OBSTRUCTIVE SLEEP APNEA
-The relationship to cardiovascular disease, diabetes mellitus, motor vehicle driving and ambient temperature

Fredrik Valham
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ABSTRACT

Background: Obstructive sleep apnea is a common disorder, especially in men. Patients with this condition often snore and suffer from excessive daytime sleepiness. It is a treatable condition related to cardiovascular disease, road traffic accidents and obesity.

Aims: To study whether snoring and witnessed sleep apnea are related to diabetes mellitus and whether sleepy subjects who snore or report sleep apneas drive more than others. To investigate whether sleep apnea is related to stroke, mortality and myocardial infarction in patients with coronary artery disease. To study the effect of ambient temperature on sleep apnea, morning alertness and sleep quality in patients with obstructive sleep apnea.

Methods and results: Questions on snoring, sleep apnea, daytime sleepiness and yearly driving distance were included in the northern Sweden component of the WHO MONICA study. Analyzed were 7905 randomly selected men and women aged 25-79 years. Snoring and witnessed sleep apnea were related to diabetes mellitus in women, (OR 1.58, p = 0.041 and OR 3.29, p = 0.012 respectively), independent of obesity, age and smoking, but not in men. Sleepy snoring men drove a mean of 22566 km per year which was more than others who drove 17751 km per year independent of age, BMI, smoking and physical activity (p = 0.02). Sleepy men reporting sleep apnea also drove more (p = 0.01). 392 men and women with coronary artery disease referred for coronary angiography were examined with overnight sleep apnea recordings and followed for 10 years. Sleep apnea was recorded in 211 (54%) of patients at baseline. Stroke occurred in 47 (12%) patients at follow up. Sleep apnea was associated with an increased risk of stroke (HR 2.89, 95% CI 1.37 - 6.09, p = 0.005) independent of age, BMI, left ventricular function, diabetes mellitus, gender, intervention, hypertension, atrial fibrillation, a previous stroke or TIA and smoking. The risk of stroke increased with the severity of sleep apnea. 40 patients with obstructive sleep apnea were investigated with overnight polysomnography in ambient temperatures of 16°C, 20°C and 24°C in random order. Total sleep time was a mean of 30 minutes longer (p = 0.009), sleep efficiency higher (p = 0.012), patients were more alert in the morning (p = 0.028), but sleep apnea was more severe when sleeping in 16°C (p = 0.001) and 20°C (p = 0.033) vs. 24°C. The AHI was 30 ± 17 in 16°C room temperature, 28 ± 17 in 20°C and 24 ± 18 in 24°C.

Conclusions: Snoring and witnessed sleep apneas are related to diabetes mellitus in women. Sleepy men who snore or report sleep apnea drive more than others. Sleep apnea is independently associated with the risk of stroke among patients with coronary artery disease. Subjects with obstructive sleep apnea sleep longer, are more alert in the morning after a night’s sleep, but sleep apnea is more severe when sleeping in a colder environment.
ORIGINAL PAPERS

The thesis is based on the following papers, which will be referred to in the text by their assigned roman numerals.


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DEFINITIONS

Apnea  A cessation of airflow for ≥10 seconds.

Hypopnea  A reduction of airflow of 50% from baseline or a marked reduction in airflow followed by desaturation of >3% or an arousal. The event must last for ≥10 seconds.

Apnea hypopnea Index (AHI)  The mean number of apneas and hypopneas per hour of sleep.

Obstructive sleep apnea (OSA)  An obstructive apnea hypopnea index of 5 or more.

Obstructive sleep apnea syndrome (OSAS)  An obstructive apnea hypopnea index of 5 or more in combination with symptoms such as excessive daytime sleepiness.

BMI  Weight/Height$^2$ (kg/m$^2$).

CPAP  Continuous positive airway pressure.

WHO  World Health Organization.

MONICA  Multinational Monitoring of Trends and Determinants of Cardiovascular Disease.
SVENSK SAMMANFATTNING


Syftet med de 4 genomförda studierna var: Att undersöka om snarkning och bevittnade andningsuppehåll under sömnen är relaterat till diabetes mellitus och om dagtrötta personer som anger att de snarkar eller har nattliga andningsuppehåll kör mer bil än andra. Att undersöka om sömnnapné är relaterat till stroke, hjärtinfarkt och förtida död. Att undersöka om rumstemperaturen påverkar sömnnapné, sömnkvalitet och vakenhet hos patienter med obstruktiv sömnnapné.

Frågor om snarkning, andningsuppehåll under sömnen, dagtrötthet och årlig körsträcka inkluderades i WHO:s MONICA frågeformulär i norra Sverige som skickades till slumpvis utvalda personer i Norrbotten och Västerbotten. 7905 män och kvinnor i åldrarna 25-79 år analyserades. Diabetes mellitus var hos kvinnor relaterat till snarkning (OR 1.58, p = 0.041) och bevittnade andningsuppehåll under sömnen (OR 3.29, p = 0.012) oberoende av fetma, ålder och rökning. Detta samband sågs inte hos män. Sömniga snarkande män hade en genomsnittlig körsträcka på 22566 kilometer per år vilket var mer än andra som i genomsnitt körde 17751 km per år oberoende av ålder, BMI, rökning och fysisk aktivitet (p = 0.02). Sömniga män som angav att de hade bevittnade andningsuppehåll under sömnen körde också mer jämfört med andra grupper (p = 0.01). Dagtrötthet och snarkning eller andningsuppehåll under sömnen var inte relaterat till årlig körsträcka hos kvinnor efter kontroll för ålder, BMI, fysisk aktivitet och rökning.

392 män och kvinnor med kranskärlassjukdom gjorde sömnnapneutredning i samband med kranskärllsröntgen och följdes i 10 år. Sömnnapné konstaterades hos 211 (54%) av patienterna vid studiestart. Stroke drabbade 47 (12%) av patienterna under uppföljningstiden. Sömnnapné var associerat till en ökad risk för stroke (HR 2.89, 95% CI 1.37 - 6.09, p = 0.005) oberoende av ålder, BMI, vänsterkammarfunktion, diabetes mellitus, kön, kardiall intervention, högt blodtryck, förmaksflimmer, tidigare stroke eller TIA och rökning. Risken för stroke ökade med ökad svårighetsgrad av sömnnapné.

40 patienter med obstruktiv sömnnapné undersöktes med nattlig polysomnografi i rumstemperatur på 16°C, 20°C och 24°C i slumpvis ordning. De sov 30 minuter längre och var piggare på morgonen i 16°C jämfört med 24°C. Däremot ökade svårighetsgraden av sömnnapné då patienterna sov i 16°C och 20°C jämfört med 24°C. Apne-hypopne index var 30 ± 17 i 16°C rumstemperatur och 28 ± 17 i 20°C och 24 ± 18 i 24°C.
INTRODUCTION

Summary introduction to the present studies
Patients with sleep apnea snore, have an increased upper airway resistance, and are tired during daytime. Sleep apnea is related to cardiovascular disease, hypertension and an increased risk of traffic accidents and can be treated with CPAP and mandibular repositioning appliance.

There is an increased interest in the association between snoring, sleep apnea and diabetes mellitus. A relationship between snoring and diabetes mellitus independent of obesity has been shown in women and between snoring and impaired glucose tolerance in non-obese men 1-4. We therefore investigated the relationship between snoring, witnessed sleep apnea and diabetes mellitus in men and women.

Patients with sleep apnea run an increased risk of being involved in traffic accidents and perform poorly on traffic simulators 5-15. However, no previous study has systematically explored the driving distance among subjects with daytime sleepiness, snoring or sleep apnea. We therefore investigated the yearly driving distance among 7904 men and women from the northernmost counties in Sweden: Norrbotten and Västerbotten.

Sleep apnea is common among patients with coronary artery disease 16-25. Some previous studies report an increase in mortality related to sleep apnea while others do not 21, 26-29. Mooe et al. investigated 408 patients with coronary artery disease during 1992 to 1995 19. We have followed these patients for a 10 year period to assess whether sleep apnea is a risk factor for stroke, myocardial infarction and death.

Sleep apnea is a common disorder and it is therefore important to examine possible factors that can alleviate or prevent the condition. Anecdotally individual patients investigated for sleep apnea have reported an improved quality of sleep and feeling more alert in the morning when sleeping in cooler temperatures. We hypothesized that obstructive sleep apnea would diminish in a colder environment. We therefore investigated 40 patients with sleep apnea in 16°C, 20°C and 24°C indoor temperature to study the effect of ambient temperature on sleep apnea, sleepiness and sleep quality.

History of obstructive sleep apnea
Obstructive sleep apnea as a diagnosis has grown in prominence over the last four decades. Early studies by Guilleminault et al. defined the disease 30. Gislason observed that snoring and sleep apnea was common in a study on male subjects from Uppsala, Sweden 31. Young et al. showed that sleep apnea is a common disorder in the population affecting approximately 24% of men and 9% of women 32. In 1981 treatment with CPAP was introduced by Sullivan et al. 33. Additionally, surgical treatment with uvulopalatopharyngoplasty (UPPP) was introduced also in
In 1981 the treatment method of mandibular repositioning appliance was put forward by Soll et al. \textsuperscript{35}.

**Pathophysiology and risk factors for obstructive sleep apnea**

Subjects with obstructive sleep apnea have repetitive apneas and hypopneas during sleep. They snore and are often tired during daytime. Obstructive apneas are either described as complete, apneas, or partial, hypopneas. Such apneas are mainly due to reduced muscle tone of the upper airway and tongue during sleep resulting in blockage of the airway in patients who are susceptible to sleep apnea. Obstructive sleep apnea is considered when there are at least 5 apneas or hypopneas per hour of sleep. For the diagnosis obstructive sleep apnea syndrome the patient must also exhibit symptoms such as excessive daytime sleepiness. Definitions and diagnostic criteria for obstructive sleep apnea and obstructive sleep apnea syndrome are found in this thesis appendix on page 25.

Anatomical factors that predispose to obstructive sleep apnea are a large tongue, large tonsils, a short mandible and obesity with an increased deposition of fat in tissues surrounding the neck and throat \textsuperscript{36-39}. Other predisposing factors are male sex, age greater than 65 years and sleeping in supine position \textsuperscript{40-46}. Sex-specific predisposing factors for obstructive sleep apnea are large tonsils, a high tongue base and a wide uvula in males and large tonsils and an underbite in females \textsuperscript{47}. There is also an increased risk of developing obstructive sleep apnea if a first degree relative is suffering from the syndrome \textsuperscript{48-50}.

The prevalence of sleep apnea was estimated by Young et al. in a random sample of 602 US state employees between 30-60 years of age. 9 \% of women and 24 \% of men suffered from sleep apnea defined as an AHI of 5 or more. Furthermore it was estimated that 2\% of women and 4\% of men met the diagnostic criteria for the sleep apnea syndrome i.e. AHI of 5 or more and concomitant excessive daytime sleepiness \textsuperscript{32}. Duran et al. reported a prevalence of obstructive sleep apnea (AHI $\geq$5) of 26\% in men and 28\% in women \textsuperscript{51}. Bixler et al. found a obstructive sleep apnea prevalence of 7.2\% for men and 2.2\% in women with an AHI of $\geq$15 \textsuperscript{52}.

**Excessive daytime sleepiness**

Excessive daytime sleepiness is a common symptom in obstructive sleep apnea which can be measured from different sleepiness scales.

The Epworth Sleepiness Scale (ESS) is a patient questionnaire assessing a subject’s likeliness to fall asleep in 8 given situations. The subject scores each situation from 0 to 3. Maximum point given is 24 and 10 points or more is considered excessive daytime sleepiness \textsuperscript{53}.

The Karolinska Sleepiness Scale (KSS) is a questionnaire assessing the subjective sleepiness at a given moment. It consists of a ten-grade scale in which the patient assesses his or her level of sleepiness from extremely alert to extremely sleepy \textsuperscript{54}. 
Snoring
Snoring is regularly described as a loud noise due to vibration of structures in the pharynx and oropharynx while breathing during sleep but there is a lack of objective measurements and definition for snoring. Snoring is therefore primarily based on subjective reports from the patient or a close relative of the patient. Gislason et al. reported a prevalence of 15.5% for habitual snoring and of 29.6% of occasional snoring. In a study by Kayukawa et al outpatients from a general hospital in Japan had a prevalence of habitual snoring of 16% in men and 6.5% in women.
DIAGNOSTIC PROCEDURES

Polysomnography (Figure 1)
Polysomnography is the gold standard for sleep apnea recordings. It includes overnight continuous recordings of sleep using electroencephalograms (EEG), electromyograms (EMG) and electrooculograms (EOG). Respiratory airflow is measured by thermistors or nasal pressure cannulae. Respiratory movements are measured with abdominal and chest piezo-electric belts, respiratory inductive plethysmography (RIP) or esophageal pressure. Oxygen saturation is measured with a pulseoximetry. Measurements also include an electrocardiogram (V5) and body position sensor.

Figure 1. Polysomnography equipment.
Simplified sleep apnea recordings (Figure 2)
Due to the high cost of polysomnography, especially the analysis and measurements of EEG, various simplified sleep apnea recordings are available. This method of investigation is common in clinical practice. According to the Swedish Council on Technology Assessment in Health Care (SBU) there is a high sensitivity (0.93) and specificity (0.92) if recordings are manually scored and include measurements of respiratory movements, oronasal airflow and oxygen saturation.

Figure 2. Simplified sleep apnea recordings.
TREATMENT OF OBSTRUCTIVE SLEEP APNEA

Continuous positive airway pressure (CPAP) (Figure 3)
Sullivan et al. introduced continuous positive airway pressure (CPAP) via a nose mask as a treatment for obstructive sleep apnea in 1981. CPAP remains the most effective treatment for obstructive sleep apnea. The majority of patients with moderate to severe sleep apnea tolerate this treatment. There is evidence that CPAP treatment diminishes obstructions in the upper airway and reduces daytime sleepiness according to the Cochrane collaboration and the Swedish Council on Technology Assessment in Health Care (SBU).

![Figure 3. Continuous positive airway pressure applied with a nose mask.](image)

Mandibular repositioning appliance (Figure 4)
In 1985 Soll et al. introduced a treatment method for snoring and sleep apnea with a mandible repositioning appliance (MRA). The appliance works by extending the mandible together with the tongue enabling the airway to stay open. Marklund et al. found that frequent use of MRA resulted in less headaches, less excessive daytime sleepiness and less nighttime awakenings weekly. This treatment is indicated in mild to moderate and position dependent sleep apnea. MRA is a common treatment in Sweden and internationally. According to the Swedish Council on Technology Assessment in Health Care (SBU) and Cochrane collaboration there is evidence that treatment with MRA reduces daytime sleepiness and improves apnea hypopnea index in patients with mild to moderate sleep apnea syndrome, but to a lesser degree than CPAP.
Surgery
Fujita et al. introduced upper airway surgery namely uvulopalatopharyngoplasty (UPPP) as a treatment for obstructive sleep apnea in 1981. The surgical procedure involves removal of excess soft tissue comprising the uvula, tonsils, and part of the soft palate. Other surgical methods utilized are laser assisted uvulopalatoplasty (LAUP) and temperature controlled radio frequency tissue volume ablation (TCRAFTA). There is however a lack of evidence on the effect of surgery on sleep apnea. The number of surgically treated patients has declined over the past few years.

Weight reduction
There are few randomized controlled trials assessing the effect of weight reduction on obstructive sleep apnea. Two studies report that weight reduction after a liquid “Very Low Calorie Diet” with lifestyle counseling reduces the severity of obstructive sleep apnea. The initial improvements after dietary treatment were maintained over a one year follow-up but there is a lack of long term studies.
COMORBIDITIES IN SLEEP APNEA

Cardiovascular disease, stroke and obstructive sleep apnea

Obstructive sleep apnea is an independent risk for fatal and non-fatal cardiovascular events and stroke according to 4 prospective studies \(^{65-68}\) (table 1).

<table>
<thead>
<tr>
<th>Author</th>
<th>n</th>
<th>Time of follow-up</th>
<th>AHI</th>
<th>OR/HR</th>
<th>Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with obstructive sleep apnea</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yaggi et al. (^{65}) (2005)</td>
<td>1022</td>
<td>3.4 years</td>
<td>≥5</td>
<td>1.97</td>
<td>Stroke &amp; death</td>
</tr>
<tr>
<td>Marin et al. (^{66}) (2005)</td>
<td>1387</td>
<td>10.1 years</td>
<td>&gt;30</td>
<td>fatal 2.87 nonfatal 3.17</td>
<td>Fatal and non-fatal cardiovascular event</td>
</tr>
<tr>
<td>General population studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Munoz et al. (^{67}) (2006)</td>
<td>394</td>
<td>6 years</td>
<td>≥30</td>
<td>2.52</td>
<td>Ischemic stroke</td>
</tr>
<tr>
<td>Redline et al. (^{68}) (2010)</td>
<td>5422</td>
<td>8.7 years</td>
<td>&gt;19</td>
<td>Male 2.86</td>
<td>Incident ischemic stroke</td>
</tr>
</tbody>
</table>

Table 1. Prospective studies on cardiovascular disease and stroke.

Coronary artery disease and obstructive sleep apnea

Obstructive sleep apnea is overrepresented in patients with coronary artery disease with prevalence’s ranging from 22-76% \(^{16-19,21-24,26,69,70}\) (table 2). Mehra et al. observed a prevalence of obstructive sleep apnea in 66% of patients suffering from acute coronary syndrome \(^{70}\).

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>n</th>
<th>AHI limit</th>
<th>OSA Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>De Olazabal et al. (^{16}) (1982)</td>
<td>17</td>
<td>n/a</td>
<td>76%</td>
</tr>
<tr>
<td>Andreas et al. (^{17}) (1996)</td>
<td>50</td>
<td>&gt;10</td>
<td>50%</td>
</tr>
<tr>
<td>Mooe et al. (^{18}) (1996)</td>
<td>142</td>
<td>≥10</td>
<td>37%</td>
</tr>
<tr>
<td>Mooe et al. (^{69}) (1996)</td>
<td>102</td>
<td>≥5</td>
<td>54%</td>
</tr>
<tr>
<td>Moruzzi et al. (^{22}) (1999)</td>
<td>67</td>
<td>≥10</td>
<td>22%</td>
</tr>
<tr>
<td>Peker et al. (^{21}) (1999)</td>
<td>62</td>
<td>≥10</td>
<td>31%</td>
</tr>
<tr>
<td>Mooe et al. (^{19}) (2001)</td>
<td>408</td>
<td>≥10</td>
<td>34%</td>
</tr>
<tr>
<td>Sanner et al. (^{23}) (2001)</td>
<td>68</td>
<td>≥10</td>
<td>31%</td>
</tr>
<tr>
<td>Hagenah et al. (^{26}) (2005)</td>
<td>50</td>
<td>AI &gt;10</td>
<td>50%</td>
</tr>
<tr>
<td>Mehra et al. (^{70}) (2006)</td>
<td>104</td>
<td>≥10</td>
<td>66%</td>
</tr>
<tr>
<td>Prinz et al. (^{24}) (2010)</td>
<td>257</td>
<td>≥5</td>
<td>51%</td>
</tr>
</tbody>
</table>

Table 2. Prevalence of obstructive sleep apnea (OSA) in patients with coronary artery disease. AI = Apnea Index. AHI = Apnea Hypopnea Index.

Nocturnal angina and sleep apnea

Two studies report that sleep apnea can provoke both subjective and objective signs of nocturnal ischemia among patients with coronary artery disease. Franklin et al
found that sleep apnea induce nocturnal ischemia and ST-depression, reversible with CPAP, among patients with coronary artery disease. ST-segment depression is common amongst patients with coronary artery disease and obstructive sleep apnea according to Mooe et al. Moreover, most ST-segmental depressions were coupled to a preceding series of apneas or desaturations or both. The presence of ST-segmental depression was increased among patients with established ischemic heart disease untreated for obstructive sleep apnea in a study by Peled et al. CPAP treatment reduced the duration of ischemic events.

Cardiovascular adaptation to sleep apnea
Meng et al. reported increased intraventricular septal thickness and increased incidence of 2-vessel disease among patients with obstructive sleep apnea and coronary artery disease. Whilst a study by Steiner et al. found an increased number of coronary collateral vessels in patients with co-existing coronary artery disease and obstructive sleep apnea suggesting a cardiac adaptation.

Stroke and sleep apnea
The WHO definition of stroke is rapidly developing clinical signs of focal (or global) disturbance of cerebral function that lasted for at least 24 hours with no apparent cause other than a vascular origin. Established risk factors for stroke are hypertension, atrial fibrillation, diabetes mellitus, smoking, hyperlipidemia and carotid stenosis. Approximately 30 000 persons suffer a stroke each year in Sweden according to the Swedish Hospital Discharge Register at the Swedish National Board of Health and Welfare. The mean age of a person suffering a stroke in 2009 was 73.4 years for men and 78.3 years for women. Approximately 80% of strokes have an ischemic aetiology whilst 20% are secondary to intracranial or subarachnoid bleedings.

Sleep apnea is very common in stroke victims with a prevalence ranging from 17 to 91% (table 3). Silent brain infarction i.e. cerebrovascular disease with small infarctions resulting in tissue damage to the brain but without transient ischemic attack or stroke is more prevalent in patients with obstructive sleep apnea compared with control. Silent brain infarction was seen in 25% of patients with moderate to severe obstructive sleep apnea, 6.7% in obese control subjects and 7.7% in patients with mild obstructive sleep apnea. There is an increased prevalence of silent brain infarction among patients with moderate to severe obstructive sleep apnea compared to patients with less severe illness.
<table>
<thead>
<tr>
<th>Author (year)</th>
<th>n</th>
<th>OSA Prevalence</th>
<th>AHI limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyken et al. (1996)</td>
<td>24</td>
<td>OSA 77%</td>
<td>AHI ≥10</td>
</tr>
<tr>
<td>Bassetti et al. (1999)</td>
<td>80</td>
<td>OSA 63%</td>
<td>AHI ≥10</td>
</tr>
<tr>
<td>Parra et al. (2000)</td>
<td>161</td>
<td>OSA 52%</td>
<td>AHI ≥10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CSA 39%</td>
<td></td>
</tr>
<tr>
<td>Wessendorf et al. (2000)</td>
<td>147</td>
<td>OSA 61%</td>
<td>AHI ≥5</td>
</tr>
<tr>
<td>Sandberg et al. (2001)</td>
<td>133</td>
<td>OSA 22%</td>
<td>AHI ≥10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CSA 26%</td>
<td></td>
</tr>
<tr>
<td>Iranzo et al. (2003)</td>
<td>50</td>
<td>OSA 30%</td>
<td>AHI ≥10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CSA 4%</td>
<td></td>
</tr>
<tr>
<td>Turkington et al. (2004)</td>
<td>120</td>
<td>OSA 61%</td>
<td>AHI &gt;10</td>
</tr>
<tr>
<td>Bassetti et al. (2006)</td>
<td>152</td>
<td>Sleep apnea</td>
<td>AHI ≥10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>58%</td>
<td></td>
</tr>
<tr>
<td>Rowat et al. (2006)</td>
<td>156</td>
<td>CSA 24%</td>
<td>AHI n/a</td>
</tr>
<tr>
<td>Brooks et al. (2010)</td>
<td>45</td>
<td>OSA 91%</td>
<td>AHI ≥10</td>
</tr>
</tbody>
</table>

Table 3. Prevalence of sleep apnea among stroke victims. OSA = Obstructive Sleep Apnea. CSA = Central Sleep Apnea. AHI = Apnea Hypopnea Index.

Sleep apnea is associated with a worse functional outcome and increased mortality in patients with stroke. Sahlin et al. recently reported that stroke victims with obstructive sleep apnea (AHI ≥15) have an increased risk for early death at 10 year follow up compared with those without sleep apnea or central sleep apnea. In patients treated with CPAP the percentage of patients with neurological improvement after 1 month is higher and time to appearance of further cardiovascular events is longer.

The goal of cerebral vascular auto regulation is to ensure stable tissue perfusion at any given time and is coupled to both local neurovascular and metabolic control but the sympathetic innervation of blood vessels is considered to be inadequate or absent. The neurovascular coupling responds to changes in activation of particular brain regions leading to a locally raised metabolic demand and a requirement for increased blood flow and proportional increase of blood flow velocity. The metabolic coupling responds to changes in blood levels of PCO₂ and PO₂. A raise in PCO₂ due to increased metabolism results in vascular dilatation and increased blood flow. However the cerebral auto regulatory mechanisms seem to be disturbed in patients with sleep apnea. In 1998 Diomedi et al. reported an association between obstructive sleep apnea syndrome and a reduced cerebral vasodilator reserve. Reichmut et al. detected an impaired cerebral vasodilator response to hypoxia and hypercapnia in patients with obstructive sleep apnea. In a recent study on a population based sample, subjects with sleep apnea had a diminished hypercapnic vasodilative capacity associated with hypoxemia during sleep.

Bålfors and Franklin postulated that rapid changes in cerebral blood flow and blood pressure during obstructive sleep apnea episodes cause sleep apnea induced stroke. Cerebral blood flow velocity increases during an obstructive apnea and decreases after apnea termination, concomitant with decrease in arterial pressure and cerebral blood flow. The variation could be due to either changes in arterial blood pressure in
passive cerebral blood vessels or fast blood pressure changes superseding auto regulation. The combination of hypoxemia and reduced cerebral perfusion may predispose for nocturnal cerebral ischemia in patients with obstructive sleep apnea. Foster et al. observed that such changes in cerebral blood flow were eliminated with CPAP.

**CPAP treatment of stroke patients with sleep apnea**
In a randomized controlled trial Sandberg et al. found less depressive symptoms and better scores in “activities of daily living” (ADL) among patients with stroke when receiving treatment for obstructive sleep apnea. Compliance to CPAP treatment is often a problem for patients who have suffered a stroke. Most authors report a low tolerance and compliance with CPAP amongst patients having suffered a stroke except for one study that reported good tolerance.

**Hypertension and obstructive sleep apnea**
Hypertension is defined as an arterial blood pressure of more than 140/90 mmHg or in patients with diabetes mellitus or kidney disease at 130/80 mmHg. Hypertension is according to the WHO responsible for approximately 13% of deaths worldwide due to cardiovascular disease as a consequence of non optimal blood pressure. Together with tobacco use, high blood glucose, physical inactivity and obesity hypertension is responsible for raising the risk of chronic diseases such as heart disease, diabetes and cancers.

Hypertension is a major risk factor for cardiovascular disease and is also associated with sleep apnea. In an early crosssectional study Kales et al. reported a 30% prevalence of sleep apnea among patients with hypertension. A prospective study by Peppard et al. found that patients with obstructive sleep apnea run an increased risk of hypertension. The risk of hypertension was augmented with increased severity of sleep apnea. In patients with an AHI of 15 or above the risk of simultaneous hypertension was approximately tripled.

Several studies have investigated the effect of CPAP treatment on blood pressure in patients with obstructive sleep apnea independently of a history of established hypertension. Some studies report a reduction of blood pressure of 2-9.9 mmHg while other studies found no effect on blood pressure. Two recent randomized controlled trials investigating patients with hypertension and obstructive sleep apnea report a reduction in blood pressure with CPAP. Duran-Cantolla et al. reported a reduction in mean 24 hour blood pressure of 1.5 mmHg. Lozano et al. observed a 6 mmHg reduction in daytime diastolic blood pressure in treatment group.

The increased prevalence of hypertension among patients with sleep apnea could be due to an increased activity in the sympathetic nervous system. Blood and urinary levels of norepinephrine and normetanephrine are elevated among patients with sleep apnea. Hedner et al. investigated patients with sleep apnea with overnight and daytime measurements of sleep and muscle nerve activity. They
observed a higher muscle nerve sympathetic activity both in awake and during sleep in patients with sleep apnea compared to control\textsuperscript{127}. Another possible mechanism for sleep apnea induced hypertension is a distortion in the synthesis of or the expression of endothelial dilators and vasoconstrictors. Gjørup et al. reported a correlation between the vasoconstrictor Endothelin-1 and obstructive sleep apnea reasserting the results from an earlier study by Philips et al. from 1999\textsuperscript{128,129}. From the results of Lattimore et al. it also seems that obstructive sleep apnea inhibits the synthesis of endothelial nitric oxide, a potent vasodilator, and that CPAP treatment improves baseline endothelial nitric oxide release\textsuperscript{130}.

Blood pressure has been found to be highly unstable during and after obstructive sleep apneas. In recent years blood pressure variability and instability has been the focus of increasing attention given its role in the pathophysiology of cardiovascular disease. It is possible that variation and instability in blood pressure can increase tissue and organ damage promoting the occurrence of vascular events\textsuperscript{131,132}.

**Diabetes mellitus and obstructive sleep apnea**

According to the WHO the prevalence of diabetes mellitus for all age groups worldwide is estimated to 2.8\%\textsuperscript{133}. In Sweden the prevalence of diabetes mellitus is estimated to approximately 4\% among adults\textsuperscript{134-136}. The proportion of type 2 diabetes mellitus is estimated to be 80-90\%. Globally the total number of people with diabetes mellitus is thought to increase from 171 million in the year 2000 to become 366 millions in 2030\textsuperscript{133}. The additional global mortality attributable to diabetes mellitus in the year 2000 has been estimated to be 2.9 million deaths, equivalent to 5.2\% of all deaths\textsuperscript{137}. Major risk factors for developing type 2 diabetes mellitus is obesity, physical inactivity and to a degree hereditary and genetic factors\textsuperscript{138-141}.

The diagnostic criteria for diabetes mellitus are fasting blood glucose ≥6.1 mmol/l or plasma glucose ≥7.0 mmol/l on two separate occasions. Diagnosis can also be confirmed with an oral glucose tolerance test (OGTT) if blood glucose levels are ≥10.0 mmol/l or plasma glucose levels are ≥11.1 mmol/l 2 hours after oral intake of a standard dose of glucose\textsuperscript{142-144}. Insulin resistance describes as a state of insufficient biological response to a normal level of circulating insulin or lowered insulin sensitivity.

The prevalence of type 2 diabetes mellitus is reported in between approximately 14-30\% in patients with obstructive sleep apnea\textsuperscript{145-149}. In a population sample cohort of 400 women aged 20-70 years in Uppsala, Sweden the investigators found an independent association between obstructive sleep apnea and decreased insulin sensitivity\textsuperscript{150}. Foster et al. recently found an 86\% prevalence of sleep apnea amongst obese men and women with diabetes mellitus\textsuperscript{151}.

Some prospective studies report that incident diabetes mellitus is increased among both snorers and patients with sleep apnea but others do not\textsuperscript{3,146,152}. In the Nurses’ Health Study the investigators found an increased risk of developing diabetes
mellitus in snoring female nurses \(^3\). Marshall et al. reported that severe obstructive sleep apnea is an independent risk factor for incident diabetes mellitus during a 4 year follow-up period \(^{152}\). However Reichmut et al. did not find an association between sleep apnea and development of diabetes mellitus in long term follow-up \(^{146}\).

Other prospective studies investigating the effect of CPAP treatment on glucose metabolism in obstructive sleep apnea patients report improved glucose metabolism while others do not \(^{153}-^{156}\). Harsch et al. reported improved insulin sensitivity in patients with obstructive sleep apnea syndrome after CPAP treatment for 2 days, an effect which continued at 3 months \(^{155}\). Dawson et al. found improved glucose control after CPAP treatment of patients with diabetes mellitus and obstructive sleep apnea \(^{156}\). Botros et al. studied patients referred for sleep apnea investigation and noticed an attenuation in the risk of new-onset diabetes in patients with regular use of CPAP \(^{154}\). However, Chuadaroglu et al. found no association between AHI and insulin resistance following CPAP treatment \(^{153}\).

Evidence from randomized controlled trials investigating the effect of CPAP treatment on glucose metabolism in patients with obstructive sleep apnea is scarce and the results are conflicting. Some studies report improved glucose metabolism while others do not \(^{122, 157, 158}\). Lam et al. observed improved insulin sensitivity after one week of CPAP treatment in full study group of non-diabetic males and continued improved insulin sensitivity after 3 months in subjects with BMI ≥25 \(^{158}\). West et al. reported no difference in glycaemic control or insulin resistance after 3 months of CPAP treatment in patients with diabetes mellitus and obstructive sleep apnea \(^{157}\). Coughlin et al. investigated 34 CPAP naïve patients from a sleep disorder clinic and found no difference in insulin resistance or metabolic profile at 6 week follow up \(^{122}\).

The link between diabetes mellitus and obstructive sleep apnea is confounded by common risk factors. Increased activity in the sympathetic nervous system due to sleep apneas and the release of inflammatory cytokines from cyclic hypoxia, distorted serum cortisol levels from sleep deprivation and fragmented sleep are suggested as a possible mechanism linking obstructive sleep apnea with diabetes mellitus \(^3, 126, 127, 155, 159-163\).
The most common cause of death in Sweden is cardiovascular disease and it is the underlying disease for 37% of women and 40% of men. The second most common cause of death is neoplasm’s and constitutes 23% of all deaths for women and 27% of deaths for men. Some previous studies report an increase in mortality related to sleep apnea while others do not. Partinen et al. reported increased mortality in patients receiving conservative treatment (weight loss treatment and sleep hygiene advice) as compared to invasive treatment including tracheostomy after a 5 year follow-up. In a recent study by Shah et al. patients with obstructive sleep apnea ran an increased risk of suffering myocardial infarction, of needing a myocardial revascularization procedure or death from cardiovascular causes compared to patients without obstructive sleep apnea.

In patients suffering coronary artery disease or heart failure the presence of co-existent sleep apnea constitutes an increased risk of an additional cardiovascular event or death. Mooe et al. observed an increased risk of suffering the combined endpoint of stroke, myocardial infarction or death in patients with coronary artery disease and sleep apnea at 5 year follow-up. Furthermore, Wang et al. reported increased mortality in patients with heart failure and obstructive sleep apnea. In a prospective study of patients considered for heart transplantation, Roebuck et al. found a harmful impact of sleep apnea on survival early (within 500 days) but not in long term follow-up (52 months).

Patients with CPAP treatment have a better prognosis than untreated patients or patients non-compliant to treatment. Marin et al. enrolled patients with obstructive sleep apnea from a sleep disorder unit as well as a control group of healthy men and followed the participants for 10 years. They found an approximately threefold risk of the composite endpoints of fatal or nonfatal cardiovascular events among untreated patients compared to healthy participants. Doherty et al. reported increased cardiovascular mortality in untreated patients with obstructive sleep apnea and a protective effect of CPAP treatment. In a prospective study Milleron et al. observed a decrease in the composite endpoint of cardiovascular death, acute coronary syndrome, hospitalization for heart failure or need for coronary revascularization in the group receiving CPAP treatment versus patients with no treatment. Buchner et al. followed obstructive sleep apnea patients not accepting CPAP treatment and found a threefold increase in fatal and nonfatal cardiovascular events at a 6 year follow up. No randomized controlled trial has followed a cohort of treated versus untreated obstructive sleep apnea patients.
OBSTRUCTIVE SLEEP APNEA AND MOTOR VEHICLE ACCIDENTS

Traffic accidents are one of the top ten causes of death globally according to estimations by WHO. During 2004 1.3 million people were killed in road traffic accidents worldwide. According to Transport Analysis (Trafik Analys), a Swedish government agency, 249 people died in traffic in Sweden during 2010. The same year police reported 16500 traffic accidents where there were personal injuries. 2325 people were severely injured and 13 930 people sustained minor injuries. There are considerable differences in the incidence of traffic accident injuries in different parts of the country. In 2009 Västerbotten, Gotland and Dalarna county had the highest national incidence with 140-150 severely injured people per 100 000 residents.

According to Swedish law and the Swedish Transport Administration (Trafikverket) it is illegal for a person to drive if suffering from sleep apnea or other illnesses with sleep disturbance unless successfully treated.

Sleep apnea, snoring and the risk of traffic accidents has been investigated in several studies. Obstructive sleep apnea as well as snoring is associated with an increased risk of traffic accidents. Patients with sleep apnea perform worse in traffic simulators compared to control groups. Treatment of sleep apnea with CPAP reduces the risk of traffic accidents and improves the simulator performance. According to The Swedish Council on Technology and Assessment in Health Care (SBU) there is an association between obstructive sleep apnea and traffic accidents independent of kilometers driven and daytime sleepiness. (Tables 4-5)
<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Study design, No of participants</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sleep apnea and traffic accidents</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Findley et al.          (1988)</td>
<td>Case/control n = 29/35</td>
<td>OSA: OR 7.0 for accident.</td>
</tr>
<tr>
<td>Horstmann et al. (2000)</td>
<td>Case/control n = 156/160</td>
<td>OSA 12.4% accident vs. 2.9% for control.</td>
</tr>
<tr>
<td>Mulgrew et al. (2008)</td>
<td>Case/control n = 783/783</td>
<td>Severe OSA: RR 2.0 for accident.</td>
</tr>
<tr>
<td><strong>Snoring and traffic accidents</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haraldsson et al. (1990)</td>
<td>Case/control n = 140/142</td>
<td>Snoring + sleep disturbance + EDS OR = 12.0 for accident.</td>
</tr>
<tr>
<td><strong>Sleep apnea and simulator performance</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barbe et al. (1998)</td>
<td>Case/control n = 60/60</td>
<td>OSA OR 2.3 for accident vs. control</td>
</tr>
<tr>
<td>Risser et al. (2000)</td>
<td>Case/control n = 15/15</td>
<td>OSA increased instability in driving and increased crash rate vs. control.</td>
</tr>
<tr>
<td>Juniper et al. (2000)</td>
<td>Case/control n = 12/12</td>
<td>OSA significantly worse performance in steering, attention, off road events.</td>
</tr>
<tr>
<td>Turkington et al. (2001)</td>
<td>Experimental n = 150</td>
<td>Age, female sex, alcohol strongest determinant for simulator result. ESS score assoc. with near miss accident and falling asleep at the wheel.</td>
</tr>
<tr>
<td>Pichel et al. (2006)</td>
<td>Experimental n = 129</td>
<td>Alcohol &amp; SF-36 associated to poor result on simulator.</td>
</tr>
<tr>
<td>Philip et al. (2008)</td>
<td>Case-control n = 38/14</td>
<td>Poor simulator result correlated with MWT, KSS and ESS.</td>
</tr>
<tr>
<td><strong>Retrospective studies</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Young et al. (1997)</td>
<td>General population n = 913</td>
<td>Habitual snorer OR 3.4, AHI 5-15 OR 4.2, AHI &gt;15 OR 3.4 for accident during past 5 yrs.</td>
</tr>
<tr>
<td>George et al. (1999)</td>
<td>Case-control n = 460/581</td>
<td>Accident rate/year increased among OSA vs. control. Patient with OSA 2 times more traffic fines vs. control.</td>
</tr>
</tbody>
</table>

**Table 4.** Sleep apnea, snoring and the risk of traffic accidents  
(ESS=Epworth Sleepiness Scale, KSS=Karolinska Sleepiness Scale, RR=Relative Risk, OSA=Obstructive Sleep Apnea, OR=Odds Ratio, MVT=Maintenance of Wakefulness Test).
<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Study design, No of participants</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cassel et al. (1996)</td>
<td>Cohort n = 59</td>
<td>Sig. reduced accident rate with 12 months CPAP treatment.</td>
</tr>
<tr>
<td>Krieger et al. (1997)</td>
<td>Cohort n = 547</td>
<td>Sig. reduced no of patients with accident or near miss accident after CPAP treatment.</td>
</tr>
<tr>
<td>Yamamoto et al. (2000)</td>
<td>Cohort n = 47</td>
<td>33% of participants with accident before treatment. None after/during CPAP for 2 yrs.</td>
</tr>
<tr>
<td>George et al. (2001)</td>
<td>Case/control n = 210/210</td>
<td>Untreated OSA patient increased accidents vs. control. After CPAP treatment risk of accident reduced equal to control.</td>
</tr>
<tr>
<td>Turkington et al. (2004)</td>
<td>Case/control n = 18/18</td>
<td>Sig. improved performance in simulator after 7 days of CPAP treatment.</td>
</tr>
<tr>
<td>Mazza et al. (2006)</td>
<td>Case/control n = 320/20</td>
<td>Longer reaction time and doubled no of accidents in untreated patients. After CPAP treatment no difference between groups.</td>
</tr>
<tr>
<td>Barbe et al. (2007)</td>
<td>Case/control n = 80/80</td>
<td>OSAS patient increased risk of accident (RR 2.57). After 2 yrs of CPAP treatment reduced risk of accident (RR 0.41).</td>
</tr>
</tbody>
</table>

Table 5. Sleep apnea and effect of CPAP treatment on simulator performance

RR = Relative Risk, OSA = Obstructive Sleep Apnea, CPAP = Continuous Positive Airway Pressure.
APPENDIX
Definitions and diagnostic criteria According to the American Academy of Sleep Medicine

Obstructive sleep apnea/hypopnea event
An obstructive event is characterized by a transient reduction, or a complete cessation of breathing. These events must fulfill criteria 1 or 2, plus criterion 3:

1. A clear decrease (>50%) from baseline in the amplitude of a valid measure of breathing during sleep. Baseline is defined as the mean amplitude of stable breathing and oxygen in the two minutes preceding onset of the event.
2. A clear amplitude reduction of a validated measure of breathing during sleep that does not reach the above criterion but is associated with either an oxygen desaturation of 3% or an arousal.
3. The event lasts 10 seconds or longer.

Obstructive sleep apnea syndrome
Obstructive sleep apnea syndrome (OSAS) is characterized by recurrent episodes of partial or complete upper airway obstructions during sleep. This manifests as a reduction (hypopnea) or a complete cessation of airflow despite ongoing inspiratory efforts resulting in oxygen desaturations and arousals. Daytime symptoms such as excessive sleepiness are thought to be related to sleep disruption (repetitive arousals) and possibly to recurrent hypoxemia.

Diagnostic criteria
A person must fulfill criterion A or B, as well as criterion C.
A. Excessive daytime sleepiness that is not better explained by other factors.
B. Two or more of the following that are not better explained by other factors:
   - Choking or gasping during sleep
   - Recurrent awakenings from sleep
   - Unrefreshing sleep
   - Daytime fatigue
   - Impaired concentration
C. Overnight monitoring demonstrating five or more obstructive breathing events per hour during sleep. These events may include any combination of obstructive apneas/hypopneas or respiratory effort-related arousals.

Central apnea/hypopnea event
An event characterized by reduced or absent breathing and respiratory effort. These events must meet each of the following criteria:
1. Reduction in airflow.
2. A clear reduction in esophageal swings from baseline. There is no relative or absolute reduction in esophageal pressure that can be used to distinguish central hypopneas from obstructive hypopneas. The reduction in esophageal pressure should parallel chronically to the reduction in airflow.
3. The events last 10 seconds or longer.
Apnea-hypopnea index
The apnea hypopnea index (AHI) is defined as the total number of apneas plus hypopneas divided by the hours of sleep in a single night's study.

Severity of obstructive sleep apnea
Severity of the OSAS has two components: severity of daytime sleepiness and of overnight monitoring. A severity level should be specified for both components. The rating of severity for the syndrome should be based on the most severe component.

A. Sleepiness

1. Mild: Unwanted sleepiness or involuntary sleep episodes occur during activities that require little attention. Examples include sleepiness that is likely to occur while watching television, reading, or traveling as a passenger. Symptoms produce only minor impairment of social or occupational function.

2. Moderate: Unwanted sleepiness or involuntary sleep episodes occur during activities that require some attention. Examples include uncontrollable sleepiness that is likely to occur while attending activities such as concerts, meetings or presentations. Symptoms produce moderate impairment of social or occupational function.

3. Severe: Unwanted sleepiness or involuntary sleep episodes occur during activities that require more active attention. Examples include uncontrollable sleepiness while eating, during conversation, walking or driving. Symptoms produce marked impairment in social or occupational function.

B. Sleep related obstructive breathing events

1. Mild: 5 to 15 events per hour.
2. Moderate: 15 to 30 events per hour.
3. Severe: greater than 30 events per hour.
AIMS

To analyze the relationship between snoring, witnessed sleep apnea and diabetes mellitus in men and women.

To investigate whether sleepy men and women who snore or report witnessed sleep apneas drive more than others.

To study whether sleep apnea is related to stroke, myocardial infarction or death in patients with coronary artery disease.

To investigate whether ambient temperature affects sleep apnea, morning alertness and sleep quality in patients with obstructive sleep apnea.
SUBJECTS AND METHODS

Subjects
Study I and II: 10,756 men and women, 25 - 79 years old, were randomly selected from the population register in Sweden’s northernmost counties, Norrbotten and Västerbotten, in 1999 and 2004. 7,905 (73%) subjects participated in the study.
Study III: 392 out of 424 invited men and women with coronary artery disease referred for coronary angiography were included.
Study IV: 40 out of 53 invited untreated male and female patients with obstructive sleep apnea and an apnea hypopnea index of 10 - 30 were included.

Questionnaire (Studies I, II)
Questions on snoring, sleep apnea, daytime sleepiness and yearly driving distance were included in the Northern Sweden component of the WHO MONICA study in 1999 and 2004. All participants also underwent a physical examination.

Simplified sleep apnea recordings (Study III)
Consisted of measurements of airflow using oro-nasal thermistor. Oxygen saturation and heart rate were estimated by pulse oximetry with a finger probe. Respiratory and body movements were measured using a pressure sensitive bed and sleep position was assessed with a body position indicator.

Polysomnography (Study IV)
Overnight polysomnographic recordings using Embla (Flaga hf, Iceland) which included electroencephalograms, electrooculograms, submental electromyograms, airflow with nasal pressure cannula sensor. Respiratory effort, heart rate and body movements were detected using piezo-electric belts, finger pulsoximetry, electrocardiogram and a body position sensor.

Statistics
Study I: Fischer’s exact test to test for differences between proportions and Multiple logistic regression was employed.
Study II: A two sided t-test was used to analyze whether mean levels differed between groups of subjects and a Pearson $\chi^2$ test was used to analyze difference in proportions. Uni and multivariate analysis using linear regression was also utilized.
Study III: Cox proportional hazard regression was used for analysis.
Study IV: Linear mixed model was applied.

A significance was considered when the 95% confidence interval (CI) did not include the value one corresponding to a p-value of <0.05.
RESULTS AND DISCUSSION

Snoring and witnessed sleep apnea is related to diabetes mellitus in women (Study I)

Results
Diabetes mellitus occurred in 6.5% of snoring women vs. 3.0% in non-snoring women (p <0.001). Habitual snoring was associated with diabetes mellitus among women, OR 1.58 (95% CI 1.02 - 2.44, p = 0.041), independent of smoking, age, BMI and waist circumference.

Diabetes mellitus was observed in 11.8% of women reporting witnessed sleep apnea versus 2.8% in remaining women (p = 0.001). Witnessed sleep apnea was independently associated with diabetes mellitus in women OR 3.29 (95% CI 1.20 - 8.32, p = 0.012).

Neither snoring, nor witnessed sleep apnea was related to diabetes mellitus among men except for in men younger than 55 years of age.

Discussion
Snoring women had a 58% increased frequency of diabetes mellitus and women reporting witnessed sleep apnea had an over 3-fold increased frequency of diabetes mellitus independent of age, BMI, waist circumference and smoking. We found a gender difference as these relationships were only observed in women.

Previous studies which included women only or both genders have reported an association between snoring and diabetes mellitus \(^2, 3, 152, 189, 190\). Out of four cross-sectional studies which included both men and women \(^2, 152, 189, 190\), three observed an association between habitual snoring and diabetes mellitus in both genders \(^2, 152, 190\), while one only found an association between snoring and diabetes mellitus in older women \(^189\). The gender difference observed in our study could explain why snoring was related to diabetes mellitus in some studies but not in others. The underlying mechanism for this association however, is unknown. Both diabetes and sleep disordered breathing is related to obesity and influenced by sexual hormones. Sleep apnea increases after menopause and can be reduced or alleviated with hormone replacement therapy \(^191-194\). In premenopausal women polycystic ovary syndrome is a common disorder as approximately 7% suffers from the condition \(^195\). Many women with polycystic ovary syndrome develop diabetes mellitus and they often suffer from sleep apnea \(^196, 197\). It is possible that a part of the observed gender difference could be explained by preexisting or simultaneous polycystic ovary syndrome. Another factor that might influence this relationship is that men have a shorter life expectancy and a higher cardiovascular risk profile than women. Men who are affected by sleep apnea and diabetes mellitus could be deceased. The association between diabetes mellitus and witnessed sleep apnea in men younger than 55 years of age support this hypothesis.
Snoring men with daytime sleepiness drive more than others: A population-based study (Study II)

Results
Men accounted for 73.6% of the total automotive driving distances and reported a higher prevalence of habitual snoring compared to women (25.8% in men vs. 14.1% in women, $p < 0.001$). Men more frequently had witnessed sleep apnea (21.0% vs. 6.2% respectively, $p < 0.001$) and also had a higher yearly driving distance ($p < 0.001$). Women stated daytime sleepiness more often than men (14.5% vs. 10.1% respectively, $p < 0.001$).

Habitual snoring and excessive daytime sleepiness was found in 4.7% of men and they drove a mean of 22566 km per year (95% CI 18550 - 26582) which was more than non snoring men without daytime sleepiness who drove 17751 km annually (95% CI 17076 - 18427) ($p < 0.001$) (fig. 5). This difference remained significant when controlled for age, BMI, physical activity and smoking ($p = 0.02$). 4.3% of men reported witnessed sleep apnea and excessive daytime sleepiness and this group drove a mean of 23424 km per year (95% CI 19203 - 25645) which was significantly more than non sleepy men without witnessed sleep apnea who drove a yearly distance of 18205 km (95% CI 17477 - 18933) ($p < 0.001$) (fig. 6). This difference also remained significant after adjustments for confounders ($p = 0.01$).

Daytime sleepiness and snoring or witnessed sleep apnea was not related to driving distance in women when controlling for confounders.

Figure 5. Mean and 95% confidence interval of the distance driven in kilometers (km) a year among men and women with regard to snoring and excessive daytime sleepiness (EDS) before adjustments for confounders.
Figure 6. Mean and 95% confidence interval of the distance driven in kilometers (km) a year among men and women with regard to witnessed sleep apnea and excessive daytime sleepiness (EDS) before adjustments for confounders.

Discussion

We found that men reporting excessive daytime sleepiness and habitual snoring or witnessed sleep apnea drive more than others independent of confounders. Accidents increase with the annual driving distance however this association is not linear as drivers who have a higher yearly mileage have lower accident rates per kilometer than those who drive fewer kilometers\textsuperscript{198-202}. Men tend to drive more than women and they also suffer more frequently from snoring and sleep apnea. Most earlier publications investigating car driving and sleep apnea have studied men and seldom include women. In fact there is to date no evidence that women with sleep apnea run an increased risk of traffic accidents\textsuperscript{15, 186, 203}.

One theory to this association could be systemic as well as local inflammation due to inhalation of car exhaustion particles when in traffic. Zanobetti et al. analyzed subjects from the Sleep Heart Health Study and found an association between increases in sleep disordered breathing and desaturation during sleep and augmented levels in air pollution (<PM10)\textsuperscript{204}.

Our study results encourage a more active search to identify male car drivers with obstructive sleep apnea and snorers who are tired during daytime. Not only are these men a danger to themselves and their fellow drivers, they also drive more than others.
Increased risk of stroke in patients with coronary artery disease and sleep apnea: A 10-Year Follow-Up (Study III)

Results
Sleep apnea with an AHI ≥5 was found in 211 (54%) patients at baseline. 47 patients had suffered a stroke during follow-up, 38 patients with sleep apnea and 9 patients without sleep apnea (p <0.001). 80 patients were deceased at follow up, 46 patients with sleep apnea and 34 patients without sleep apnea (p = 0.46). 78 patients had suffered a myocardial infarction at follow-up, 44 patients with sleep apnea and 34 patients without sleep apnea (p = 0.609). Patients with sleep apnea had an increased risk of stroke, HR 2.89 (95% CI 1.37 - 6.09, p = 0.005) independent of age, BMI, gender, left ventricular function, coronary artery intervention, diabetes mellitus, hypertension, previous stroke/TIA, atrial fibrillation and smoking (fig. 7). There was a dose response relationship between the severity of sleep apnea and risk of stroke (table 6).

Figure 7. Cumulative risk of stroke during 10 years of follow-up. Patients with sleep apnea and an apnea-hypopnea index (AHI) >5 had an increased risk of stroke compared with those with an AHI <5 (P<0.001).
Table 6. Hazard ratios for stroke according to the apnea-hypopnea index at baseline.

<table>
<thead>
<tr>
<th>Apnea-hypopnea index (events/hr)</th>
<th>Unadjusted hazard ratio (95% CI)</th>
<th>Adjusted hazard ratio (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - &lt;5</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>5 - &lt;15</td>
<td>3.28 (1.36-6.74)</td>
<td>2.44 (1.08-5.52)</td>
</tr>
<tr>
<td>≥15</td>
<td>5.34 (2.43-11.7)</td>
<td>3.56 (1.56-8.16)</td>
</tr>
<tr>
<td>P for trend</td>
<td>&lt;0.001</td>
<td>0.011</td>
</tr>
</tbody>
</table>

*Adjusted for age, body-mass index, gender, left ventricular function, intervention, diabetes mellitus, hypertension, previous stroke, atrial fibrillation and smoking.

Myocardial infarction was not related to sleep apnea HR 1.06 (0.66 - 1.70, p = 0.816). Death was also not associated with sleep apnea HR 0.99 (0.63 - 1.60, p = 0.996). 77% of the patients underwent coronary intervention (CABG/PCI), these patients had a significantly reduced risk for death, HR 0.35 (95% CI 0.20 - 0.59, p <0.001).

**Discussion**

We found that sleep apnea is an independent risk factor for stroke among patients with coronary artery disease. Possible factors linking sleep apnea with an increased risk of stroke is hypertension, nocturnal cerebral ischemia and an increased risk of arteriosclerosis.

Cerebral blood flow velocity increases during obstructive sleep apnea and decreases after apnea termination concomitant with changes in arterial pressure. Low cerebral blood flow, low arterial pressure and hypoxemia after apnea termination may predispose for nocturnal cerebral ischemia. Sleep apnea is also associated with an increase in prothrombotic factors, an activation of the sympathetic nervous system, endothelial dysfunction and elevation of inflammatory factors. Drager et al. observed early signs of arteriosclerosis in sleep apnea patients in the form of increased carotid intima-media thickness and diameter changes. Treatment with continuous positive airway pressure for 4 months reduced the thickness of the intima media layer as well as C-reactive protein and catecholamine levels. An increased prevalence of atherosclerotic plaque in the carotid artery among stroke patients with obstructive sleep apnea has been reported by Dziewas et al. Taken together, these studies support the hypothesis that sleep apnea could promote the development of arteriosclerosis and consequently increase the risk of stroke among patients with coronary artery disease in line with our findings.
**Results**

The obstructive sleep apnea hypopnea index was significantly higher at 16°C room temperature vs. 24°C (p = 0.001) and at 20°C room temperature vs. 24°C (p = 0.033). The AHI was 30 ± 17 at 16°C, 28 ± 17 at 20°C and 24 ± 18 at 24°C. Total sleep time was significantly longer at 16°C room temperature vs. 24°C with a difference of 30 minutes (p = 0.009). Sleep efficiency was significantly higher at a room temperature of 16°C (77 ± 11%) vs. 24°C (71 ± 13%) (p = 0.012). The Karolinska sleepiness scale was significantly lower at 16°C vs. 24°C (p = 0.028) indicating that patients felt more alert in the morning (fig. 8-10).

![Figure 8](image)

**Figure 8.** Mean obstructive apnea-hypopnea index at 16°C, 20°C and 24°C (95% confidence interval).
Figure 9. Mean total sleep time at 16°C, 20°C and 24°C (95% confidence interval).

Figure 10. Mean Karolinska sleepiness scale at 16°C, 20°C and 24°C (95% confidence interval).
Discussion
This is the first study investigating the effect of ambient temperature on patients with sleep apnea. We found increased total sleep time, increased sleep efficiency and improved morning alertness at lower room temperature, however, sleep apnea was worsened. Our hypothesis for conducting this study was that breathing cold air would diminish obstructive sleep apnea thus improve sleep and sleep quality. The result was slightly unexpected as the apnea hypopnea index increased in cooler temperatures.

A possible mechanism for our findings could be autonomic neuropathy in the upper airway. Previous studies have observed that patients with obstructive sleep apnea have an impairment in two-point discrimination in the upper airways and that patients with upper airway resistance syndrome have a normal response. Sunnergren et al. recently reported that the threshold for cold receptors in the upper airway is significantly higher (i.e. reduced sensitivity) in patients with obstructive sleep apnea versus non snorers and snorers due to neuropathy from the vibration trauma of snoring. This increased threshold for cold receptors in patients with obstructive sleep apnea could explain why there was no decrease in the apnea hypopnea index while sleeping in a cold room. However, the mechanism behind the increase in the apnea-hypopnea index while sleeping in a cold room remains unclear.

In the present study we found that the apnea hypopnea index was higher in colder temperatures. It is therefore not possible to recommend a specific temperature in the sleeping environment for untreated patients with obstructive sleep apnea. A low room temperature could, however, be suggested if the patient experience residual daytime sleepiness after successful treatment of sleep apneas.
GENERAL DISCUSSION

Before writing this thesis it was known that obstructive sleep apnea was a common disorder related to cardiovascular disease, snoring, excessive daytime sleepiness and traffic accidents. Treatment with continuous positive airway pressure and mandibular repositioning appliance had evidence of effect on apneas and daytime sleepiness.

In one cross-sectional study we found that snoring and witnessed sleep apneas was associated with diabetes mellitus in women but not in men. In another cross-sectional study we found that sleepy men who snore and have witnessed sleep apneas drive more than others. This association was not seen in women. The result of these studies indicates a gender difference in the outcome of sleep apnea. These studies are, however, limited by design and it is therefore not possible to draw conclusions concerning cause and effect. A recent prospective study published by Botros et al. in 2009, predominantly on males, strengthened the evidence that obstructive sleep apnea is a risk factor for diabetes mellitus in both men and women. They reported that obstructive sleep apnea was an independent risk factor for diabetes mellitus (OR 1.43) and increased severity of sleep apnea was associated with an augmented risk of diabetes mellitus. Treatment with CPAP attenuated the risk of diabetes mellitus.

Study II is the first study investigating the yearly car driving distance among sleepy snorers and subjects reporting sleep apneas and daytime sleepiness. According to Swedish law it is prohibited to drive when suffering from sleep apnea or other illnesses with daytime sleepiness unless treated successfully, since they have an increased risk for traffic accidents. Surprisingly, in study II we observed that it is the very people at risk for traffic accidents, the sleepy snorers and subjects reporting sleep apneas, who reports the longest yearly driving distances. It is a challenge to find and treat these subjects. Of special interest are professional drivers since they by far have the longest annual car driving distances. Perhaps there should be a national program for sleep apnea screening among professional drivers?

In study III we followed 392 patients with coronary artery disease during a 10 year span. Out of this group 54% had sleep apnea at baseline investigations. These patients were shown to have a 3-fold increased risk for stroke independent of confounders. There was a dose response relationship in sleep apnea severity and the risk of stroke. Coronary artery disease is a prevalent illness and is treated with percutaneous coronary artery intervention, coronary artery bypass graft and pharmacological agents including lipid lowering statins. These treatments aim to prolong life, alleviate symptoms and avoid another myocardial infarction. However these patients are seldom treated to prevent a future stroke occurring in 12% during a 10 year follow-up, and almost exclusively among patients with coronary artery disease and sleep apnea. In support for the hazard of sleep disordered breathing in patients with coronary artery disease, a Swedish study reported a tripled risk for death among heavy snorers within 28 days from onset of a myocardial infarction.
The present thesis demonstrates a clear need to investigate and treat more subjects for sleep apnea. Not only are these patients at risk for cardiovascular disease, but also for diabetes mellitus and traffic accidents due to sleepiness. All patients suffering from coronary artery disease should be considered for investigation of sleep apnea since approximately 50% of patients with coronary artery disease are at risk for stroke and heavy snorers have an increased risk for death during the first 4 weeks after myocardial infarction.

CPAP is still the most efficient treatment for sleep apnea yet many patients, for example stroke patients, do not tolerate this therapy. A mandibular repositioning appliance is one alternative, nonetheless new treatment modalities are needed. We therefore tested whether a cold environment would alleviate sleep apnea. Patients sleeping in a cold environment slept longer and they were more alert in the morning but the severity of sleep apnea worsened. A cold temperature is therefore not a treatment option unless the patient has residual sleepiness after successful treatment of sleep apneas.

A cross sectional design was used in study I and in study II since we were interested to investigate whether there is any correlation between snoring as a surrogate marker for sleep apnea and diabetes mellitus and yearly driving distance among men and women. We found a gender related association. This study design is hypothesis generative but it is not conclusive and it is not possible to determine causality. We used a prospective design in study III when following a cohort of 392 patients with coronary artery disease during 10 years. They were investigated for sleep apnea at baseline and we used patient related outcomes (i.e. stroke, myocardial infarction and death). The study is therefore of high quality and we can draw conclusions on cause and effect.

According to Bradford Hills there are 9 criteria that must be considered and some of them met to be able to establish causation. 1. The strength of the association. A strong association, (i.e. a large relative risk or hazard ratio) is less likely to be due to chance or unknown factors. 2. Consistency. It strengthens causality if several studies have the same findings on different study populations and under different circumstances. 3. Specificity. Can be established when a single supposedly harmful exposure gives rise to a specific effect. 4. Temporality. The exposure or factor thought to affect the study subjects must come first and be followed by the effect. 5. Is there a dose response relationship (i.e. increased exposure followed by increased effect)? 6. Biological plausibility. Is it according to known biological mechanisms possible that the exposure could cause the effect? 7. Experimental evidence. Is there any evidence on previous experiments on animals or humans? 8. Coherence. Is the cause and effect relationship possible with the known facts of the natural history and biology of the disease? 9. Reasoning by Analogy. A common phenomenon in one area can sometimes be applied in another area. 3 out of 9 criteria are met in study III.

A randomized controlled study design was used in study IV. This design is the best design to assess treatment effect. One benefit of the randomized study design is that
the randomization process minimizes the effect of possible unknown factors that can influence the outcome. Another benefit is that randomization reduces the effect of possible systemic errors when identifying or recruiting subjects to a study (i.e. selection bias) \(^{223}\).

With the increased number of patients diagnosed with sleep apnea there is a need for more randomized controlled trials answering the following questions: Does the treatment of obstructive sleep apnea prevent future stroke in patients with coronary artery disease? Does treatment reduce diabetes mellitus? Does treatment prevent traffic accidents in male car drivers who snore and are tired during the daytime?
CONCLUSIONS

Snoring and witnessed sleep apneas are related to diabetes mellitus in women.

Men suffering from excessive daytime sleepiness who snore habitually or report witnessed sleep apneas drive more than other men.

Sleep apnea is associated with the risk of stroke among patients with coronary artery disease. Death and acute myocardial infarction were not associated with sleep apnea among the present patients.

Patients with obstructive sleep apnea sleep longer, have better sleep efficiency and are more alert in the morning after a night’s sleep at a room temperature of 16°C versus 24°C but obstructive sleep apnea is more severe at 16°C and 20°C compared with 24°C.
ACKNOWLEDGEMENTS

This thesis could not have been accomplished without the help of many people. I would like to thank all of you that believed in me and supported me throughout this time.

**Associate Professor Karl Franklin, MD.** My main supervisor. For introducing me to sleep apnea and sharing your wide knowledge in this field. For your lightning fast intellect and your patience.

**Professor Birgitta Stegmayr.** My co supervisor. For your support and constructive comments on my papers and my thesis. For introducing me to the “faster-testet”.

**Eva Normran, MD, PhD.** My co supervisor. For your endless good mood, patience and useful comments and tips on both my papers and on my thesis. For good badminton matches!

**Associate Professor Thomas Mooe, MD.** For inviting me to analyze your cohort of patients with coronary artery disease.

**Carin Sahlin, PhD.** For your expert knowledge of polysomnography recordings and for helping me interpret and understand sleep apnea better.

**Marie Eriksson, PhD.** For your expert knowledge in statistics and your support when taking on the statistical program SPSS.

**Associate Professor Hans Stenlund.** For making statistics understandable and your pedagogic approach.

**Professor Thomas Sandström, MD.** For your support and helpful tips on how to write my thesis.

**Professor Ellinor Ädelroth, MD.** Head of the Department of Public Health and Clinical Medicine. For your kindness and support.

**Ragnberth Helleday MD, PhD.** Head of the Department of Medicine for giving me time and resources to continue my research for all these years.

**AnnCatrin Edlund.** For all your hard work and support. For helping me recruit participants to studies.

**Jenny Boson, MD, PhD.** For your help with linguistics, your friendship and support.

**Andreas Strand.** My friend and dive buddy. For being an excellent travel companion and for your support throughout the thesis.
Martin Andersson, MD and Magnus Lundbäck MD, PhD. For your friendship and valuable critic of my thesis.

Tiina Salonen. For your love and support. For believing in me and for your patience during my long working hours. For making me calm when I’m nervous.

Frida Holmström och Annika Johansson. For excellent coffee-breaks and for making the day brighter.

My colleagues and all staff on the Andningsenheten (Respiratory unit) and the lung ward for taking care of the patients.

The secretaries at Medicinmottagningen for helping me find the patient journals. Especially Karin Appelvik and Sonja Gustavsson.

The MONICA Project and its secretariat.

My parents Henrik and Birgitta, my brother David and my sister Josefin for your love and support.

These studies has been supported by the grants from:

Swedish Heart-Lung Foundation.
The Swedish Research Council.
King Gustaf V 80th Anniversary, and King Gustaf V and Queen Viktoria Foundations.
Västerbotten and Norrbotten County Councils.
Swedish Road Administration, Skyltfonden.
The Swedish Heart and Lung Association.
The Heart Foundation of Northern Sweden.
The Medical Faculty at Umeå University.
The Research and Development Unit, Jämtland County Council.
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