmented with extreme daytime hypersomnolence, accompanied with hypoventilation and awake respiratory failure, pulmonary hypertension and heart failure (11, 17).

Definitions

Snoring

Snoring is the well-known sound generated by the vibrations of partially collapsed and unstable pharyngeal airway walls and the soft palate. However, even though everyone knows what snoring is, there is still uncertainty about how to define it and there is no standard and uniformly accepted technique for the objective measurement of it (18). Measurements of snoring are still not performed routinely during nocturnal polysomnography.

In epidemiological studies, the most frequently used method for estimating snoring is by questionnaires. Even within this field, there are frequent methodological differences which make it difficult to compare the results of different studies. As there is no "golden standard" for objective measurements, the validation of such questionnaires remains a problem. In most of the validated questionnaires which have been described in literature, the validation did not deal with objectively measured snoring sounds but with their usefulness as a predictor of sleep apnea (19, 20). Due to the uncertainty of the definition, the use of identical questionnaires is necessary to enable adequate comparisons between populations or for changes with time.

To standardize the questionnaires used in the Nordic countries, a task group set up by the Scandinavian Sleep Research Society drew up the Basic Nordic Sleep Questionnaire (BNSQ) in 1995 (21).

Apneas, hypopneas

Pauses in breathing are often regarded as the most important feature of sleep apnea. An apnea is defined as a cessation of airflow for at least 10 seconds (22). The definition of hypopneas varies a great deal (23). However, it is most frequently defined as a 50% reduction in airflow and there is often a requirement for simultaneous oxygen desaturation and/or arousal to fulfil the criteria for hypopnea. In general, apneas and hypopneas are classified as central, obstructive, or mixed. During an obstructive apnea, the ventilatory drive is maintained, but, despite increasing respiratory efforts, no air can pass to the lungs due to upper airway occlusion. In contrast, central apneas occur as a result of an absence of neural output from the respiratory centres of the brainstem, which leads to a lack of inspiratory effort (Figure 2). In mixed apneas, there is a cessation of airflow and an absence of respiratory effort early in the episode, followed by the resumption of unsuccessful respiratory effort in the latter part of the episode (24). Central sleep apnea is a much more rarely observed condition in the sleep laboratories. In the following text, sleep apnea only refers to obstructive events.

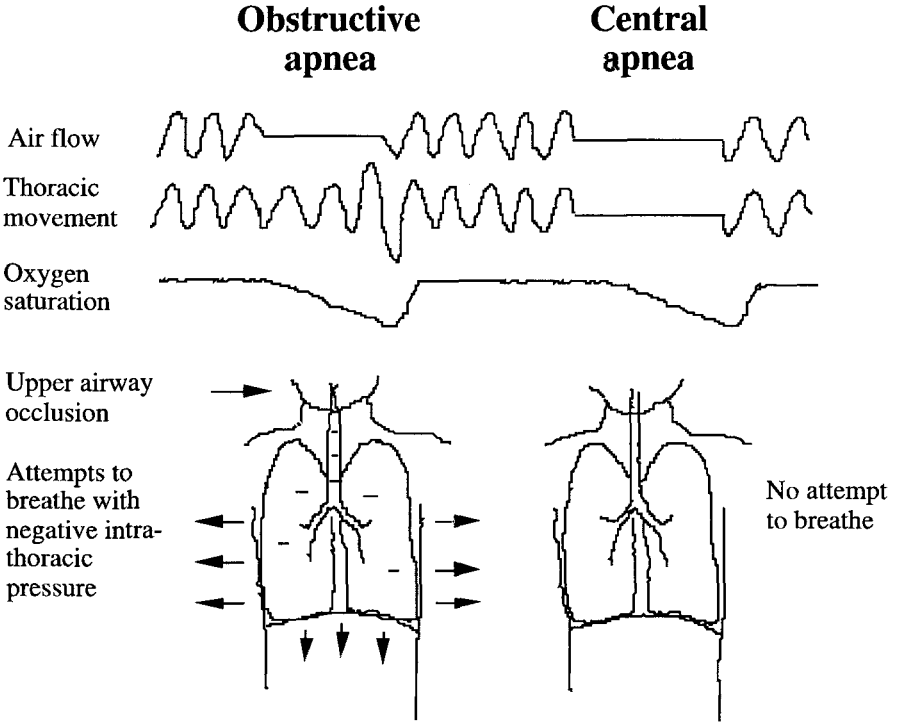


Figure 2.
Mechanisms in obstructive and central apneas.

Apnea-hypopnea index (AHI)

It is general accepted that a small number of apneas and hypopneas during the night is normal, while a large number is pathological. To measure the severity of sleep apnea, an index is calculated for the mean number of apneas and hypopneas during one hour of sleep, the apnea-hypopnea index (AHI). The existence of an increased AHI is called obstructive sleep apnea (OSA). Since the early 1970s, the central question "How many apneas during sleep are normal?" has been discussed. On the basis of the results from healthy, non-obese and mainly young volunteers and adult sleep-disorder patients, Guilleminault and Dement defined the upper limit of normality as an AHI of 5 (25), a cut-off point which is still commonly used to indicate pathology. However, a high prevalence of AHI > 5 has been found in elderly populations (26, 27) and cut-off points of AHI 10, 15 and even 20 have been proposed (28).

Obstructive sleep apnea syndrome (OSAS)

At the State of the Art Conference held by the Swedish Medical Research Council in 1993, the definition of OSAS as "intermittent, complete or partial, upper airway obstruction during sleep causing mental and/or physical effects" was adopted (29, 30). This definition emphasizes the fact that there are consequences of the breathing disturbances during sleep.

When apneas and hypopneas occur, they are frequently followed by short arousals. This leads to the sleep becoming fragmented (31), resulting in excessive daytime sleepiness (EDS), which, apart from snoring, is the most commonly reported symptom. Nocturnal awakenings, excessive sweating at night and morning headache are other frequent complaints. Nycturia is commonly reported and some patients even present with enuresis (32) due to the increased release of atrial natriuretic peptides (ANP) (33). Cognitive impairment and psychosocial consequences were first reported in patients with severe OSAS (34, 35). However, even in less severe cases, impairment in cognitive function can be seen, as well as irritability and memory problems. The result of a recent study suggested that an AHI of 15 was equivalent to a decrement in psychomotor efficiency associated with five additional years of age (36). The cognitive function improves at an early stage when the sleep disorder is treated (37).

Erectile problems are common in OSAS patients and a high prevalence of OSA has been reported in patients with erectile dysfunction (38). When sleep apnea is successfully treated, relieved erectile dysfunction occurs in about one-third of the patients (39).

Upper airway resistance syndrome (UARS)

More recently, UARS has been described; this is a syndrome characterized by the need for increased effort to breathe and micro-arousals but no prominent

apneas or hypopneas (40). The patients, most often snorers, suffer from excessive daytime sleepiness and are immediately improved by nCPAP therapy. Whether UARS is a specific entity or an intermediate state between simple snoring and OSAS is not clear.

Pathogenesis

Both snoring and apneas are manifestations of a sleep-induced increase in upper airway resistance. The patency of the trachea and bronchi is maintained by cartilaginous support and the patency of the smaller intrapulmonary airways is maintained by the elastic recoil properties of the surrounding lung parenchyma. In contrast, the patency of the upper airway depends critically on the action of its dilator muscles. During sleep, the tone of the upper airway muscles and their reflex response to the subatmospheric airway pressures generated during inspiration are reduced (41, 42). It appears that a certain combination of upper airway structure and function distinguishes non-apneic non-snorers (large airway area, low airway compliance) from non-apneic snorers (smaller airway area, higher airway compliance) and from patients with fully developed sleep apnea (smallest airway area, highest airway collapsibility) (43). Predisposing factors include structural narrowing as a result of tonsillar hypertrophy, hyperplasia of the upper airway soft tissue, retrognathia or micrognathia. Other etiological conditions are somatic diseases which influence the upper airway properties, such as acromegaly (44) and hypothyroidism (45).

Compared with non-snorers, heavy snorers and patients with OSAS have histopathological changes in their soft palate (46). Friberg et al. recently reported a progressive neurogenic lesion in an upper airway muscle in patients with different degrees of upper airway obstruction, including non-apneic heavy snorers. The authors suggested that these findings could be explained by mechanical trauma resulting from heavy snoring, indicating the progressive nature of snorer's disease (47).

When an apnea is finally terminated by a brief awakening or arousal seen on the electroencephalography, airway patency is restored. After a few deep breaths, the patient returns to sleep and the cycle of events is repeated, sometimes 200-400 times during one night of sleep.

The exact causal mechanism which makes apneas give rise to arousals is not clear. Intermittent nocturnal hypoxemia during nCPAP treatment for OSAS does not diminish the objective improvement in daytime somnolence seen with nCPAP treatment in the absence of nocturnal hypoxemia, thereby indicating that hypoxia alone does not disrupt sleep (48).

A significant correlation has been found between daytime sleepiness and respiratory effort during apneas when evaluated by measuring esophageal pressure swings using an esophageal balloon (49). Furthermore, in studies performed on young healthy men during full-night sleep studies, the results

indicated that the increasing ventilatory effort is the stimulus to arousal rather than arterial chemistry (hypoxia or hypercapnia) (50). Whether these results are applicable to older patients with OSAS remains to be clarified.

Prevalence

The prevalence of snoring is strongly dependent on its definition, as well as on the age and gender of the studied population. On the basis of epidemiological studies, 9 to 50% of men and 4 to 17% of women report habitual snoring (51-57).

Only 10-15 years ago, OSAS was still regarded as an extremely rare disorder. Previous estimates have established that 300-900 polysomnographic studies are needed in a non-selected population if the prevalence of OSAS is 1-3% and a standard error one-third that size is considered acceptable (58). In studies performed in at least two stages with a screening procedure followed by polysomnographic recordings in a small number of subjects, the obtained lower limit of OSAS prevalence has been 0.3-2.7% in men (59-63) and 1.1-2.5% in women (56, 63).

In 1993, Young et al. reported the results of the most extensive prevalence study performed within this field so far. In a random sample of state employees aged 30-60, a two-stage sampling procedure was used and polysomnography was performed in not less than 602 subjects. In this American, middle-aged, working population, the estimated prevalence of sleep-disordered breathing, defined as an AHI of $\geq$ 5, was 9% for women and 24% for men. The minimal diagnostic criterion for OSAS was an AHI of $\geq$ 5 and daytime hypersomnolence. This criterion was fulfilled by 2% of the women and 4% of the men (64).

Risk factors

Male gender

Regardless of the definition which is used for snoring, all the studies including both genders, report a higher prevalence of snoring in men than in women (52-54, 57, 65).

In clinical populations, approximately 90% of patients with diagnosed OSAS are men (66, 67). However, in population-based studies, the ratio of men:women with OSAS is about 2:1 (63, 64). The reason for this male predominance is not exactly clear. Possible explanations include the effects of hormonal influences affecting upper airway muscles and collapsibility (68, 69), gender differences in the distribution of body fat and differences in pharyngeal anatomy and function. In women, the menopause is followed by an increase in the prevalence of OSAS and a protective effect by progestin and estrogen when it comes to the development of OSAS has been suggested (70).

Age

The prevalence of snoring increases with age (53, 71, 72). However, in some studies in which older subjects have also been included, a decline in the prevalence of snoring has been reported after the age of 50-60 (54, 62, 73).

The prevalence of OSAS has also been found to increase with age (74). It has further been observed, on the basis of laboratory criteria alone, that older people have a greater prevalence of sleep apnea than the young (27, 75). In contrast, in clinical populations with OSAS based on sleep laboratory criteria plus clinical findings, the age distribution is not monotonic (66). In a recent population-based study of the prevalence and severity of OSAS in men aged 20-100 years, Bixler et al. found that the prevalence of sleep apnea tended to increase with age. On the other hand, the maximum prevalence of OSAS, defined as an AHI of $\geq$10 *and* the presence of daytime symptoms, was in the middle age group aged 45 to 64. Furthermore, within given levels of AHI, the severity of sleep apnea, measured as minimum oxygen saturation, decreased with age. The authors concluded that, even though the number of apneas increases with age, the clinical significance (severity) of apnea decreases (75).

Obesity

There is no question that obesity is a major risk factor for snoring and sleep apnea (52, 71, 73, 76, 77). The distribution of adipose tissue is important as central obesity with increased neck circumference explains most of the link between obesity and sleep apnea (78-80).

Obesity is believed to predispose to OSAS because of mass loading the upper airway of the neck (81). However, in 1,464 males investigated by Grunstein et al., waist circumference was a better predictor of sleep apnea than neck circumference or BMI, suggesting that the link between obesity and sleep apnea cannot be explained solely by neck fat deposition (74). Despite the important relationship with obesity, it is important to remember that not all subjects with obesity or with fat necks suffer from sleep apnea (79, 82) and that about one-third of OSAS patients are non-obese.

Smoking

An association between smoking and snoring has been found in a number of cross-sectional epidemiological surveys (54, 57, 71, 73, 83, 84). In an Australian population where snoring was monitored in 294 men, smokers snored for 41% of the night on average compared with 31% of non-smokers (77). Wetter et al. found a dose-response relationship between smoking and sleep-disordered breathing, while former smoking was unrelated to snoring as well as the AHI (85).

Even though it seems clear that smoking is a risk factor for snoring and sleep apnea, Schrand has hypothesized that sleep apnea might be a

predisposing factor for tobacco use since nicotine reduces the symptoms of daytime sleepiness and helps to avoid weight gain (86).

Alcohol

In studies performed in the laboratory, alcohol increases both the number of apneas as well as the duration of apnea (87, 88). When the relationship between alcohol and snoring or sleep-disordered breathing has been analysed in epidemiological studies, the results have diverged as an association has been found by some (71, 76) but not by others (54, 73, 77, 89).

Physical inactivity

In most studies designed to study the prevalence of snoring, physical activity has not been taken into account. However, in a Finnish study by Koskenvuo et al., men with a reported low level of physical activity had a higher prevalence of snoring which could not be explained by age or obesity (76).

Evolution

Despite the extensive literature that currently exists on sleep-disordered breathing, most studies have been cross-sectional in design and our knowledge of the natural evolution of this disease is still limited.

In the first report on the incidence and remission of habitual snoring, Honsberg et al. studied the population in the Tucson Epidemiologic Study of Obstructive Airway Disease. Of an original sample of 3,714 men and women aged 18 or more, 1,476 answered the question about snoring at baseline and at the follow-up approximately six years later. The authors reported an habitual snoring cumulative incidence rate of 10.5% and an habitual snoring cumulative remission rate of 35.5% during the follow-up period. In the whole population, the prevalence of habitual snoring increased from 10.7% to 14.3% between baseline and follow-up. Multivariate analysis revealed male sex, repiratory symptoms and obesity as independent risk factors for the incidence of habitual snoring. No significant influence was found for age, smoking and the use of alcohol and/or medication as sleeping aids. In contrast, significant predictors of remission in habitual snoring were age older than 65 years, not being obese and the absence of respiratory symptoms. When males were analysed separately, the only predictor of remission in snoring was older age (90).

In patient populations, OSAS is most commonly diagnosed among subjects in the fifth to seventh decades of life. However, sleep apnea patients often report a history of loud snoring and excessive daytime sleepiness which may precede the diagnosis of sleep apnea by many years or decades (66, 91). On the basis these results, Lugaresi and coworkers proposed that OSAS is a progressive disease which begins with simple snoring and continues to OSAS of increasing severity (91).

In the few studies performed to evaluate the outcome of untreated OSAS patients, the theory that OSAS is a progressive disease has been supported by two (92, 93), while the result of one indicated that OSAS is stable with time (94). In 42 patients with mild to moderate OSAS screened with oximetry, followed after at least six months by polysomnography, Svanborg et al. found an increase in the desaturation index of $\geq$ 50% in 62% of the patients (92). Pendlebury et al. performed full polysomnography on 55 patients with moderate OSAS. No interventional treatment was given and, after a mean interval of 77 weeks, the mean AHI had increased from 21.8 to 33.4 (93). In contrast, Sforza et al. reported that in 32 patients with more severe OSAS (mean AHI 52.2), no significant changes in apnea frequency were found at a follow-up at least five years later (94). However, in their subgroup of seven patients who had deteriorated (increase in AHI of more than 35% from baseline), the AHI at baseline was significantly lower than in the group which had improved (mean 14.1 v. 56.3, $p<0.001$).

Consequences of sleep-disordered breathing

Even in the absence of apneas, daytime sleepiness and morning headache are more common among snorers than among non-snoring individuals (95, 96). As a result of excessive daytime sleepiness (EDS), snoring has also been found to be highly associated with subjective work performance problems (97).

Accidents

In addition to impairing quality of life (98), EDS increases the risk of accidents, such as motor vehicle accidents (99). Compared with controls, OSAS patients perform less well in simulated driving tests, some even worse than control subjects impaired by alcohol (100). OSAS patients are involved in automobile accidents two to three times more often than the general population (101). With an estimated prevalence of 1% of OSAS in the adult driving population in the United States alone 38,800 accidents a year could potentially be prevented if these impaired drivers were identified and treated (99).

Significant improvements in driving performance have been reported after the treatment of OSAS (102, 103). Since 1996, Swedish drivers with untreated sleep-disordered breathing have not been allowed to retain their driving licence.

Cardiovascular consequences

In patients with coronary heart disease (CHD) and sleep apnea, the CHD can be aggravated by insufficient arterial oxygen supply due to cumulative phases of apnea and hypoventilation. Franklin et al. reported that of 10 consecutive patients suffering from nocturnal angina, nine were found to have OSA. Their angina, as well as the number of objectively measured myocardial

ischaemic events, was improved during the treatment of sleep apnea by nCPAP (104).

In patients with CHD, bradyarrhythmias have been found to correlate with apnea activity (105). Effective treatment of the apneas eliminates these apnea-associated arrhythmias (106-108).

Analysing whether snoring and OSAS are a cause of cardiovascular disease is more complicated since many of the known risk factors for OSAS are important health risks *per se*. When OSAS is not considered, central obesity is associated with an increased risk of myocardial infarction, stroke, hypertension and diabetes (109, 110).

Previous surveys in which the association between sleep-disordered breathing and cardiovascular disease have been investigated have mainly been designed in three different ways:

a) Epidemiological cross-sectional studies investigating the prevalence of snoring and/or OSA and its relationship with concomitant diseases,
b) Case-control studies analysing the prevalence of OSA in patients with cardiovascular disease and healthy controls
c) Case-control studies in which a history of snoring has been compared in patients with cardiovascular disease and controls.

In a number of these studies, significant associations have been reported between sleep-disordered breathing and cardiovascular disease. However, the results have not been conclusive.

Hypertension

As early as 1978, Lugaresi and coworkers reported their finding of increased systemic blood pressure as well as pulmonary artery pressure during sleep in sleep apnea patients (111). Heavy snorers were in an intermediate state with an increase in systemic and pulmonary artery pressures during sleep compared with normals but much less pronounced compared with patients suffering from sleep apnea. However, the question of whether this leads to sustained daytime hypertension is still being intensively discussed (112).

In epidemiological studies designed to investigate the relationship between snoring and hypertension, an association has been found by some authors (51-53, 56) but not by others (54, 71, 76, 113) (Table 1). The limitations of the studies that have been criticized include the lack of a standard definition of snoring, the use of unvalidated questionnaires, failure to account for confounding variables and the lack of prospective studies within this field (114). When monitoring 441 subjects aged 34 to 69 years for sleep-disordered breathing (SDB), Olson et al. reported that, compared with non-snorers, those with SDB had a crude OR for hypertension of 3.8.

Table 1. *Epidemiological studies examining association between reported snoring and hypertension.*

Reference	Population: gender, age	Confounders adjusted for	Association snoring - hypertension
Lugaresi E, 1980 (53)	F+m, 8-82 ?	Age, BMI	Significant in normal-weight f+m and in young obese males
Koskenvuo M, 1985 (52)	F+m, 40-69 n=7,511	Age, BMI	m: RR 1.5 f: RR 2.8
Gislason T, 1987 (51)	M, 30-69 n=3,201	Age, BMI	Significant association in 40-49 age group
Stradling JR, 1990 (113)	M, 35-65 n=748	Age, BMI, alcohol	n.s.
Schmidt-Nowara WW, 1990 (54)	F+m, > 18 n=1,222	Gender, age, smoking, obesity	n.s.
Gislason T, 1993 (56)	F, 40-59	Age, BMI	RR 1.7
Jennum P, 1993 (71)	F+m, 30-60 n=1,504	Age, BMI, sex, tobacco, alcohol	n.s.
Koskenvuo M, 1994 (76)	M, 40-59 n=3,750	Age, smoking, obesity, alcohol, physical activity, dyspnoea, hostility, morning tiredness	n.s.

RR = Relative risk

However, adjustment for age, sex, BMI, alcohol consumption and smoking reduced the OR to 1.5 and it was no longer significant. No data were presented for separate age groups (115).

In normal human beings, both heart rate and blood pressure, as well as the variability of blood pressure, decrease during sleep (116). In contrast, OSAS is associated with large swings in nocturnal arterial blood pressure and the absence of the reduction in systemic blood pressure normally seen during sleep (117, 118). At the beginning of an apnea, the blood pressure falls to keep pace with inspiratory effort against obstruction, whereas it rises abruptly at the end of the apnea, coinciding with an electroencephalographic (EEG) arousal. In subjects both with and without pre-existing cardiovascular disease, a correlation has been found between blood pressure variations during sleep and apneas/hypopneas (119, 120) as well as arousals (121).

Snoring is a widespread finding among subjects with hypertension and sleep apnea has been demonstrated in 22% to 48% of them (89, 122-125). Among patients with therapy resistant hypertension, Isaksson et al. found an OSA prevalence as high as 56% compared with 19% in successfully treated hypertensives matched for age and BMI (126). In a recent study, the prevalence of OSA in hypertensive subjects was 38%, regardless of whether or not they were on antihypertensive drug treatment, compared with 4% among normotensive controls. This difference was only partially explained by the confounding variables BMI, age, sex and alcohol consumption (89).

On the other hand, systemic hypertension is frequently found in patients with OSAS, with reported prevalences ranging from 40 to 72% (66, 127-129). This high prevalence is partly explained by age and obesity. Carlson et al. reported that age, obesity and sleep apnea are independent and additive risk factors for hypertension (129).

However, when age and obesity are accounted for, no significant relationship between AHI and the prevalence of hypertension was reported in two studies of patients with sleep-disordered breathing of varying severity (130, 131). Grunstein et al. found that morning but not evening blood pressure was related to sleep apnea activity (74). On the basis of polysomnographic data, Lofaso et al. identified a group of 50 non-apneic snorers with sleep fragmentation defined as a mean number of arousals of 10 or more/hour of sleep and compared them with 50 non-apneic snorers without sleep fragmentation. Although there were no significant differences between the groups in terms of age, BMI, sex ratio or daytime sleepiness, the prevalence of systemic hypertension was significantly higher in the sleep-fragmented group (132).

Coronary heart disease

In a population of 7,511 subjects aged 40-69 investigated by questionnaires, Koskenvuo et al. found a significant increase in the risk ratio of 2.01 ($p<0.01$)

for angina in habitually snoring men after adjustment for hypertension and obesity. However, they failed to confirm a significant association in women and detected no increased risk of myocardial infarction (52).

High prevalences of OSA have been reported in patients with CHD. In a case-control study including 101 male survivors of acute myocardial infarction, Hung et al. found an AI higher than 5 in 36% of the patients compared with only 3.8% of the control subjects. After adjustment for age, BMI, smoking, cholesterol level and hypertension, men with an AI of > 5.3 had a 23.3 times (95% CI 3.9-139.9) higher risk of myocardial infarction compared with men with an AI of < 0.4 (133). Even in patients with angiographically verified coronary artery disease, a significant increase in the prevalence of OSA has been reported in both males (134) and females (135). The increased prevalence of OSA could not be explained by age, BMI, hypertension, diabetes or smoking.

Case-control studies have further revealed that a history of snoring is significantly more common in patients with acute myocardial infarction (136) and cardiovascular disease (137) than in controls.

Arrhythmia

The most common dysrhythmia observed in patients with OSAS is a sinus bradytachyarrhythmia. Cyclical variation in heart rate has been reported in more than 75% of patients with OSA (138). The onset of bradycardia generally coincides with the cessation of air flow and the extent of slowing correlates with apnea duration and the severity of the oxyhemoglobin desaturation (139). Following apnea termination, there is a sudden increase in heart rate believed to result from the combined effects of decreased vagal parasympathetic tone and increased sympathetic neural activity related to hypoxemia and arousal. In patients with OSA, sinus pauses of two to 13 seconds' duration have been reported in about 10%, second-degree atrioventricular block in 4 to 8% and ventricular ectopy during sleep in 57 to 74% (140, 141). However, these prevalences are almost the same as would be expected in middle-aged men and it appears that severe oxyhemoglobin desaturations are required to induce a significant increase in ventricular arrhythmias in otherwise healthy patients (107, 141).

Stroke

Patients with recent stroke often display high AHIs (142) which might at least in part be secondary to the stroke.

However, several case-control studies have revealed that a history of habitual snoring is significantly more common in patients with stroke. The adjusted risk associated with habitual snoring ranges from 1.9-10.3 (137, 143-145). When following patients with recent stroke until death or six months,

Spriggs et al. reported that previous stroke and regular snoring were the only two risk factors adversely to affect mortality (146).

Prospective surveys

In the few prospective surveys hitherto performed to investigate the relationship between sleep-disordered breathing and cardiovascular consequences, the results have also been somewhat divergent.

When analysing the data from 4,388 men aged 40-69 who were followed up for three years, Koskenvuo et al. found that snoring was a risk factor for ischaemic heart disease with an age-adjusted odds ratio of 1.91 (95% CI 1.18-3.09). Further adjustment for BMI, history of hypertension, smoking and alcohol use only slightly reduced the OR to 1.71 (95% CI 0.96-3.05) (147).

Jennum et al. classified almost 3,000 men aged 54-74 according to self-reported snoring habits. The population was then followed up for six years to identify the incidence of ischaemic heart disease. Among the younger half of the cohort, the age-adjusted incidence of IHD was slightly but not significantly increased in snorers (RR=1.2, 0.8-1.9), while in the older half there was no increased risk in snorers (148).

Zaninelli and coworkers followed 400 patients aged 30-80, divided into four groups matched for age, sex and BMI. During the next five years, snorers with risk factors for cardiovascular disease (hypertension, diabetes, obesity, smoking, high serum cholesterol level) had a significantly higher morbidity and mortality from cardiovascular disease compared with non-snorers with risk factors (36% v. 10% and 17% v. 4% respectively). Among patients without risk factors, both snorers and non-snorers had a low incidence of cardiovascular disease (7% and 3% respectively) and the difference between these groups was not significant (149).

Mortality

When investigating 460 consecutive cases of sudden death, Seppälä et al. found that a cardiovascular cause of death was significantly more common among the subjects who had snored habitually or often compared with occasional and never-snorers. The results further revealed that habitual snorers died more often while sleeping and that snoring was a risk factor for sudden death between 4 am and noon among those who died of cardiovascular causes (150).

In studies designed to investigate mortality in OSAS patients, the results have diverged, since increased mortality has been found by some but not by others. As tracheostomy was the first effective treatment for OSAS, the longest follow-ups relate to patients treated with tracheostomy. In a retrospective study by He et al., OSAS male patients with an AI of > 20 had a probability of eight-year survival of 0.63 $\pm$ 0.17 (SE) v. 0.96 $\pm$ 0.02 for an

AI of ≤ 20. The differences were most pronounced in untreated patients below the age of 50. None of the patients treated with tracheostomy or nasal CPAP died during the follow-up. In contrast, the cumulative survival of the group treated with uvulopalatopharyngoplasty (UPPP) was no different from the survival of untreated patients with an AI of > 20 (151). However, the study has been criticised for having many weaknesses; the authors failed to follow up 45% of the original sample, the results were based on reported data on deaths without validation and there were no data on pre-existing morbidity or causes of death.

In a similar retrospective review of 198 patients with OSAS, mortality over a five-year interval was compared between 127 patients treated conservatively with recommendations for weight reduction and 71 patients treated with tracheostomy. Despite a lower mean apnea index and BMI at baseline, the mortality as well as the cardiovascular mortality was significantly higher in the conservatively treated group (127) and the differences remained significant at seven years of follow-up (152). In contrast, Gonzalez-Rothi et al. reported no significant differences in mortality between 91 patients with OSAS and 35 non-apneic snorers during 1-103 months of follow up (153).

Lavie et al. compared mortality in 1,620 OSAS patients (mean age 48) with the national mortality data. After adjustment for age, BMI, hypertension, heart disease, lung disease and diabetes, there was still an association between AI and mortality from all causes, while only age, BMI and hypertension predicted death from myocardial infarction (154).

In four follow-up studies of general elderly populations (mean ages 67 to 82 years) investigated by sleep recordings at baseline, no independent influence by AHI on mortality was reported in three (26, 155, 156), while one reported a significant association only in women (157).

Treatment

General aspects

Alcoholic beverages and drugs which reduce muscular tone should be avoided before bedtime by patients with snoring and sleep apnea (87, 158).

In some patients, snoring can be reduced by dilating the narrow nasal valve area with a plastic nasal device such as Nozovent® (159). When snoring and apneas predominantly occur when sleeping in a supine position, position training may be enough to treat the condition (160).

Weight loss

Weight reduction in obese patients with OSA, using either an intensified dietary regimen or weight reduction surgery, cures or significantly improves OSA (82, 161). The relationship between weight loss and improvement in the number of apneas/hypopneas is, however, not linear. In obese patients, the

weight loss often has to be of a large magnitude to improve OSAS. On the other hand, a large improvement can occur in some patients with fairly minimal weight loss (162). Losing weight leads to a decrease in upper airway collapsibility and the resolution of sleep apnea appears to depend on the absolute level to which the upper airway critical pressure falls (163).

Nasal Continuous Positive Airway Pressure (nCPAP)

As nCPAP is highly effective in abolishing apneas (164) and improves survival in patients with OSAS (151), it is currently the most widely used treatment for severe OSAS. Continuous positive pressure is applied to the upper airway by a nose mask. By producing positive pressure within the upper airway, the nCPAP acts as a pneumatic splint which restores unobstructed airways during sleep (165). The success of the treatment is directly dependent on the compliance of the patient in using the device. When starting to use the nCPAP, the effect on apneas and symptoms is immediate. However, nCPAP does not cure the disorder and failure to use nCPAP for even a single night can result in the reappearance of pretreatment levels of nocturnal sleep disturbance and daytime hypersomnolence (166).

Surgical treatment

Nasal surgery

In patients with nasal obstruction, surgical correction is beneficial as it improves the tolerance of nCPAP. Even other types of therapy are usually not effective unless the nose is well open. As a single procedure in the treatment of OSAS, the efficacy of nasal surgery is, however, limited (167).

Pharyngeal surgery

In 1981, Fujita et al. showed that uvulopalatopharyngoplasty (UPPP), a surgical treatment hitherto used to stop snoring, significantly reduced the frequency of sleep apnea and improved patients (168). During the 1980s, there was enthusiasm for UPPP as the treatment of choice for OSAS. However, long-term follow-up studies have indicated the incomplete resolution of nocturnal breathing abnormalities as well as a frequent relapse of symptoms. In a follow-up a mean of four years postoperatively, Larsson et al. found that 50% were non-responders in terms of oxygen desaturation index (169). The long-term effect of UPPP is better in mild to moderate OSAS than in severe cases (170) and preoperative obesity is a negative predictor of response (169). However, the association between changes in AHI and subjective evaluations of outcome is poor as a subjective improvement is common, even in non-responders (169). For those who not respond to the treatment or in whom OSAS reoccurs, previous UPPP may compromise nasal CPAP therapy by increasing mouth air leak and reducing the maximum level of pressure that can be tolerated (171).

Tracheostomy

Up to 1981, tracheostomy was the only treatment available for sleep apnea, in addition to weight loss recommendation. Despite being highly effective in all patients, as it provides an alternative source of air to the occluded upper airways, it is often associated with medical and psychosocial disadvantages (106). Nowadays, tracheostomy is only performed in patients with severe symptomatic OSAS where other treatments have failed to work.

Oral appliances

Oral appliances modify the upper airway by changing the posture of the mandible and tongue. Snoring is improved and often eliminated and OSA improves in the majority of patients. However, in unselected OSAS patients, only approximately 50% of those who improve achieve an AHI of < 20 (172). In a randomized cross-over study of OSAS patients, treatment success was less common with oral appliances compared with nCPAP. On the other hand, among those who tolerated both treatments, there was greater patient satisfaction with the oral appliance (173). There is still a lack of data on the long-term effect of oral appliances and more research is needed to optimize patient selection.

METHODS

Population

A random sample of 4,021 men aged 30-69 was drawn from the population registry of the city of Uppsala in Sweden, in 1984. A postal questionnaire was sent to all subjects in December 1984 and, after two reminders, the total response rate was 79.6% (n=3,201) (51, 174-175). In November 1994, all the survivors among the subjects who replied in 1984 (n=2,975) were invited to take part in the follow-up and to answer a new postal questionnaire. Reminders were sent to non-responders after one and two months. From those subjects who responded in 1984, the total response rate for the survivors at the follow-up was 89.7% (n=2,668) (Figure 3, Study design).

The results on evolution of snoring and associations between snoring and hypertension are based on the data from the 2,668 subjects who responded in both 1984 and 1994.

The mortality data were analysed for the whole of the original sample (n=4,021). All the subjects who had omitted either the question on snoring or the one on EDS in the questionnaire in 1984 were regarded as non-responders in this case.

In 1984, a sample of men with symptoms related to OSAS had been identified. On the basis of a previous methodological evaluation (58), a sub-sample of 61 of these men was investigated using all-night polysomnography

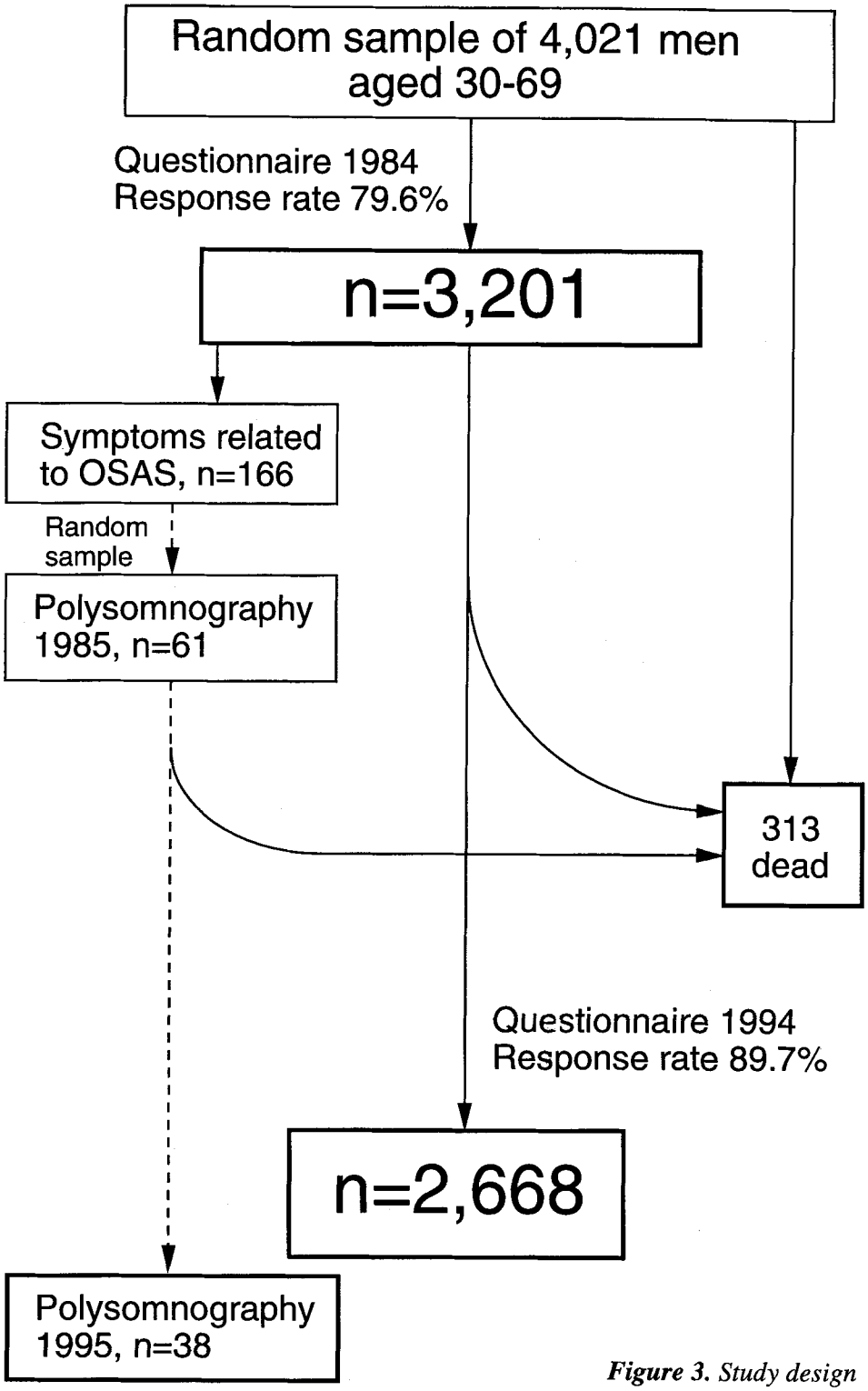


Figure 3. *Study design*

in 1985 (61). Of the 54 subjects who were still alive in 1995, 38 (70%) participated in this follow-up.

Questionnaires

The questionnaire used in 1984 consisted of 26 questions including questions about snoring, EDS, somatic diseases, medication, height and weight (51, 175). In the questionnaire used in 1994, the first part was identical to that used in 1984. In the second part, 45 new questions were added, including questions about current and past smoking habits, alcohol use and physical activity.

Snoring and EDS (1984 & 1994)

To assess the prevalence of snoring, the subjects were asked to state the frequency of their "loud and disturbing snoring" using a five-point scale. The five response alternatives were "never", "seldom", "sometimes", "often", or "very often". The responses to the question about daytime sleepiness were also given on a five-point scale. The subjects were asked to state how many problems they experienced from daytime sleepiness. Possible responses were "no problems", "small", "moderate", "severe" and "very severe" problems.

To categorize the subjects according to snoring and EDS, the following approaches were applied:

When studying the prevalences of snoring, subjects with scores of 1 (never) and 2 (seldom) were defined as non-snorers, those with a score of 3 (sometimes) were occasional snorers, while those with scores of 4 (often) or 5 (very often) were regarded as habitual snorers. When analysing the development of snoring, the subjects were divided into non-habitual (scores 1-3) and habitual (scores 4-5) snorers.

When analysing the association between snoring and hypertension, subjects with scores of 1-3 were regarded as non-habitual snorers and those with scores of 4 and 5 as habitual snorers. The terms persistent non-snorers and persistent snorers were used to characterise those subjects who were in the same category in both 1984 and 1994.

When analysing the association between snoring, EDS and mortality, the population was divided into non-snorers (scores 1-2) and snorers (scores 3-5). In a similar manner, EDS was defined as the experience of daytime sleepiness as a moderate to very severe problem (scores 3-5). On the basis of these criteria, symptoms at baseline were categorised in four groups: 1) No snoring and no EDS, 2) Snoring but no EDS, 3) EDS but no snoring, 4) Both snoring and EDS.

Somatic diseases (1984 & 1994)

The participants were asked to indicate whether they had hypertension, cardiac disease or diabetes. In addition, three general questions were included about regular medical examinations, previous hospital care and medication.

The subjects were classified as having hypertension if they reported attending regular medical check-ups for hypertension and/or answered "yes" to the question "Do you have high blood pressure?". Subjects reporting hypertension in 1994 *but not* in 1984 were classified as "new hypertensives".

Diabetes was defined as answering "yes" to the question "Do you have diabetes?". Subjects were regarded as suffering from heart disease if they answered "yes" to the question "Do you have cardiac disease?", or reported attending regular medical check-ups due to angina pectoris or previous myocardial infarction, or had been in hospital as a result of any of these diagnoses.

Smoking (1994)

Smoking habits were assessed by six questions; the subjects were asked if they had ever smoked regularly for at least six months, if they were current smokers or ex-smokers. Current and ex-smokers were asked at what age they had started and when they had quit. From the answers, it was possible to establish whether or not the subject had been a smoker in 1984. As no one in this population reported that he had started smoking during the ten-year period, smoking habits were categorised in three groups: 1) Non-smoker at baseline and at the follow-up, 2) Smoker at baseline, non-smoker at the follow-up, 3) Smoker both at baseline and at the follow-up.

Physical activity (1994)

A four-point scale was used to describe physical activity during leisure time (176, 177). In the subsequent statistical evaluation, the level of physical activity was categorized in three groups: 1) Physical inactivity was defined as score 1; spending most time in front of the TV, reading or other sedentary activities, 2) Medium level defined as score 2; some physical activity like cycling or walking to work at least four hours a week, 3) High level of physical activity, defined as scores 3-4, including regular physical activity like swimming, jogging, tennis, aerobic exercise for at least three hours a week or even more vigorous activities on a weekly basis.

Alcohol use (1994)

Alcohol dependence was estimated by using the CAGE questionnaire, which has been found to be highly sensitive to and specific for the recognition of alcohol dependence, as defined by DSM-III (178, 179). When translated into Swedish, one of the questions has been slightly modified to match the Swedish conditions more effectively. The questions which were used were: "Have you ever felt you should cut down on your drinking?", "Have you ever annoyed people by your drinking?", "Have you ever felt guilty about your drinking?" and "Have you ever taken a drink in the morning to get rid of a hangover

('eye-opener')?". Alcohol dependence was defined as positive answers to at least two of these questions.

Mortality data

Mortality data for the 10-year period 1985-1994 were collected for the complete sample (n=4,021). Death certificates were obtained from the National Cause of Death Register in Sweden for all subjects who had died within the country. Of those who had moved abroad, three were reported as dead with a known date of death, but no information on the cause of death was obtained. The remaining subjects who emigrated were censored from the date of emigration or, if no date of emigration was obtained, from 1 January 1985.

Cardiovascular causes of death were defined as ICD-9 codes 401-414 (hypertension and ischaemic heart disease), 425 (cardiomyopathy), 426-429 (arrhythmia, heart failure and unspecified heart disease) and 431-441 (cerebrovascular disease, atherosclerosis and aortic aneurysm).

Anthropomorphic calculations

Body mass index (BMI) was calculated using the formula "body weight divided by the square of the height". Delta-BMI (ΔBMI) was calculated as BMI 1994 - BMI 1984. As it appears that the relationship between BMI and morbidity is not linear, BMI was categorised when analysing the effect on developing hypertension (< 27, $\geq 27 kg/m^2$) and mortality (< 21, 21-28, $> 28 kg/m^2$).

Interview by telephone

Before the polysomnography in 1995, a structured interview was performed by telephone. The subjects were asked about their general health, medication and whether they had ever attended medical check-ups or had been admitted to hospital due to hypertension, cardiac disease or stroke. All the subjects were asked to state whether their symptoms of snoring and EDS had decreased, increased or been stable during the 10-year period. They were also asked whether they had ever sought medical advice because of any of these symptoms and, if so, what kind of investigation and/or treatment they had been offered. Medical records were obtained from the relevant departments.

Polysomnography

The subjects arrived at the sleep laboratory at the Department of Psychiatry, Akademiska sjukhuset, Uppsala in the late afternoon or the evening. A physical examination of the lungs, heart, blood pressure and pulse was performed and height and weight were measured. In the two subjects who used a CPAP, the sleep recordings were performed after three nights of CPAP withdrawal. The all-night polysomnography was performed in a similar manner to that used in 1985. The electroencephalogram (EEG), electrooculogram (EOG) and submental electromyogram (EMG) were

recorded on a 21-channel polygraph (Nihon Koden) with a paper speed of 1 cm/s (180). Airflow was measured using the sum of nasal and buccal thermistor signals and also by tracheal sound recording. Respiratory movements were monitored with abdominal and thoracic strain gauges, by a static charge sensitive bed (Biorec OY) and by movement sensors (Siemens, 230). Oxygen saturation was measured continuously using a pulse oximeter (BIOX III).

The polysomnogram was scored manually, using 30-sec epochs (180). Identical criteria were used in the scoring in 1985 and in 1995: An apnea was defined as a complete cessation of oronasal air flow for at least 10 seconds and hypopnea as a marked decrease in air flow for at least 10 seconds, followed by a reduction in oxygen saturation of at least 4% from the baseline level and/or an arousal (181). The apnea-hypopnea index (AHI) was calculated as the total number of such events divided by hours of sleep. ΔAHI was calculated as AHI 1995 - AHI 1985.

Statistical methods

The computations were performed on a Macintosh Ilci computer using the Statistica 4.0 software package (StatSoft Inc, Tulsa, OK, USA). Comparisons between subgroups were performed using the unpaired t-test for continuous variables, the Mann-Whitney U test for variables on an ordinal scale and the chi-square test for proportions. Significance tests for changes between baseline and the follow-up were conducted using the paired t-test for continuous variables and the chi-square test for proportions. Correlations between continuous variables and variables on an ordinal scale were performed using the Spearman rank correlation test. To achieve normal distributions for continuous variables, the variables were log transformed. The null hypothesis was rejected at a level of $p < 0.05$.

To study the influence of several possible explanatory variables on a dependent variable, such as habitual snoring or hypertension at the follow-up, multiple logistic regressions were performed. The results are presented as odds ratios (OR) with 95% confidence limits. To determine whether differences between age groups were significant according to specific risk factors, a multiple logistic regression for the whole population was performed in which an interaction term "risk factor * age group" was included in the model.

Survival analysis was performed using the Kaplan & Meier Survivorship Function. To study the influence of possible explanatory variables on mortality, the Cox proportional hazards model was used. The results are presented as adjusted hazard ratios with 95% confidence limits.

Ethical aspects

All the study protocols were approved by the Ethics Committee of the Medical Faculty at Uppsala University and all the participants gave their informed consent.

RESULTS

Response rate, non-responders

The questionnaire in 1994 was initially completed by 2,469 subjects. We were not able to find the mailing address of 49 persons (32 of them lived abroad). The first reminder resulted in 136 usable questionnaires and the second in 63. From those subjects who responded in 1984, the total response rate for the survivors at the follow-up was 89.7% (n=2,668). Of the 2,668 men, 98.3% (n=2,622) answered the question about snoring in 1984 and 97.4% (n=2,598) in 1994. Snoring status for both 1984 and 1994 was available for 95.5% (n=2,557). The questions about alcohol and physical activity were answered by 96.0% and 98.4% respectively. The BMI in 1984 was possible to calculate for 99.6% and the ΔBMI for 97.8%. In 1994, the question about current smoking was answered by 2,649 (99.3%) and smoking habits in 1984 could be calculated for 2,553 men (95.7%).

When it came to the 312 men who were still alive but did not respond to the questionnaire in 1994 ("non-responders"), the mean age was somewhat lower compared with the responders (53.7 ± 11.6 v. 55.1 ± 11.1 years, $p<0.01$), but no significant differences were found when it came to mean BMI in 1984 or the prevalence of habitual snoring in 1984. Reported hypertension and cardiac disease in 1984 did not differ significantly between the groups, while diabetes was more common among the non-responders (3.6 v. 1.9%, $p<0.05$). The non-responders had also reported excessive daytime sleepiness more often (8.4 v. 5.3%, $p<0.05$).

Characteristics of the study population

The characteristics of the population by snoring category in 1984 are presented in Table 2.

During the 10-year period, the overall prevalence of current smoking in this population decreased from 33.5% (95% CI 31.7-35.4%) to 20.0% (95% CI 18.5-21.6%) and no one had started smoking. Of the smokers in 1984, the 332 subjects who had quit smoking during the 10-year period had a higher ΔBMI compared with the 524 who still smoked in 1994 (1.5 ± 1.9 v. 0.7 ± 2.1 kg/m^2, $p<0.001$).

During the 10-year-period, the mean BMI in the population increased from 24.4 ± 2.8 to 25.3 ± 3.1 kg/m^2 ($p<0.001$). The ΔBMI was inversely associated with age ($r=-0.28$, $p<0.001$) but was positive in all age groups.

In 1994, 2,031 subjects (76.9%) reported that they usually shared a bedroom with another person. Among the younger men, no association was found between sharing a bedroom and the prevalence of reported habitual snoring in 1994 (23.6% v. 22.6%, ns). In the elderly subjects, however, the prevalence of habitual snoring was significantly higher among subjects who slept alone (18.5% v. 11.5% $p<0.01$).

TABLE 2. *Characteristics of the participants, total and by snoring status in 1984.*

	Total		Snoring category 1984*						
			Never		Occasional		Habitual		p†
Participants, n (%)‡	2,668	(100)	1,465	(54.9)	764	(28.6)	393	(14.7)	
Age 1984, mean (SD)	45.1	(11.1)	43.5	(11.0)	47.0	(11.0)	47.0	(10.3)	<0.001
BMI 1984, mean (SD)‡	24.4	(2.9)	23.9	(2.7)	24.9	(2.8)	25.5	(3.0)	<0.001
BMI $\geq$ 27 kg/m^2 1984, n (%)‡	435	(16.4)	174	(11.9)	154	(20.2)	102	(26.1)	<0.001
Δ BMI, mean (SD)‡	0.9	(1.8)	1.0	(1.8)	0.8	(1.8)	0.5	(2.0)	<0.001
Smokers 1984, n (%)‡	856	(33.5)	402	(28.4)	274	(37.8)	164	(44.3)	<0.001
Smokers 1994, n (%)‡	530	(20.0)	251	(17.3)	162	(21.4)	108	(27.6)	<0.001
Alcohol dependence 1994, n (%)‡	256	(10.0)	153	(10.9)	65	(8.8)	34	(8.9)	n.s.
Level of physical activity 1994,									
Low, n (%)‡	410	(15.6)	239	(16.5)	103	(13.7)	62	(16.1)	n.s.
Medium, n (%)‡	1,663	(63.3)	867	(59.9)	513	(68.4)	259	(67.3)	n.s.
High, n (%)‡	553	(21.1)	341	(23.6)	134	(17.9)	64	(16.6)	<0.05
EDS 1984 (scores 3-5), n (%)‡	569	(21.5)	292	(20.1)	159	(21.0)	110	(28.1)	<0.001
Snoring category 1994									
Never, n (%)‡	1,228	(47.3)	967	(67.5)	196	(26.4)	46	(12.0)	<0.001
Occasional, n (%)‡	841	(32.4)	349	(24.4)	351	(47.3)	127	(33.2)	n.s.
Habitual, n (%)‡	529	(20.4)	117	(8.2)	195	(26.3)	209	(54.7)	<0.001
Hypertension 1984, n (%)‡	217	(8.1)	95	(6.5)	67	(8.8)	51	(13.0)	<0.001
"New hypertension" 1994, n (%)‡	218	(8.2)	94	(6.4)	70	(9.2)	49	(12.5)	<0.001

* Forty-six subjects did not answer the question about snoring in 1984.
† Habitual snorers versus non-habitual snorers.
‡ Means and percentages relate to the subjects who answered the questions relating to the respective category.

Evolution of snoring and predictive factors

In both 1984 and 1994, the prevalence of snoring increased until age 50-60 and then decreased (Figure 4). In men aged 50 and under, there was a trend during the 10-year period towards developing habitual snoring and the increase was most pronounced in the youngest age category. Among men aged 50-59, a change to non-habitual snoring was more common. In the oldest age group, significantly more men changed from habitual to non-habitual snoring than the reverse.

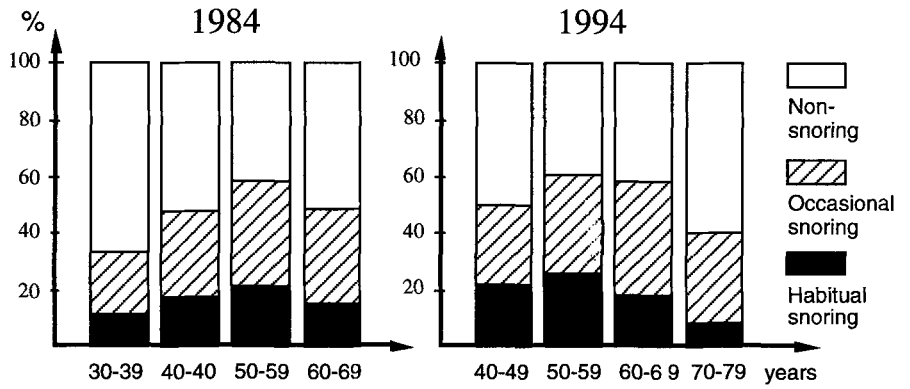


Figure 4.
Prevalence of snoring by age group in 1984 and in 1994.

In 1984, the number of habitual snorers in this population was 393 (15.0%, 95% CI 13.6-16.4%) and, in 1994, this number had increased to 529 (20.4%, 95% CI 18.8-21.9%). Among the men who answered the question on snoring both at baseline and at the follow-up, there were 2,175 subjects who did not snore habitually in 1984 and were thus at risk of developing habitual snoring. Of these, 312 snored habitually in 1994, giving a cumulative incidence rate of 14.3% during the 10-year period. Of the 382 habitual snorers in 1984, 173 reported non-habitual snoring 10 years later, giving a cumulative remission rate of 45.3% during the 10 years.

Risk factors for being an habitual snorer at the follow-up were investigated using multiple logistic regression with adjustments for previous snoring status, age, BMI, weight gain, smoking habits and physical activity. In men aged 30-49 at baseline, the independent predictors of habitual snoring at the follow-up, in addition to previous snoring status, were persistent smoking (adjusted OR, 95% CI: 1.4, 1.1-1.9), BMI at baseline (1.1, 1.02-1.1/kg*m^{-2}) and weight gain (1.1, 1.03-1.2/kg*m^{-2}). Among men aged 50-69, in addition to previous snoring status and lower age, weight gain was the only significant risk factor for developing habitual snoring (1.2,1.05-1.4/kg*m^{-2}).

Snoring and risk of developing hypertension

Of the habitual snorers in 1984, 12.5% (49 of 393) had developed "new hypertension" in 1994, compared with 7.4% (164 of 2,229) of the non-habitual snorers ($p<0.001$). In the whole population, there was a significant association between "new hypertension" and age, BMI 1984 and ΔBMI. After adjustments for age, "new hypertension" was also associated with alcohol dependence and physical inactivity.

Among the men without hypertension in 1984, a significantly higher prevalence of "new hypertension" was found among habitual snorers, even after dividing the population on the basis of BMI, ΔBMI, smoking, alcohol dependence and physical inactivity. When the population was subgrouped according to age, however, the higher prevalence of "new hypertension" was only found among habitual snorers aged 30-49 (Table 3).

Table 3.
Incidence of "new hypertension" during the 10-year period in subjects with non-habitual snoring and habitual snoring in 1984.

		Non-habitual snorers 1984	Habitual snorers 1984	p
BMI 1984:	<27	7.1	10.6	*
	≥27	13.8	28.0	**
ΔBMI:	<2	7.7	12.5	**
	≥2	9.0	21.7	**
Age 1984:	30-49	6.6	15.5	***
	50-69	11.3	12.2	n.s.
Smoking 1984:	No	7.9	14.1	**
	Yes	7.7	15.6	**
Alcohol dependence:	No	7.7	13.2	**
	Yes	9.2	23.3	*
Physical inactivity:	No	7.5	13.0	**
	Yes	10.1	20.0	*

* $p<0.05$, ** $p<0.01$, *** $p<0.001$

Risk factors for the development of hypertension were analysed by multivariate analyses including all the subjects who did not report hypertension in 1984. In addition to snoring status, adjustments were made for age, BMI 1984 ≥ 27, ΔBMI, smoking 1984, alcohol dependence and physical inactivity in 1994. Compared with the persistent non-snorers aged 30-49 in 1984, the persistent snorers in that age group showed an increased risk of developing hypertension, with an adjusted odds ratio of 2.6 (95% CI 1.5-4.5). The habitual snorers in 1984 who became non-habitual snorers during this ten-year period also showed a tendency towards an increased risk of developing hypertension (adjusted OR 2.0, 95% CI 0.96-4.3). The other independent predictors of hypertension in the younger age group were age,

BMI 1984 ≥ 27 and ΔBMI. In the older age group, the only variable that was significantly associated with hypertension after adjustment for the other variables in the model was ΔBMI.

Snoring, sleepiness and mortality

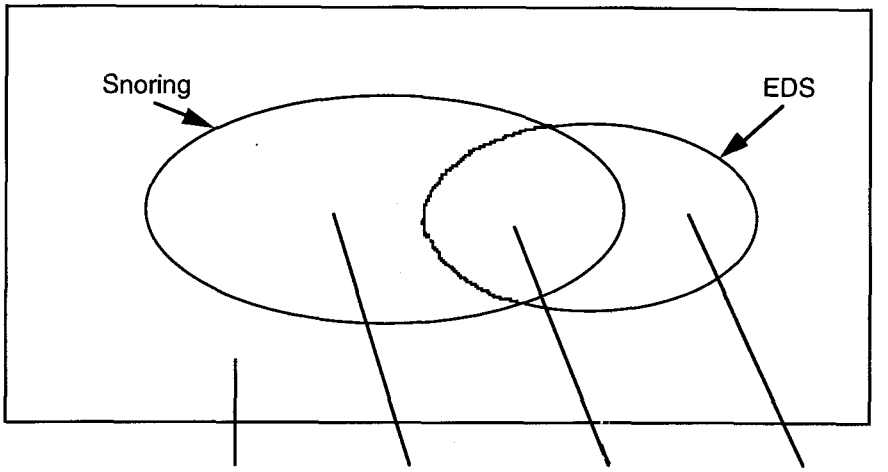
Among the responders in 1984, there were 213 deaths during the ten-year follow-up period (mortality rate 7.1%). Death certificates were available for 208, based on autopsies in 102 (49.0%) cases. The main cause of death was cardiovascular in 88 cases (42.3%), cancer in 87 (41.8%), suicide in five (2.4%), accidents in five (2.4%) and other causes in 23 cases (13.5%).
When compared with subjects with no snoring or EDS, snorers with no EDS and subjects with EDS but no snoring displayed no significant increase in the relative rates (RR) of mortality after adjustments for age. In contrast, men with both snoring and EDS displayed a significant increase in overall mortality. However, the relative rates of mortality among men with both "snoring and EDS" decreased with age and, in men aged 60 and above, no effect on mortality was found (Table 4).

Table 4.
Relative rates of mortality during the 10-year period among men with snoring and EDS compared with men with no snoring or EDS. Relative rates (RR) by age and 95% confidence intervals are presented.

Age group	RR	95% CI
30-39	6.7	2.3-19.8
40-49	5.3	1.3-21.5
50-59	1.8	0.8-3.6
60-69	1.1	0.6-1.9

When analysing the 30-59 age group separately, men with both snoring and EDS had an age-adjusted total death rate which was 2.7 times higher than men with no snoring or EDS. The corresponding age-adjusted relative ratio for cardiovascular mortality was 2.9 for subjects with both snoring and EDS (Figure 5). The different groups differed, however, not only in reported symptoms and age but also in the prevalence of overweight and somatic diseases. After adjustments for age, BMI, hypertension, heart disease and diabetes, the relative rate (RR) of overall mortality among men with both snoring and EDS was reduced to 2.2 (95% CI 1.3-3.8). The corresponding RR for cardiovascular mortality was reduced to 2.0 (95% CI 0.8-4.7).

Responders aged 30-59 in 1984



Symptom group:	No snoring, no EDS	Snoring, no EDS	Snoring *and* EDS	EDS, no snoring
(n)	1,104	837	293	312
RR mortality:	1.0	1.1 (0.8-1.6)	2.7 (1.6-4.5)	1.1 (0.6-1.9)
Cardiovasc. mort:	1.0	0.8 (0.5-1.3)	2.9 (1.3-6.7)	1.0 (0.4-2.3)

Figure 5
Subgroups of the population aged 30-59 by reported symptom in 1984. For each subgroup, the age-adjusted relative ratio for overall mortality and cardiovascular mortality is presented (95% CI).

Evolution of OSAS in sleepy snorers

Of the 61 men who were investigated using whole-night polysomnography in 1985, 54 were still alive in 1995 and 38 (70%) of them participated in this 10-year follow-up including questionnaires, structural interview and polysomnography.

In the whole group, the mean apnea/hypopnea index (AHI) increased from 4.4 $\pm$ 6.6 in 1985 to 7.5 $\pm$ 7.3 in 1995 ($p<0.05$). During the 10-year period, nine men had been treated for OSAS using continuous positive airway pressure (CPAP) or surgery. Among the 29 untreated men, the mean AHI increased from 2.1 $\pm$ 4.2 to 6.8 $\pm$ 7.2 ($p<0.01$). In 1985, four of the 29 men had OSAS defined as an AHI of > 5/h, all of whom still fulfilled this criterion 10 years later. In addition, nine of the 25 (36%) who had an AHI of < 5 in 1985 had developed OSAS at the follow-up. No significant associations were found between ΔAHI (*i.e.* AHI 1995 - AHI 1985) and age, BMI, weight gain or smoking. In the interview preceding the polysomnography in 1995, nine of the men reported that they had experienced increasing EDS during this 10-

year period. The mean ΔAHI of these nine men was 10.3 ± 9.7 compared with 2.2 ± 5.1 for the others ($p<0.01$) (Figure 6).

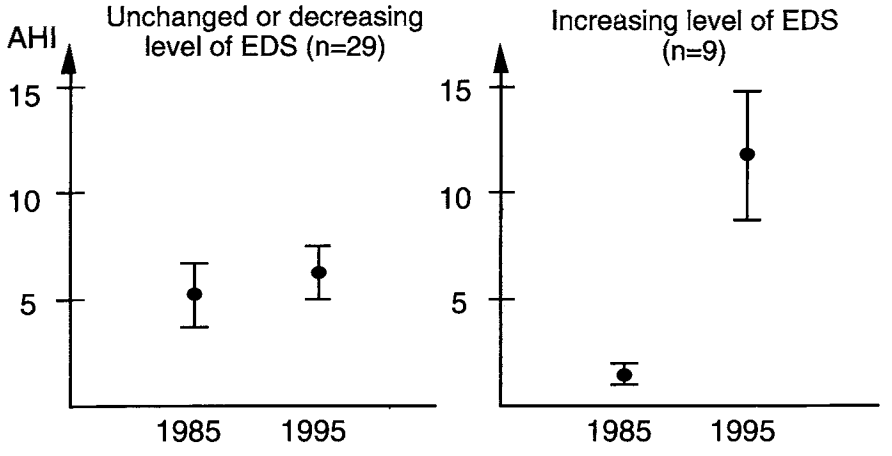


Figure 6
Mean AHI in 1985 and 1995 (± SE) in untreated men with unchanged or decreasing levels of EDS during the 10-year period and in men with increasing levels of EDS.

Snoring, sleepiness and hypertension

Persistent habitual snoring was found to be an independent risk factor for the development of hypertension among males below the age of 50 at baseline, while isolated snoring did not influence mortality. However, when analysing the association between snoring and hypertension, the influence of EDS was not taken into account. I have therefore re-analysed the data on snoring and hypertension to also take account of the occurrence of EDS. The subjects who responded to the questionnaires in both 1984 and 1994 were divided in a similar manner as when analysing the mortality data, that is into non-snorers without EDS (reference group), snorers (score 3-5) without EDS, EDS (score 3-5) without snoring and finally snorers with EDS. Multiple logistic regressions were performed for the younger and older age groups separately with adjustments for age, BMI 1984, ΔBMI, smoking, alcohol dependence and physical activity. In this model, the combination of snoring and EDS at baseline was a significant risk factor for developing hypertension among males aged 30-49 with an adjusted OR of 2.8 (95% CI 1.6-5.0), while no significant influence was found for isolated snoring or EDS. Among males aged 50 and over, neither snoring nor EDS, nor the combination of both, influenced the risk of hypertension at the follow-up.

To test the hypothesis of whether more pronounced symptoms of sleep-disordered breathing further increase the risk of hypertension, the calculations were performed with snoring and EDS defined as a score of 4-5 for each question; snoring was thus defined as "loud and disturbing snoring often or very often" and EDS as "experience of daytime sleepiness as a severe or very severe problem". With these definitions, the combination of snoring and EDS in men aged 50 and under was an independent risk factor for hypertension ten years later with an adjusted OR of 4.9 (95% CI 1.4-16.6), while, again, no significant impact on hypertension was seen in the older age group. However, with this narrow definition, snoring without EDS at baseline was also a risk factor for developing hypertension in the younger age group (OR 1.9, 95% CI 1.2-3.1), while isolated EDS was not (OR 1.6, 95% 0.7-3.6).

To test whether hypertension at baseline was a risk factor for habitual snoring at the follow-up, a multivariate analysis was performed with adjustments for the same variables as above. In this model, no significant associations could be found between hypertension at baseline and the development of habitual snoring or the combination of snoring and EDS in any of the age groups.

Validation of the questions related to snoring and EDS

During the period March 1996 to January 1998, 231 of the men in this study population were included in another study with new questionnaires and a single-night sleep recording using the Eden-Tec equipment (182). The questionnaires included the questions about snoring and excessive daytime sleepiness used in the 10-year follow-up study.

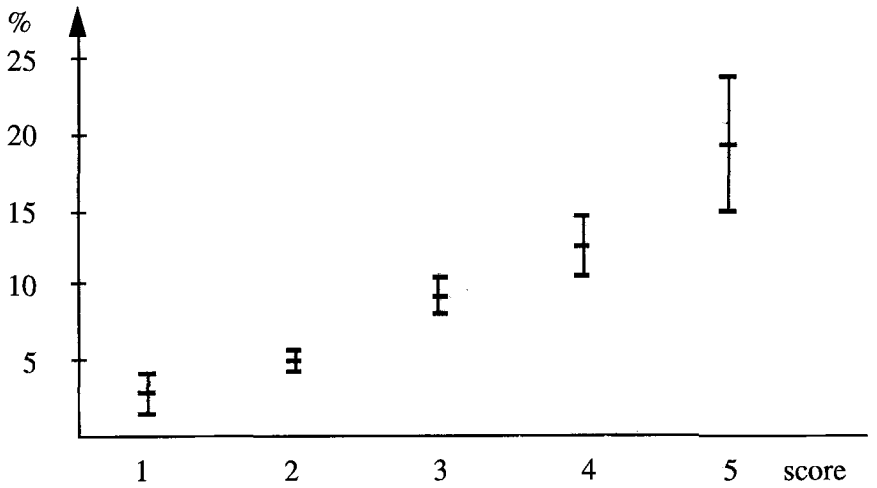


Figure 7. *Mean % (± SE) of the night with recorded snoring sound of > 90 dB by snoring score in the questionnaire (n=231).*

Validation of snoring

The sleep recording included sound recording by a microphone attached at the level of the upper right corner of the cricothyroid cartilage to record snoring sounds. Sampling was performed at 10 Hz and all sounds of > 90 dB were recorded. The percentage of the night with snoring sounds was then calculated as "total time with snoring/estimated total sleep time". There was a significant association between measured snoring and the score given to the question about snoring in the questionnaire ($r=0.38$, $p<0.0001$) (Figure 7). Even though the sensitivity was low, no significant difference was found between the older and younger age groups in the validity of responses to the question about snoring (Table 5).

Table 5

Sensitivity, specificity, predictive values expressed as raw data, a percentage and 95% CI for reported habitual snoring in a sample of 231 men from the population. Snoring here is defined as recorded snoring sounds for ≥ 10% of the night. The results are presented separately for the older and younger age groups.

	Age 40-59	(95% CI)	Age 60-79	(95% CI)
Sensitivity	18/45=40%	(26-54)	9/26=35%	(17-53)
Specificity	71/87=82%	(74-90)	64/73=88%	(81-95)
Predictive value positive	18/34=53%	(36-70)	9/18=50%	(27-73)
Predictive value negative	71/98=72%	(63-81)	64/81=79%	(70-88)

Validation of the question about EDS

To validate the question used here to measure EDS, we compared it with the Epworth Sleepiness Scale (ESS), which has been shown to correlate significantly with sleep latency measured during multiple sleep latency tests (183). A total of 230 men simultaneously answered the EDS question used here and the ESS questionnaire. Of the 172 men with scores of 1-2 for the EDS question, the mean ESS score was 5.9 ± 3.4 and this is close to the ESS scores of 5.9 ± 2.2 described for healthy controls. The 58 men with scores of 3-5 for the EDS question had a mean ESS score of 8.7 ± 4.1, which is slightly lower than the mean score of 9.5 ± 3.3 described for patients with mild OSAS (183).

DISCUSSION

The main findings in this study are that the evolution of snoring is strongly age-dependent and that the association with cardiovascular diseases also differs with age. The third important finding is that the concomitant occurrence of EDS strongly influences the adverse health effects of snoring. Regardless of age, subjects with symptoms related to OSAS run a high risk of developing apneas.

The follow-up period in this study is longer than that previously discribed in the literature within this field. The strengths of this investigation further include the fact that it was population-based, the response rate after ten years was high - almost 90% - and that the questions relating to snoring, EDS and hypertension were identical in 1984 and 1994.

It should be borne in mind that the study population consisted only of men. This is due to the design of the original study, reflecting the opinion of the early 1980s when OSAS was believed to be a predominantly male problem.

One disadvantage is the fact that questions relating to alcohol and physical activity were only included in the 1994 questionnaire. It is possible that changes with time in these parameters might influence the result to some extent. The CAGE questionnaire used here has high validity in measuring alcohol dependence. It is possible, however, that it does not correlate well with the amount of alcohol consumed.

During the 10-year period, the overall prevalence of current smoking in this population decreased from 33.5% to 20.0% and no one reported that he had started smoking. Since the 1980s, numerous campaigns have been launched in Sweden in an attempt to make people stop smoking. A marked decrease in the prevalence of smoking, as well as an increase in mean BMI, has also been found in other population-based Swedish surveys (184).

In this study, no significant association was found between physical inactivity and snoring -84. This is in contrast to the data of Koskenvuo et al. (76). In their paper, however, the authors defined physical inactivity as subjects who did not jogg at leisure and thereby included 83% of the studied population as physically inactive. If we use the same definition, which best corresponds to categories 1-2 of physical activity in our questionnaire, 77% of the responders would be defined as physically inactive. With this wide definition of physical inactivity, a significant association between snoring -84 and physical inactivity was also found in our study.

Evolution of snoring

The increasing prevalence of snoring with age followed by a decrease after age 50-60 also agrees with the results of previous cross-sectional studies (54, 62). In contrast, a high prevalence of sleep-related respiratory disturbances

has been reported among the elderly (27, 185). When reported snoring is regarded as mirroring the prevalence of obstructive sleep apnea syndrome, these findings appear to be confusing and the question of why subjects aged 60 and above report less snoring arises. A change in the validity of sleep questionnaires with age could be a possible explanation, but no changes in validity by age could be identified here.

Young suggested an heuristic model with sleep apnea as both an age-related disorder seen preferentially at lower ages and an age-dependent condition in the elderly with a potential overlap in the 60- to 70-year-old age range (186). If the age-dependent condition is less associated with snoring, the results obtained here would fit this model well.

Snoring and hypertension

In a systematic review by Wright et al. of epidemiological studies of sleep apnea and morbidity published in 1997, all the identified studies of sleep apnea and hypertension were cross-sectional (16). In the ongoing debate on the impact of sleep apnea on public health, Wright and Sheldon recently stated that the temporal relationship was thereby not possible to define and that the dose-response relationship was contradictory (187). Among the younger men in this population, however, the combination of snoring and EDS at baseline was a significant risk factor for hypertension at the follow-up, while the reverse was not true. This indicates that the relationship is causal rather than being due to any unidentified confounder. Furthermore, there appears to be a dose-response relationship, as the ORs increased with more severe symptoms.

Snoring, sleepiness and mortality

In previous surveys designed to study mortality in OSAS patients, increased mortality was found by some researchers (127, 151, 154) but not by others (26, 153, 155). In the four studies in which younger OSAS patients were also included, a higher mortality rate was reported in three (127, 151, 154), while, in the retrospective study conducted by Gonzalez-Rothi et al. including 91 OSAS patients (24 of whom were untreated), no increase in mortality was found. In that study, however, the mean follow-up time was less than three years and the reference group consisted of 35 non-apneic patients with symptoms suggestive of OSAS (153).

Evolution of OSAS in sleepy snorers

Among patients who even according to trained physicians have a high predicted probability of OSAS, a considerable number of subjects will turn out to be non-apneic (188). The practical question is how to proceed with these subjects. Our results indicate that these patients with snoring and daytime sleepiness but with an insignificant number of apneas run a high risk

of deteriorating over a 10-year period and developing full-blown OSAS. None of the studied risk factors at baseline could be used to identify those subjects who would develop OSAS during the follow-up period, while a deterioration in sleep-disordered breathing was often accompanied by increasing daytime sleepiness.

General discussion

These results do not explain why sleep-disordered breathing is more often associated with cardiovascular consequences in younger subjects. It is possible that, in the older age group, the relative effects of risk factors other than snoring become greater. Another speculative possibility is that some people are more vulnerable to snoring, upper airway resistance and/or obstructive sleep apnea syndrome in terms of vascular consequences and therefore develop their hypertension or cardiovascular disease early in life. Other subjects may, for some unknown reason, be less sensitive and can continue to be heavy snorers without side-effects on health.

Even though sleep apnea increases with age, it has recently been found that the severity of sleep apnea, as indicated by both the maximum intraeosophageal pressure and minimum oxygen saturation, decreases with age (75, 189). As elevations in blood pressure have been documented as accompanying arousals with periodic leg movements (190), as well as arousals experimentally induced with auditory stimuli (191), it has been suggested that the cyclical blood pressure elevations seen in OSAS patients are due to arousals. This theory is supported by our data which demonstrate that only snorers with simultaneous daytime sleepiness have a higher mortality risk. In a report by Lofaso et al. on blood pressure response to arousals in non-apneic snorers, the lowest blood pressure response was found in a 65-year-old patient, the only one in that study who was more than 50 years old (192). Furthermore, direct and indirect evidence that activation of the sympathetic nervous system plays a major role in the systemic hypertensive response has been provided by a number of studies (193-195). In an animal model using beagles, Hajduczok et al demonstrated that sympathetic activity is impaired with increasing age (196).

Sleep-disordered breathing is a relatively new field of research and our understanding of it is still in its infancy. In this study, the combination of symptoms of upper airway resistance (snoring) and of disturbed sleep (EDS) was an independent risk factor for hypertension and mortality. Subjects who reported these symptoms at baseline but turned out to be non-apneic run a high risk of developing apneas over 10 years.

As the size of the population was relatively small and the number of end-points were fairly limited among younger subjects, the conclusions cannot be regarded as definitive until this result has been confirmed by others. However, on the basis of these results, it is possible to speculate about why

diverging results have been obtained in previous studies designed to study the health effects of sleep-disordered breathing:

1. The health consequences of snoring and EDS appear to decrease with increasing age. In the Finnish cohort study, the relative risk of hypertension in habitual snorers also decreased with age and in men it was only significant below the age of 50 (RR 2.68 in males aged 40-49, 1.73 at 50-59 and 1.16 at 60-69). In females, the relative risk was significantly higher than 1.0 in all age groups, but here, too, a decrease from 4.44 at 40-49 to 2.12 at 60-69 was found (52). In most previous papers, the results have otherwise been calculated for the whole study population. Adjustments for age do not rule out different RRs at different ages and the final result will then depend on the age distribution in the population.

2. A number of studies based on sleep recordings have failed to identify a dose-response relationship between the severity of OSAS and blood pressure. However, there is still uncertainty about how to define OSAS. Most patients with increased AHIs do *not* report EDS (64). In addition, some patients with upper airway resistance but no apneas suffer from severe sleepiness (40) and UARS also appears to be related to hypertension (132, 197). Furthermore, when analysing the overnight beat-to-beat blood pressure in patients with partial upper airway obstruction, it has recently been reported that nonapneic-nonhypopneic obstructive events are followed by systemic arterial pressure increases, the magnitude of which varies with the grade of the arousal (192). It is therefore not surprising that, in previous surveys, no significant differences have been found between OSAS patients and non-apneic sleepy snorers in terms of the prevalence of hypertension (198) or mortality (153). Despite this, AHI is universally used as the only objective criterion for the severity of sleep-disordered breathing. Perhaps it will emerge that AHI is only a marker of OSAS and that other criteria, such as arousals or intrathoracic pressure, are more important when it comes to the severity of the disorder.

CONCLUSIONS

1. In middle-aged men, the prevalence of snoring increases until age 50-60 followed by a decrease. The results indicate that the risk factors for developing habitual snoring also differ with age.

2. Persistent habitual snoring over a 10-year period is a risk factor for developing hypertension in men aged 30-49 at baseline. The increased risk is independent of age, obesity, weight gain, smoking, alcohol dependence and level of physical activity. In men aged 50 and over, habitual snoring does not appear to influence the risk of developing hypertension.

3. Compared with men with no snoring or EDS, men with isolated snoring or EDS display no significant increase in mortality over a 10-year period. In contrast, the combination of reported snoring and EDS is associated with an increased mortality rate, but the effect is age-dependent. The increased mortality is partly explained by an association between "snoring and EDS" and cardiovascular disease. In men aged 60 and over, the combination of reported snoring and EDS does not appear to influence mortality.

4. Middle-aged men who report the combination of snoring and EDS are a high-risk group for developing OSAS during the following ten years, regardless of the results of the sleep recordings at baseline. Increase in daytime sleepiness is often accompanied by a deterioration in terms of respiratory disturbances during sleep.

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