Sleep apnea and atrial fibrillation: cause or comorbidity?

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2023

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ISBN 978-91-8069-431-5 (hard copy)
ISBN 978-91-8069-432-2 (e-pub)
http://hdl.handle.net/2077/77771

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Printed by Stema Specialtryck AB, Borås, Sweden

SVANENMÄRKET
Trycksak
3041 0234

"Humans can't live in the present, like animals do. Humans are always thinking about the future or the past. So it's a veil of tears, man. I don't know anything that's going to benefit me now, except love. I just need an overwhelming amount of love. And a nap. Mostly a nap."

– Townes van Zandt

ABSTRACT

Background: Obstructive sleep apnea (OSA) and atrial fibrillation (AF) are common conditions, associated with morbidity and mortality. Both OSA and AF often go undetected. It has been suggested that OSA may be a modifiable risk factor for AF development. OSA has been linked with AF prevalence in general cohorts and with enlargement of the atria in sleep lab cohorts. In addition, OSA has been associated with postoperative AF (POAF) after coronary artery bypass graft (CABG) in coronary artery disease (CAD) cohorts.

Aims: The papers described in this thesis aim to address the following issues: (1) the association between OSA and AF prevalence, (2) the association between OSA and left atrial enlargement in a general population, (3) whether OSA severity and excessive daytime sleepiness (EDS) were associated with AF, (4) whether OSA severity was associated with OSA incidence in a sleep clinic cohort, and (5) whether OSA was associated with POAF in a CAD cohort.

Methods and Results: This thesis consists of five papers, with data from three cohorts. Paper I and paper II are based on the longitudinal cohort "The Study of Men Born in 1943", consisting of a random sample of men from the general population living in Gothenburg, Sweden, recruited in 1993. In 2014, the 653 remaining men were invited to a re-examination, of whom 536 participated. This re-examination included a physical examination, ECG, two-week thumb ECG, a home sleep apnea test (HSAT), an echocardiographic examination, and questionnaires. The 412 participants with complete data from the HSAT were included. Paper I showed that AF is much more common among men with severe OSA compared to men with no, mild, or moderate OSA. While the association with severe OSA was found to be significant in adjusted analyses, it may be mediated by known confounding factors, mainly heart failure. Paper II showed an independent linear association between left atrial enlargement and OSA severity. Paper III and paper IV are based on the "Sleep Apnea Patients in Skaraborg" cohort. All consecutive patients referred to the sleep clinics at Skaraborg Hospital in southwestern Sweden between January 2005 and December 2011 were included. Patients were screened using HSAT and they filled out questionnaires concerning EDS. Follow-up of comorbidities, through review of hospital records ended in April 2018. A total of 4239 adult patients were included in the cohort. Paper III showed an independent association between severe OSA and AF prevalence in OSA patients without EDS. In paper IV, OSA severity was associated with shorter survival free time concerning AF incidence, and moderate and severe OSA were associated with AF incidence in unadjusted analyses. In adjusted analyses, this association was no longer significant, indicating that heart failure and age are major confounders and are involved in AF incidence. Paper V is a secondary analysis of data from the Randomized Intervention with Continuous Positive Airway Pressure (CPAP) in Coronary Artery Disease and Obstructive Sleep Apnea (RICCADSA) trial. This secondary trial includes 147 patients who underwent HSAT after CABG between December 2005 and November 2010. Paper V showed a linear association between OSA severity and POAF within 30 days, and severe OSA was significantly associated with POAF.

Conclusions: OSA severity, and foremost severe OSA, was associated with AF prevalence and left atrial enlargement in a general male population. In our sleep clinic cohort, severe OSA without EDS was associated with AF, a patient group for which CPAP treatment may be challenging. Severe OSA was associated with AF in the survival analyses. Furthermore, severe OSA was associated with AF after CABG. Overall, severe OSA was associated with worse outcomes when compared to patients with no, mild, or moderate OSA. AF or POAF was more prevalent in patients with severe OSA in all cohorts.

Keywords: Obstructive sleep apnea, atrial fibrillation, excessive daytime sleepiness

ISBN 978-91-8069-431-5 (hard copy) http://hdl.handle.net/2077/77771
ISBN 978-91-8069-432-2 (e-pub)

LIST OF PAPERS

The thesis is based on the following five studies, referred to in the text by their respective Roman numerals:

I Holtstrand Hjälm, H, Hansson, PO, Fu, M, Mandalenakis, Z, Thunström, E. Association between obstructive sleep apnea and atrial fibrillation in a general population sample of 71-year-old men.
Submitted to Journal of Sleep Research 2023

II Holtstrand Hjälm, H, Fu, M, Hansson, PO, Zhong, Y, Caidahl, K, Mandalenakis, Z, Morales, D, Ergatoudes, C, Rosengren, A, Grote, L, Thunström, E. Association between left atrial enlargement and obstructive sleep apnea in a general population of 71-year-old men.
J Sleep Res. (2018) 27, 254–260. doi: 10.1111/jsr.12585

III Holtstrand Hjälm, H, Thunström, E, Glantz, H, Karlsson, M, Celik, Y, Peker, Y. Obstructive sleep apnea severity and prevalent atrial fibrillation in a sleep clinic cohort with versus without excessive daytime sleepiness.
Sleep Medicine 112 (2023) 63–69. doi.org/10.1016/j.sleep.2023.09.012

IV Holtstrand Hjälm, H, Thunström, E, Glantz, H, Karlsson, M, Peker, Y. Association between obstructive sleep apnea and incident atrial fibrillation in a sleep clinic cohort.
Manuscript

V Peker, Y, Holtstrand-Hjälm, H, Celik, Y, Glantz, H, Thunström, E. Postoperative Atrial Fibrillation in Adults with Obstructive Sleep Apnea Undergoing Coronary Artery Bypass Grafting in the RICCADSA Cohort.
J.Clin. Med. 2022,11,2459. doi: 10.3390/jcm11092459

CONTENTS

ABBREVIATIONS

AASM	American Academy of Sleep Medicine
AF	Atrial fibrillation
AHI	Apnea–hypopnea index
BMI	Body mass index
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
COPD	Chronic obstructive pulmonary disease
CPAP	Continuous positive airway pressure
CVD	Cardiovascular disease
ECG	Electrocardiogram
EDS	Excessive daytime sleepiness
EEG	Electroencephalography
ESC	European Society of Cardiology
ESS	Epworth Sleepiness Scale
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HR	Hazard ratio
HSAT	Home sleep apnea testing
ICSD-3	International Classification of Sleep Disorders, 3rd edition
LAE	Left atrial enlargement
MSLT	Multiple sleep latency test
MWT	Maintenance of wakefulness test
OCG	Electrooculogram
ODI	Oxygen desaturation index
OSA	Obstructive sleep apnea
OSAS	Obstructive sleep apnea syndrome
POAF	Postoperative atrial fibrillation
PSG	Polysomnography
QoL	Quality of life
RDI	Respiratory disturbance index
RICCADSA	Randomized Intervention With CPAP in Coronary Artery Disease and Sleep Apnea
RCT	Randomized controlled trial
REM	Rapid eye movements
RERA	Respiratory-effort-related arousal
SAPIS	Sleep Apnea in Patients In Skaraborg
TIA	Transient ischemic attack
UPPP	Uvulopalatopharyngoplasty

INTRODUCTION

"Believe me, you have to get up early if you want to get out of bed."
– Groucho Marx

Sleep was long viewed as a passive state or process, a view which was universally accepted until the discovery of rapid eye movements (REM) during sleep. Before, sleep was generally not separated from other states of unconsciousness such as coma, intoxication, anesthesia, and stupor[1]. In The Philosophy of Sleep, published in the early 1830s, Scottish surgeon Robert MacNish stated: "*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*"[2]

There is no doubt that sleep is a dynamic behavior and an advanced function of the brain[1]. Sleep, a biological factor as important to life as food and water[3], mainly occurs in repeated periods of REM and non-REM sleep. The body is in an anabolic state during sleep, restoring and maintaining important neural, immunological, endocrine, muscular, skeletal, and internal systems[4]. The body adapts functions and behavior via the suprachiasmatic nucleus, a biochemical oscillator synchronized by light. If all is well, it keeps the circadian rhythm intact.

There are many definitions of sleep, and sleep medicine has long focused on the quantifications, definitions, and treatment of sleep-related problems, while the broader term 'sleep health' is seldom used and not easily defined[5]. In the Merriam-Webster dictionary, sleep is defined as:

> *"the natural, easily reversible periodic state of many living things that is marked by the absence of wakefulness and by the loss of consciousness of one's surroundings, is accompanied by a typical body posture (such as lying down with the eyes closed), the occurrence of dreaming, and changes in brain activity and physiological functioning, is made up of cycles of non-REM sleep and REM sleep, and is usually considered essential to the restoration and recovery of vital bodily and mental functions"*[6]

The fifth edition of Principles and Practice of Sleep Medicine states:

> *"According to a simple behavioral definition, sleep is a reversible behavioral state of perceptual disengagement from and unresponsiveness to the environment. It is also true that sleep is a complex amalgam of physiologic and behavioral processes. Sleep is typically (but not necessarily) accompanied by postural recumbence, behavioral quiescence, closed eyes, and all the other indicators one commonly associates with sleeping."*[7]

There are many sleep and sleep-related disorders, including but not limited to the following[1]:

- parasomnias such as nightmares and dream disturbances
- sleep breathing disorders such as central sleep apnea, snoring, and pathologic upper airway resistance syndromes, and obstructive sleep apnea (OSA)
- neurologic disorders such as narcolepsy, idiopathic hypersomnia, and restless legs syndrome
- insomnias
- occupational sleep-related disorders such as shift-work disorders and jet lag

The importance of sleep is now internationally acknowledged as a human rights issue, and in 2012 the Supreme Court of India declared sleep to be a basic human right and a legal right[8].

> *"I can't go to sleep until I'm so tired that I can't stay awake."*
> – Blaze Foley

Obstructive sleep apnea

OSA is characterized by intermittent complete collapse (apnea) or partial collapse (hypopnea) of the upper airways during sleep. These apneas and hypopneas occur despite ongoing respiratory effort, resulting in negative intrathoracic pressure[9], arousal from sleep and/or hypoxemia. OSA has been associated with coronary artery disease (CAD)[10,11], heart failure[12,13], arrhythmias[14-16], pulmonary hypertension as well as risk factors for cardiovascular disease (CVD) including obesity[17,18], insulin resistance[19], diabetes mellitus[20], hyperlipidemia[21], and hypertension[22,23]. The arrhythmia most commonly associated with OSA is atrial fibrillation (AF), and it has been hypothesized that OSA may trigger the onset of AF[24] as well as maintaining it. Further, OSA has been shown to be an independent risk factor for AF in patients with no other cardiac disorders[25]. Postoperative AF (POAF) in coronary artery bypass grafting (CABG) has also been linked with OSA[26,27], and OSA has been linked with a risk of recurrent AF after catheter ablations[28,29].

Treatment with continuous positive airway pressure (CPAP) effectively eliminates apneas by keeping the upper airways open during the respiratory cycle. While earlier observational studies have shown that compliance to CPAP treatment is protective against death from CVD[30] and new CVD events[31], later randomized control trials (RCTs) such as RICCADSA[32] have failed to show a protective effect of CPAP therapy[33,34].

The following issues require further research:

- Whether individuals in the general population with OSA have increased risk of AF has not been established.
- It has been shown that in OSA patients, severe OSA, independently of other risk factors, is associated with increased left atrial (LA) size[35]. Whether OSA is associated with left atrial size in the general population is not known.

- OSA, is a condition with several phenotypes. It has been hypothesized that patients with excessive daytime sleepiness (EDS) phenotype have worse prognosis when compared to patients without EDS[36].
- Whether OSA and OSA severity is associated with AF in sleep lab settings is not completely understood.
- The association between OSA, OSA severity, and POAF has scarcely been studied.

OSA and AF are both common conditions, sharing many risk factors, and both are often asymptomatic. Also, the prevalence of these conditions is increasing in many populations[37,38]. Prevention and detection of these conditions are therefore vital. It is important to highlight that both conditions not only share modifiable risk factors, but are also relatively cheap to detect.

Historical and literary descriptions of OSA

If the German museum dedicated to the history of snoring, the "Schnarchmuseum", is correct, the Greek god of fertility and wine, Dionysus, most likely had sleep apnea. Dionysus (or Bacchus) surrounded himself with women, the maenads, who are said to have used long sticks tipped with a pinecone to poke the deity when he snored and stopped breathing. Similarly, in "From the needles of Dionysius to continuous positive airway pressure", Kryger describes the tyrant Dionysius of Heraclea (a Greek ruler in the 4th century BC, not to be confused with the deity Dionysus) as not only exceptionally heavy, but also almost impossible to wake up without poking him with needles[39]. The similarities between these two stories are obvious. In traditional Chinese medicine, there are descriptions of symptoms of what appears to be OSA syndrome (OSAS) dating as far back as 2500 years[40].

In 1745, Fridericus Wilhelm Lust published "*RHONCHO DORMIENTIUM – Vom Schnarchen der Schlafenden*" (*on the snoring of sleepers*), his dissertation and part of his medical degree at the university of Halle Magdeburg in Germany. In 1836, Charles Dickens published the "The Posthumous papers of the Pickwick Club". In this novel, the boy Joe is described as of considerable weight. Not only does Joe consume large quantities of food and sleep with a loud snore, but he can also fall asleep during any type of situation and has severe difficulties keeping himself awake.

The term "*Pickwickian syndrome*", later obesity hypoventilation syndrome, was coined from this book. It has been claimed that during the American Revolutionary war, soldiers had cannonballs strapped to their backs to prevent snoring. In 1892 in Germany, Otto Francke developed an oral prosthetic to reduce snoring.

"Laugh and the whole world laughs with you, snore and you sleep alone."
– Anthony Burgess

When electroencephalography (ECG) was invented and developed in 1930 by German doctor Hans Berger[41], it became possible to show objective differences in brain

activity during wakefulness and sleep. The electrooculogram (OCG) was developed in 1953 by Americans Aserinsky and Kleitman[42] (the latter named by some "the father of modern sleep research"), making it possible to record slow and REM during sleep. In the ECG, sleep was associated with slow waves with high altitudes, while wakefulness was characterized by low altitude waves and alpha rhythm. American sleep researcher Dement, together with Kleitman, later related REM to cyclic variations in electroencephalography (EEG) measurements during sleep[43]. In 1956, Bickelmann used the above-mentioned term "Pickwickian syndrome" for a patient with disturbed breathing and sleepiness due to extreme obesity.

While similar cases had been mentioned earlier and elsewhere, the first clear-cut descriptions of OSA originate from two separate research groups in the same year, one in France and one in Germany. In their 1965 publications, "Pickwickian patients" showed periods during sleep found to be characterized by apneas, cyanosis, and muscular relaxation with simultaneous flattening of the EEG, which became the basis of the diagnosis of sleep apnea. Further research established that obesity was not essential in OSA. At Stanford University in the 1970s, the first sleep clinic was established. Earlier, patients with severe OSA who were in a life-threatening condition were treated with the drastic method of tracheostomy. This was, of course, not at all a viable option for most patients. Uvulopalatopharyngoplasty (UPPP) was introduced in the early 1980s as a surgical treatment.

In the 1980s, after years of study of respiratory control and the effects of hypercapnia and hypoxia during REM and non-REM sleep in dogs, Australian physician CE Sullivan developed the first CPAP device. In his 1981 study, he applied his observations in dogs to five patients[44], one of them a 13-year-old boy with severe OSA. Due to the boy's inability to keep himself awake he was deemed "mentally retarded". After three consecutive nights, the last night with CPAP applied to all five patients, he found that CPAP prevented the occlusion of the upper airways. CPAP is now the gold standard treatment for OSA. CPAP, in combination with advances in polysomnography and home sleep apnea testing (HSAT), has revolutionized the diagnosis and treatment of OSA patients.

In 1993, Young et al. published the first epidemiologic study of OSA, the Wisconsin Sleep Cohort Study, a longitudinal, population-based study of the natural history of cardiopulmonary disorders of sleep, started in 1989. The 1993 results showed that OSA was prevalent in 25% and 9% of middle-aged men and women, respectively[45]. In 1999, the American Academy of Sleep Medicine (AASM) released their recommendations regarding OSAS and measurement techniques[46]. OSA was hypothesized as, and shown to be, a risk factor for hypertension in the Wisconsin Sleep Cohort in 2000[47]. In 2002, results from the Swedish Gothenburg Sleep Cohort showed that OSA was a risk factor for CVD[48].

Definition of OSA

OSA is characterized by repetitive episodes of airflow reduction due to collapse of the upper airways during sleep[49]. These reductions of airflow (hypopneas) and complete cessations of airflow (apneas) occur despite muscular respiratory efforts. Recurrent

apneas and/or hypopneas result in not only hypoventilation and therefore hypoxemias but also recurrent arousals and provoked awakenings. During these awakenings or arousals, pharyngeal tone and therefore airflow is typically restored.

An apnea is defined as a ≥90% cessation of air flow for at least 10 seconds.

A hypopnea is currently defined as a reduction of air flow of at least 30% associated with a desaturation of ≥3% from previous baseline. This has been revised and altered through the years as diagnostic tools have developed.

Severity of sleep apnea is generally quantified using the apnea–hypopnea index (AHI), measuring the average number of apneas and hypopneas per hour of sleep. Five events or more (either apneas or hypopneas) per hour of sleep, irrespective of symptoms, is the generally used criterion for OSA diagnosis. While there are other methods to quantify OSA, such as the oxygen desaturation index (ODI) and respiratory disturbance index (RDI), AHI is the most widely used.

OSA diagnosis

In the International Classification of Sleep Disorders, 3rd edition (ICSD-3)[49], OSA is defined as follows:

EITHER A in combination with B:

A. One of the following typical symptoms:
   1. Nonrestorative sleep, fatigue, insomnia
   2. Awakenings with apneas, gasping, or choking
   3. Observed habitual snoring, witnessed apneas, or both
   4. Diagnosed hypertension, depression, cognitive dysfunction, CAD, stroke, heart failure, AF, or diabetes mellitus

B. The polygraphic or polysomnographic examination shows ≥5 predominately obstructive respiratory events (obstructive or mixed apneas, hypopneas, or respiratory-effort-related arousals (RERAs)) per hour of sleep

OR

C. The polygraphic or polysomnographic examination shows ≥15 predominately obstructive respiratory events (obstructive or mixed apneas, hypopneas, or RERAs) per hour of sleep, regardless of symptoms.

Symptoms and clinical presentation of OSA

Excessive sleepiness, fatigue, or unrefreshing sleep are reported in 73–90%, of OSA patients, while snoring during most nights is found in 50–60%. Apneas or choking, gasping observed by others, is found in 10–15%[50]. Gastroesophageal reflux (50–75%), and nocturia (30%) are also common. OSA-associated morning headaches are described as "bilateral, with a pressing quality, not accompanied by nausea, photophobia, or phonophobia"[1], and are found in 12–18% of OSA patients.

Obesity and overweight are the most commonly observed risk factors for OSA. Male sex, higher age, and postmenopausality in women are other well-established clinical factors associated with OSA[50,51]. Anatomy can play a large role in OSA, because enlarged structures in the upper airways such as tonsils, adenoids, larger neck circumference and tongue may present a mechanical obstruction[1]. Craniofacial variations and abnormalities such as retrognathia, micrognathia, and a high arched and narrow hard palate can predispose to OSA.

Since many OSA symptoms overlap with other comorbidities, especially symptoms of CVD, it has been claimed that OSA symptoms may be overlooked despite high AHI levels[11].

OSA diagnostics

Polysomnography (PSG) is the golden standard in OSA diagnostics. However, there are several levels of OSA diagnostics, as shown in Table 1.

Table 1. Levels of OSA diagnostics

Level I	Level II	Level III	Level IV
Supervised PSG in sleep lab, video recorded. Airflow, oxygen saturation, respiratory effort, ECG, EEG, snoring and movements are monitored.	At-home PSG. Unsupervised. Airflow, oxygen saturation, respiratory effort, ECG, EEG, snoring and movements are monitored.	HSAT. Unsupervised. Airflow, oxygen saturation, respiratory effort, snoring and movements are monitored.	Portable at-home testing. Unsupervised. Airflow, oxygen saturation or heart rate is monitored.

Polygraphy, home sleep apnea testing

Level III cardiorespiratory polygraphy devices, HSAT kits, consist of a nasal pressure detection cannula for air flow detection, respiratory inductance plethysmography belts for detecting respiratory movements and body position, and a finger pulse oximeter to detect heart rate and oxyhemoglobin saturation. While HSAT is not deemed suitable for general screening of asymptomatic populations, due to risk of underestimating AHI, false negatives[52] and technical failures[53], HSAT results have shown a good correlation with PSG in moderate-to-high probability of OSA. However, HSAT is best used in patients without major comorbidities[52,54,55]. Whereas PSG measures actual sleep time, in HSAT sleep time is estimated. HSAT equipment is mobile and is used in the patient's own home.

Polysomnography

Level I and II full-night PSG is the preferred method of diagnosing OSA. In addition to the information gathered in a polygraphic examination, PSG also includes EEG. Due to the EEG, the use of PSG can used for sleep staging diagnostics and more exact sleep time valuation. However, level I PSG is labor-intensive and requires an overnight stay at the sleep clinic. Also, evaluation of the test results is generally more time-consuming compared to HSAT results.

OSA quantification and scoring

In 1999, the American Academy of Sleep Medicine (AASM) task force published recommendations concerning diagnostic criteria and severity ratings for OSA. For details regarding definitions, see DEFINITIONS IN SHORT.

In 2007, the hypopnea criteria were revised, including recommended and alternative ways to score hypopneas. In 2012, the criteria were revised again. There is ongoing debate concerning the most appropriate way of defining hypopneas[1].

Apnea-hypopnea index

The AHI quantifies the number of apneas and hypopneas per hour of sleep. Using the AHI, OSA can be categorized into mild (AHI 5.0–14.9 events/h), moderate (AHI 15.0–29.9 events/h) and severe OSA (AHI ≥30 events/h). These levels are arbitrary, constructed by the AASM from findings in the Wisconsin cohort that 30 events per hour of sleep corresponded with increased risk of hypertension, and 15 was the mid-point[56].

Oxygen desaturation index

The ODI, quantifying the number of desaturations per hour of sleep, provides more information regarding frequency and severity of apneas compared to AHI. In the 2012 AASM guidelines[54], the baseline for a desaturation was lowered to ≥3% compared to the previous baseline of ≥4%. ODI can be useful when using pulse oximetry as a single screening method. While there are no general classifications of ODI (such as mild, moderate, and severe, as for AHI), desaturations of ≥90% can be considered mild, 80–89% moderate and <80% can be considered severe.

Pathophysiology of OSA

While there have been many advances in the understanding of OSA development, the pathophysiology of OSA is far from completely understood. A combination of muscular tone and anatomy of the upper airways may provide the conditions for the development of (or protection from) OSA. Factors which affect the upper airways, such as smoking, obesity, narrow upper airways including craniofacial factors, alcohol and drug intake, nasal congestion, as well as male gender and genetic factors, all play a role[22]. Low respiratory drive, linked with upper airway dilatory muscles, is associated with low upper airway dilatory muscle activity, resulting in increased airway resistance and therefore leading to increased risk of collapse of the upper airways[57].

Most patients hyperventilate after an arousal, and CO_2 levels may therefore decrease. Patients who have many arousals may be at risk of upper airway collapse due to a combination of chemoreceptor threshold and dilatory muscle response[57].

Lung volume has been associated with size and position of the upper airways. Small lung volumes correlate with a smaller cross-sectional area of the upper airways and may therefore be a risk factor for OSA[49]. Also, larger lung volume may be of benefit when maintaining oxygen levels, acting as a buffer[58] and thereby stabilizing the re-

spiratory control system. Conditions such as obesity and heart failure, which increase pressure on the airways, can also be involved in OSA development.

OSA, CVD, and sympathetic activity

Sympathetic overstimulation due to intermittent hypoxia caused by frequent arousal and sleep fragmentations has been linked to hypercoagulation, endothelial dysfunction, oxidative stress, and arterial stiffness, thereby promoting CVD[57,59,60]. Increased sympathetic overstimulation may lead to vasoconstriction and oscillations in blood pressure as well as tachycardia[9].

Oxidative stress and metabolic dysregulation in combination with endothelial dysfunction and hypercoagulability, with a slightly increased heart rate and blood pressure, results in increased atherosclerosis, which is closely associated with general CVD[59,61]. Increased sympathetic activity in OSA patients has been suggested to mask symptoms of EDS, thus possibly increasing CVD and AF risk while lowering the chances of OSA symptom vigilance.

Epidemiology

The reported prevalence of OSA varies greatly depending on where, when, by whom, why, and how it is measured. The prevalence of OSA in the general population has been estimated to be 9–38%, depending on obesity, gender, age, definitions, genetics, and subpopulations[62]. In a review from 2008, it was stated that data interpretation was burdened by differences in sampling, techniques, and equipment, as well as variability in definitions. The reported prevalence of OSA was highest in India (7.5% of men and 4.5% of women). The lowest prevalence of OSA in men was found in Australia[63] (3.1%), while the lowest prevalence of OSA in women was found in 1.2–2.0% of American women. In a more recent review including 17 studies from 16 countries, when applying a threshold of AHI ≥5 for the OSA diagnosis, it was estimated that around 900 million people worldwide have OSA. When using a threshold of AHI of ≥15, more than 400 million worldwide are estimated to have OSA, where the highest prevalence levels were found in China, USA, and Brazil[37].

As stated above, in the earliest epidemiological study, in Wisconsin, USA, in 1993, OSA was found in around 24% of men and 9% of women (of whom 4% and 2%, respectively, fulfilled the criteria for OSAS)[45]. The same study showed that obesity increased the risk of OSA up to four times compared to patients with normal BMI. However, mainly due to increasing obesity in the population since 1993, these numbers are now out of date and OSA is on the rise. In updated data from the Wisconsin sleep study of 2013, OSA prevalence was *estimated* to be 34% of men and 17% of women[64]. A 2015 study from Lausanne, Switzerland, reported the highest prevalence of OSA yet. Here, Heinzer et al found moderate OSA in up to 49.0% of men and 23.4% of women, and moderate OSA combined with daytime sleepiness was reported in around 7% of men and 3% of women[65].

An American and European perspective concerning OSA prevalence is shown in Table 2. The table shows that OSA and OSAs are more common in men than in women in all categories. Different definitions have been used in most OSA prevalence studies as well as different equipment. High prevalence reported in more recent studies has

been proposed to be associated not only with revised AASM 2012 guidelines, risk factors such as obesity, but also with use of more sensitive nasal pressure cannulas as opposed to less sensitive thermistors alone.

In short, OSA estimations vary greatly depending on scoring, techniques, and OSA definitions.

Table 2. Prevalence of OSA in selected American and European studies

Author and year	Country	Sample size	Gender		Age	AHI≥5	AHI≥15	AHI≥30	OSAS	Method	Nassal pressure	Scoring criteria
Young et al, 1993	USA	602	Men	58.5%	30-60	24%	9%		4.0%	PSG	No	"Classic"[c]
			Women	41.5%		9%	4%		2.0%			
Bixler et al, 1998 and 2001	USA	1741	Men	42.6%	20-100	17.3%	7.2%		3.9%	PSG	No	"Classic"
			Women	57.4%			2.2%		1.2%			
Durán et al, 2001	Spain	2148	Men	49.0%	30-70	26.2%	14.2%	6.8%	3.4%[a]	HSAT and PSG	No	AASM 2007
			Women	51.0%		28.0%	7.0%	2.9%	3%[a]			
Franklin et al, 2013	Sweden	400	Men	0.0%	20-70					Ambulatory PSG	Yes	Chicago 1999
			Women	100.0%		50.0%	20.0%	5.9%	17.0%			
Heinzer et al, 2015	Switzerland	2121	Men	48.0%	40-85	83.8%	49.7%			Ambulatory PSG	Yes	AASM 2007
			Women	52.0%		60.8%	23.4%					
Arnardottir et al, 2016	Iceland	400	Men	47.5%	30-65	13.6%	8.6%	2.3%	10%[b]	HSAT	Yes	AASM 2007
			Women	52.5%		11.3%	4.3%	0.8%				
Fietze et al, 2018	Germany	1264	Men	54.0%	20-81	59.4%	29.7%	11.6%	9.7%	PSG	Yes	AASM 2007
			Women	46.0%		33.2%	13.2%	4.1%	1.4%			

AHI = apnea hypopnea index, OSAS = obstructive sleep apnea syndrome, AASM = American Academy of Sleep Medicine, HSAT = home sleep apnea testing. [a]Using cutoff of AHI≥10 and symptoms, prevalence using cutoff AHI≥5 and symptoms was reported as 21% and 28% in men and women, respectively. [b]Refers to AHI≥5 with excessive daytime sleepiness. [c]"Classic" scoring criteria: apnea: 10 seconds complete cessation of airflow, hypopnea: airflow reduction and ≥4% desaturation.

Study design, study populations and study sample in short:

Young et al, 1993: random sample of state employees (n=3513). Habitual snorers (n=355) and random sample of non-snorers (n=247) included.
Bixler et al, 1998 and 2001: random sample of men (n=4364) and women (n=12219), oversampling of snorers (741 men, 1000 women). OSAS: AHI≥10 and symptoms.
Durán et al, 2001: general population, randomly selected. Two-phase study: HSAT (n=2148) of which 390 probable OSA patients and a random sample were assessed with PSG (n=695).
Franklin et al, 2013: random sample of Swedish women (n=10 000), oversampling of habitual snorers (n=230) and random (n=170).
Heinzer et al, 2015: random sample of a general population of 6733 participants, 2121 screenings performed.
Arnardottir et al, 2016: general population study, 522 invited and 415 participated.
Fietze et al, 2018: randomly selected population (n=4420), age and gender stratified.

Risk factors

Central obesity is one of several shared risk factors between OSA and CVD. OSA is prevalent in 40–80% of patients with hypertension, heart failure, CAD, cerebrovascular disease and with obesity[45,66-68].

OSA can be suspected in patients with a BMI of 30 kg/m^2 or more alone. While obesity is a stronger risk factor for OSA, overweight is also associated with OSA. Cross-sectional studies have shown a strong association between BMI and risk of OSA[18]. Severe OSA has been found in as many as 40% of obese patients, and as many as 70% of OSA patients in sleep clinics have been shown to be obese[17]. Weight loss reduces OSA and weight gain promotes it[47].

Age is closely linked with OSA[67,69,70], and is approximately 17 times more prevalent in persons aged 60–65 compared to young adults, though the association seems to decrease with age[71,72].

Male gender is an important risk factor for OSA, being two to three times more prevalent in men than in women[65]. This difference between males and females seem to decrease with increasing age particularly when comparing with post-menopausal women, indicating that there are hormonal factors involved[73].

It has been suggested that perhaps as many as 80% or more of patients with at least moderate OSA are undiagnosed, and that differences in sleep health are linked with socioeconomic status, racism, discrimination, segregation, geography, social patterns, and health care access[74]. In short, it is suggested that sleep health disparities affect populations who are already affected by overall health care disparities.

Treatment

There are many OSA treatment methods. Those that alleviate OSA without any medical or surgical involvement include weight loss, abstinence from alcohol and sedative drugs, and avoidance of the supine position during sleep. (The cannonball method mentioned previously is now usually a tennis ball attached to the back of a shirt.) Surgically, there are methods such as UPPP and tonsillectomy in select cases. Also, there are mandibular advancement devices which help with maintaining an open upper airway during sleep.

CPAP is the gold standard treatment for OSA patients with an AHI of ≥15 (at least moderate OSA) irrespective of symptoms. However, it is also recommended in patients with mild OSA (AHI 5.0-14.9) in combination with EDS, obesity, hypertension, or CVD[75,76]. By using a mask connected to a compressor, CPAP applies pressure during the respiratory cycle, thus keeping the airways open and preventing apneas. Unfortunately, because many patients experience CPAP treatment as cumbersome and claustrophobic, long-term compliance for CPAP is low. If adherence is defined as using the CPAP mask for at least four hours per night, one estimate is that over half of patients do not adhere to treatment[77].

Due to the problems related to CPAP treatment, a pharmacological alternative would be welcomed. Recently, a study in Gothenburg, Sweden, showed that sulthiame (a carbonic anhydrase inhibitor used as an anticonvulsant) reduced OSA by more than 20 events/h in selected patients[78].

OSA and gender

In general, men are more prone to developing OSA than women[63] and it has been suggested that women are underdiagnosed compared to men, with lower AHI scores but more OSA symptoms[79]. Mechanisms which may play a role regarding gender differences are upper airway configuration, morphology of face and cranium, pattern of fat deposition and exposure[18]. It has been suggested that women have a lesser extent of

collapsible upper airways[80], while men have more active chemoreceptor responsiveness and reduced carbon dioxide sensitivity[79]. Furthermore, it has been reported that women have more hypopneas relative to apneas and that these apneas are shorter[81]. After menopause, the difference in OSA prevalence between men and women decreases[68], and it has been shown that OSA is less frequent in women treated with hormone replacement therapy[82,83].

OSA phenotypes, excessive daytime sleepiness and the Epworth Sleepiness Scale

> *"I love sleep. My life has the tendency to fall apart when I'm awake, you know?"* – Ernest Hemingway

The clinical presentation of OSA patients varies – from completely asymptomatic to "Pickwickian". The 1999 AASM definitions of EDS were vague and therefore not easily used. There are many ways to quantify daytime sleepiness objectively. The multiple sleep latency test (MSLT – measuring how fast the patient falls asleep) and the maintenance of wakefulness test (MWT – measuring the patient's ability to stay awake) are two objective methods. Logically, EDS is a common complaint in clinical cohorts compared to general population cohorts[84,85].

Attempts have been made to characterize OSA phenotypes, such as in the Icelandic Sleep Apnoea Cohort, in which the clusters "disturbed sleep group", "minimally symptomatic group" and "excessive daytime sleepiness group" were presented[86]; the groups did not differ significantly in gender, BMI, or AHI. Since its introduction in the early 1990s, the Epworth Sleepiness Scale (ESS) has been commonly used for stratifying patients into those with or without EDS[87]. The ESS consists of eight questions, relating to the risk of dozing off in different everyday situations. Each question item produces a score of 0 to 3, thereby the total score can vary between 0 to 24. EDS is defined as an ESS score of 11 (or sometimes 10). While the ESS can be used to quantify EDS, the association between EDS, OSA, and OSA severity is weak. The ESS is therefore not recommended as a screening tool for OSA. Another questionnaire variant is the Berlin questionnaire, designed to identify patients at high risk of OSA[46].

A logical consequence of EDS would be an increased risk of accidents, such as traffic and work-related accidents. In 2007, the "Swedish Council on Health Technology"[88] concluded in a review that OSA covaried with accidents in traffic independently of EDS and driving exposure in men.

However, none of the included studies reported EDS as reported by the ESS as a risk factor and increased risk of accidents. However, a more recent review concluded that OSA measured by AHI does not predict fitness to drive, while EDS is a major risk factor independent of AHI score[89]. Furthermore, the authors recommend the MWT, and they conclude that compliancy to CPAP treatment reduces risk.

Atrial fibrillation

> "*When the pulse is irregular and tremulous and the beats occur at intervals, then the impulse of life fades; when the pulse is slender (smaller than feeble, but still perceptible, thin like a silk thread), then the impulse of life is small.*" – Huangdi Neijing

Historical descriptions of AF

In the book "*Huangdi Neijing", or "Inner Canon of the Yellow Emperor",* a text on ancient Chinese medicine written around 2000 years ago, AF may have been described[90]. In 1775, William Withering, English botanist and physician demonstrated the benefits of digitalis purpurea (purple foxglove) in a patient with "weak and irregular pulse", which after treatment turned into a "more full and regular pulse". Robert Adams, an Irish physicist, described an association between irregular heartbeat and mitral stenosis in 1827. When William Einthoven invented the electrocardiogram (ECG) in 1895, AF could be recorded for the first time. In 1998, French cardiologist Haïssaguerre demonstrated that AF could be terminated by isolating ectopic pulmonary vein triggers by catheter.

Worldwide, AF is the most commonly sustained arrythmia in adults[91,92] and poses a significant burden to patients, health care professionals and health care systems[26]. AF is associated with significant morbidity and increased mortality, heart failure, dementia and a five-fold risk of stroke[93]. In adults, prevalence of AF is estimated at between 2% and 4%[92] and is believed to be on the rise due to predicted aging populations and increased rates of detection of occult AF[91,94]. Age is the most important risk factor for AF with a sharp incline with increasing age, accelerating further after 65 years[38], and it has been calculated that the lifetime risk of AF is now one in every three Europeans. It has been estimated that around 18 million Europeans over the age of 55 will be affected by the year 2060[94]. Modifiable risk factors for AF include hypertension, diabetes, obesity, and OSA[26,95], which suggest that control over these factors might reduce AF incidence[26,96].

Pathophysiology

AF is characterized by rapid excitation of the atrium, resulting in lack of synchronicity in and irregular ventricular contraction. While AF may occur in absence of known structural or ECG anomalies, changes in the autonomous nervous system and atrial arrhythmogenic remodeling, including both electrical and structural remodeling is central to AF development[97]. "AF begets AF", as AF itself leads to atrial remodeling which in turn induces AF induction and increases persistence. AF remodeling can also be induced by other cardiovascular disease, such as heart failure[98], myocardial infarction, age[97] and extracardiac conditions such as chronic obstructive pulmonary disease (COPD), and severe OSA[35].

AF symptoms

Common symptoms of AF are palpitations, breathlessness, fatigue, dyspnea, angina pectoris, heart failure and increased diuresis. However, AF may be both occult and

paroxysmal[99], thus not easily detected. It has been shown that AF is asymptomatic in up to one third of AF patients[100].

AF diagnosis

AF is a diagnosis established through ECG. In an ECG presenting AF, R–R intervals are irregular with an absence of systematic rhythm ("arrythmia perpetua"). There are no p-waves while "fibrillatory waves" are seen. Heart rate in AF is often fast.

Extended monitoring beyond a single ECG may be warranted in cases of for example, stroke and transient ischemic attacks (TIA). There is ongoing disagreement concerning AF screening. Opportunistic screening is now recommended in patients aged 65 and older[101]. Screening patients aged 75 and more should be considered in patients with high risk of stroke according to the European Society of Cardiology (ESC)[26].

Current classification

The current classifications of AF include paroxysmal, persistent, and permanent AF. Atrial flutter is generally included when diagnosing AF. See DEFINITIONS IN SHORT.

Treatment – rhythm control, rate control

The goal of AF treatment is either rhythm or heart rate control, and the avoidance of adverse outcomes associated with AF, mainly stroke which is usually treated with oral anticoagulants. The main indication for rhythm control (maintaining sinus rhythm) is to reduce symptoms related to AF, and to improve quality of life (QoL). There are a number of options for rhythm control, namely cardioversion (either electrical or pharmaceutical), antiarrhythmic medication, catheter ablations, maze operation, and His-bundle ablation with pacemaker implantation

Rhythm control may be favorable in younger patients, short duration of AF, in cardiomyopathies caused by tachycardia, normal or moderate left atrial enlargement (LAE), comorbidites, difficulties with heart rate control, AF associated with acute illness, and when rhythm control is the patient's own choice[26]. Although rhythm control therapy is deemed acceptably safe, as of now it is unclear whether this strategy improves left ventricular function and reduces complications of AF[102].

If sinus rhythm is not in question, medications regulating heart rate are used (for example beta blockers and digitalis). This can be adequate for control of AF symptoms. The optimal heart rate for rate control is not known[26]. ESC guidelines suggest that a 'lenient' approach of a general heart rate target of <110 bpm is an acceptable approach[103] rather than a 'stricter' approach of <80 bpm at rest and <110 during exercise.

Treatment – preventing thromboembolic complications

The risks of TIA, stroke, artery embolism, as well as deep vein thrombosis and pulmonary embolism are high in AF. A number of risk factors have been identified. The validated CHA_2DS_2–VASc scoring system calculates aggregate risk of thromboembolic

events, were one point is awarded for either heart failure, hypertension, age 65–74, diabetes mellitus, vascular disease, female gender while two points are awarded for age ≥75 and for previous stroke and/or TIA. No anticoagulant treatment is advised in men with a score of 0 and in women with a score of 0–1. The risk of bleeding due to anticoagulant treatment can be assessed by using the HAS-BLED scale. Warfarin has been the mainstay therapy for many years, but since RCTs showed noninferior reductions of direct-acting oral anticoagulants[104], these are now first line therapy.

AF risk factors

The total burden of cardiovascular and lifestyle associated risk factors affects the lifetime risk of AF development. Age, male gender, obesity, tall stature, alcohol and caffeine use, hypertension, heart failure, CAD, diabetes mellitus, and OSA are all proposed to be risk factors for AF[38,105], and management of the modifiable risk factors has demonstrated a reduction in the AF burden[26].

AF, clinical outcomes and comorbidities

Stroke is closely associated with risk of stroke and TIA[106], in turn leading to disability or death[107]. Moreover, in patients with AF and stroke, it has been shown that AF is associated with increased morbidity, mortality and longer hospital care times when compared to stroke patients without AF[108].

AF is associated with heart failure, and both conditions affect the prognosis of each other. While pharmacological heart rate control strategies differ between patients with heart failure with preserved ejection fraction (HFpEF) and heart failure with reduced ejection fraction (HFrEF), treatment with direct-acting oral anticoagulants does not[109].

As for heart failure, acute coronary syndromes (ACS) and CVD often coexist. Risk factors for these condition overlap, and AF is a risk factor for myocardial infarction and vice versa[110].

OSA, left atrial enlargement and AF

Occlusion of the airways in OSA result in negative intrathoracic pressures, leading to increased afterload and increased transmural pressures, in turn leading to mechanical stretch and distension of the thinly walled atria[111]. While there is uncertainty whether there is a causal association between OSA and AF, it has been observed that OSA is associated with incidence, severity and prevalence of AF[14,112], and with remodeling of the atria[113-115]. Left atrial volume, a substrate for AF, has been associated with OSA in overweight patients (BMI ≥25) with and without OSA[116] and in nontreated patients with mild to moderate OSA[117]. Assessing right atrial size in supposedly highly motivated patients, results from the SLEEP-AF study showed that CPAP therapy in OSA patients resulted in reversal of atrial electrical remodeling[118].

AIMS

The general aim of the included papers was to assess whether OSA, and the severity thereof, is associated with either AF prevalence, AF incidence, or factors thought to be involved in AF development.

Paper 1
To assess the association beween OSA and AF prevalence in a general population of 71-year-old men.

Paper 2
To investigate whether there is an association of left atrial enlargement and OSA in a general population of 71-year-old men. Enlargement of the atria has previously been linked with both OSA and AF development.

Paper 3
To assess whether there is an association between AF and OSA severity in patients with and without excessive daytime sleepiness in a sleep lab cohort.

Paper 4
To assess whether there is an association between OSA severity and AF incidence in a sleep lab cohort.

Paper 5
To assess whether POAF is associated with OSA severity, in patients who underwent CABG.

PATIENTS AND METHODS

Study design

The Study of Men Born in 1943

The longitudinal cohort "Study of Men Born in 1943", was initiated in 1993 when a randomly selected sample of half of all men born in 1943 and residing in Gothenburg (n = 1463) were invited. A re-examination was made in 2003. In 2014, the 653 men still alive and residing in Sweden were invited to a third examination conducted at the research unit of Sahlgrenska Östra University Hospital, in which 536 participated (Figure 1). The examinations included a physical examination, measuring of anthropometric variables, blood testing, extensive questionnaires, and a 12 lead ECG. In 2014, the examination also included a two-week thumb ECG testing, an echocardiographic examination and all patients were offered sleep apnea screening using HSAT. The questionnaires included questions concerning medical history including comorbidities, medications, nutrition, smoking, physical activity, mental wellbeing, and subjective sleep quality, as well as the ESS form. Also, the participants' medical records were scrutinized in search for additional and missing diagnoses. AF prevalence was based on questionnaire data, medical records, and the results of the 12-lead ECG and the thumb ECG screening. The HSAT was offered to all participants without known OSA.

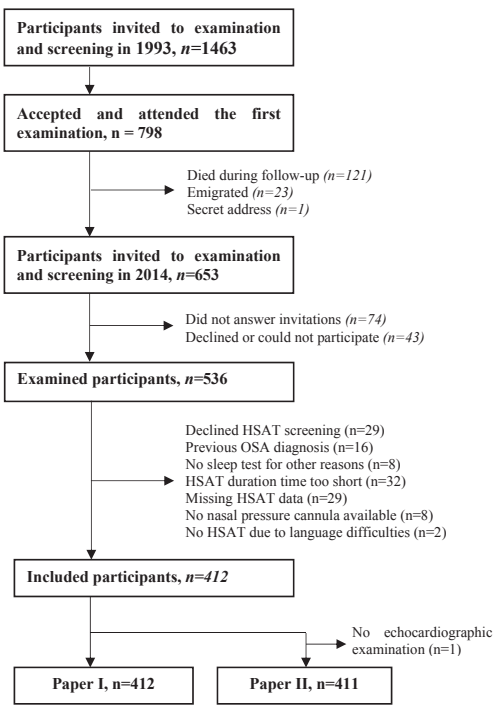

Figure 1. Flow chart of the patients in "The Study of Men Born in 1943" cohort (Paper I and II). One patient declined echocardiographic examination. HSAT = home sleep apnea testing, OSA = obstructive sleep apnea.

Sleep Apnea Patients in Skaraborg (SAPIS)

The Sleep Apnea Patients in Skaraborg (SAPIS) study is a retrospective single center two site (Skövde and Lidköping) registry study located at the at Skaraborg Hospital, located in southwestern Sweden. All patients who were investigated for OSA between the 1st of January 2005 and 31st of December 2011 at the sleep clinic were included in the study cohort. Follow-up of comorbidities ended in 30th of April 2018 (Figure 2). Patients were mainly referred from primary care units, by doctors of outpatient clinics at the Skaraborg hospital, and in few cases, treated as in-house clinic patients. All patients underwent a diagnostic cardiorespiratory HSAT. In the current studies included in this thesis, only patients over the age of 18 were included, while patients recruited for study purposes were excluded.

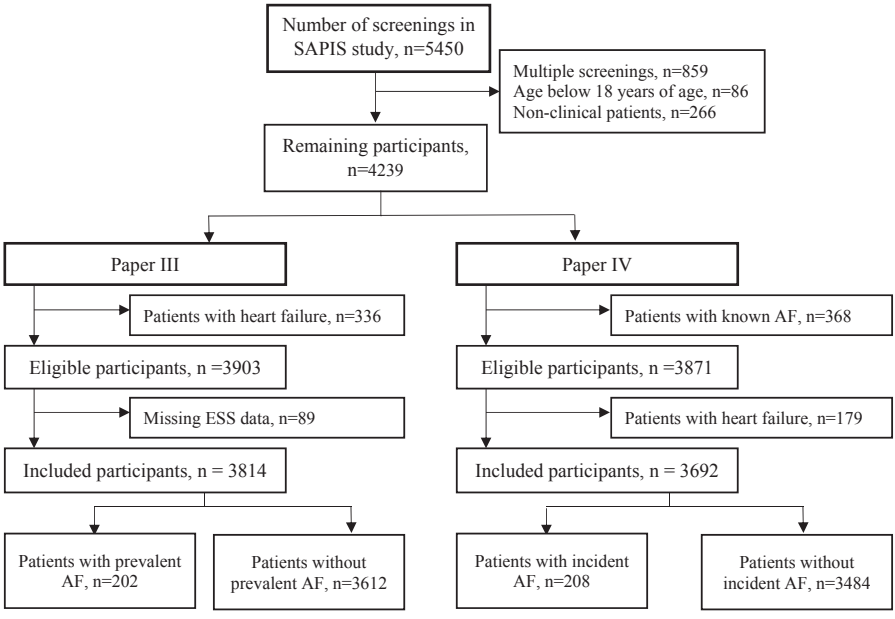

Figure 2. Flow chart for "Sleep Apnea Patients in Skaraborg" (Paper III and IV). AF = atrial fibrillation, ESS = Epworth Sleepiness Scale, SAPIS = Sleep Apnea Patients in Skaraborg.

The Randomized Intervention with CPAP in CAD and OSA (RICCADSA)

All patients in the parent RICCADSA study were adults treated in two centers (the hospitals of Skövde and Lidköping) in Skaraborg county located in Västra Götaland in southwestern Sweden. All patients had verified CAD and had undergone either PCI or CABG and were examined using HSAT while in a stable condition after the procedure. Patients were recruited between December 2005 and November 2010, and follow-up was completed as of May 2013 (Figure 3).

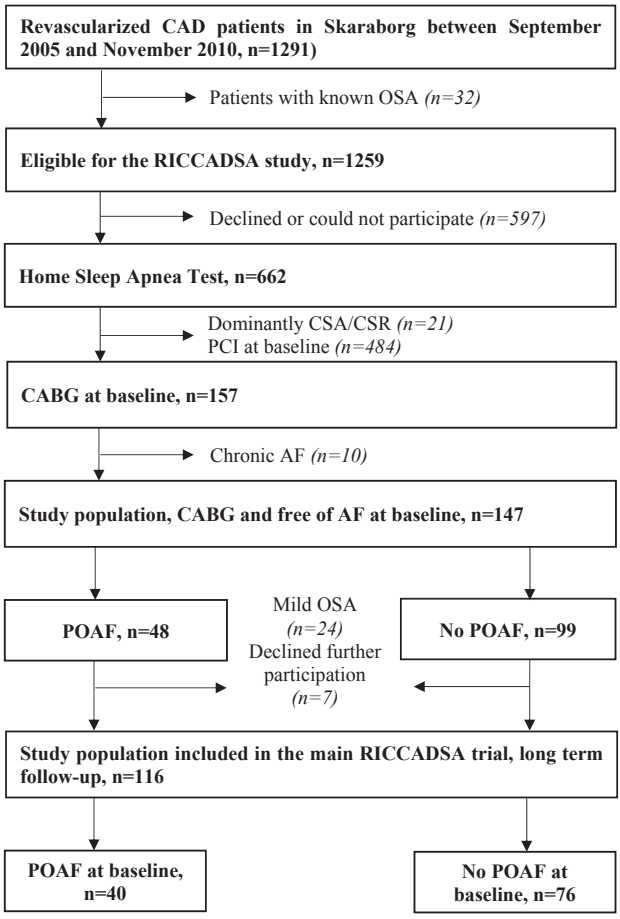

Figure 3. Flow chart for the follow-up sample of the RICCADSA study. RICCADSA = Randomized Intervention With CPAP in Coronary Artery Disease and Sleep Apnea, CSA = central sleep apnea, CSR = Cheyne Stokes respiration, CABG = coronary artery by-pass graft, OSA = obstructive sleep apnea, PCI = percutaneous coronary intervention, POAF = postoperative atrial fibrillation.

PCI was made as an either acute or subacute procedure in either Skaraborg hospital in Skövde or in Sahlgrenska University hospital in Gothenburg. All CABG were done in Gothenburg, and when clinically stable patients were moved to their respective home clinics of either Skövde or Lidköping. Eligible patients who agreed inclusion in the study and gave informed consent were referred to the Sleep Medicine Unit in Skövde for an HSAT. Patients with moderate to severe OSA (AHI ≥15) without EDS were randomized to either treatment with CPAP or no treatment, while patients with EDS were offered CPAP treatment. CAD patients with no OSA (AHI <5) were included in the observational part of the study and were followed prospectively. All patients with mainly CSA or CSR were excluded from the study. In the paper included in this thesis, only patients with CABG and without history of AF were included in the baseline cohort.

Atrial fibrillation and comorbidities definitions

Data concerning AF and other comorbidities from all the included studies ("The Study of Men Born in 1943", "SAPIS" and "RICCADSA"), are mainly based on journal reviews. Therefore, we often we do not know how AF and other comorbidities were defined. Also, the SAPIS database unfortunately does not discriminate between different types of AF.

Software

IBM SPSS (IBM Corp, Armonk, NY, USA) was used for all statistical analyses. Version 22.0 was used for paper II, version 26.0 for paper III and version 29.0 was used for paper I, IV and V.

Statistical methods

In general, categorical variables are presented as numbers and percentages. Continuous variables are presented as means ± standard deviation (SD). To measure differences between two groups of continuous variables, the independent samples t-test was used. The Chi squared test was used for detection of differences between categorical variables. All statistical tests were two-sided, and a p-value <0.05 was considered significant. Odds rations (OR) and hazard ratios (HRs) with 95% confidence intervals are reported where applicable. See methodology overview in Table 3.

Table 3. Methodology overview

Paper I	Paper II	Paper III	Paper IV	Paper V
Cross sectional	Cross sectional	Cross sectional	Longitudinal	Cross sectional and longitudinal
AF prevalence in OSA	LAE prevalence in OSA	AF prevalence in OSA	AF incidence in OSA	POAF incidence and AF reoccurrence in OSA
The Study of Men Born in 1943	The Study of Men Born in 1943	SAPIS	SAPIS	RICCADSA
Univariate and multivariate binary logistic regression	Multivariate linear regression, Mantel–Haenszel chi squared test	Univariate and multivariate logistic regression	Cox regression, Kaplan Meier survival	Binary logistic regression

AF = atrial fibrillation, LAE = left atrial enlargement, OSA = obstructive sleep apnea, POAF = postoperative atrial fibrillation, RICCADSA = Randomized Intervention With CPAP in Coronary Artery Disease and Sleep Apnea, SAPIS = Sleep Apnea in Patients In Skaraborg,

Quality control

The Study of Men Born in 1943

There are problems concerning the database of "The Study of Men Born in 1943", used in paper I and II. The results from paper II was based on the database constructed in 2015 after the rexaminations during 2014-2015. This database was revised in 2023, and around 10% of all endpoints were found to have been missed in the original database. In paper II, 54 cases of AF were found in the 411 participants. In paper II, we chose to only include patients with medical record concerning AF, or AF observed during the ECGs and therefore excluding the patients who only reported AF in questionnaires. Some patients may have been managed by private health care providers or outside of Sahlgrenska University Hospital in Gothenburg and therefore not included in the original database. In the revised database, the total number of AF cases was found to be 60 of 412 when including AF found in hospital medical records or during ECG and thumb ECG screening in the revised database. An additional 4 cases reported AF in the questionnaires, bringing the total number to 64 participants.

We do not believe that the differences between databases can be attributed to negligence, but rather that the regional database SIE-view, which includes all regional hospital records, was accessible for the 2023 revision. Nonetheless, this of course affects the results of findings from paper I vs findings in paper II.

SAPIS

All diagnoses for baseline (and follow-up) in the database were manually reviewed, which primarily is a strength. Mainly, this is because ICD codes often are either missing or incorrect. AF diagnoses from primary health care were double checked using the Western Swedish Health Care Region (VEGA) database. This did not reveal any additional AF cases but instead illustrated the risks of relying solely on ICD codes found in registries as some AF cases were reassessed or discarded due to misinterpretations of ECGs. However, using this method, there is an apparent risk of missing important information and diagnoses due to the amount of text and data, in addition to being time consuming. Approximately 10% of journals were reassessed and revised. The most common error was typing errors concerning dates; however, some missing entries were found. Outliers were reevaluated and corrected where applicable.

RICCADSA

In the RICCADSA database, 10% of all baseline data, CPAP data, primary endpoints and data concerning follow-up procedures were reassessed by an external inspector. This resulted in a few errors which were corrected. Also, variables were checked for outliers, which were checked against raw data.

Systematic and random errors

To the best of our knowledge, our data do not contain any apparent systematic errors, except for the aforementioned missing data concerning comorbidities for the men born in 1943. The relatively large size of "The Study of Men Born in 1943" and SAPIS studies lower the risk of random errors being of significance. This RICCADSA

sub study includes 147 patients, which hopefully is enough to make the risk of random errors insignificant.

Bias

It has been shown that those who choose to participate are of higher socioeconomic status and have lower mortality rates compared to their non-participant peers[119]. This creates an apparent selection bias in "The Study of Men Born in 1943". One of the most publicly recognized symptoms of OSA is EDS. However, EDS is not as prevalent in women[120], which in turn may create a gender bias in the SAPIS study where women may be underrepresented.

Methods measuring vigilance have their pros and cons, and the MSLT, MWT and ESS do not correlate well with each other[121]. In all included papers, EDS was quantified using the ESS. In the SAPIS cohort, there may be a risk of response or recall bias because EDS is evaluated with the highly subjective ESS form. Results from the ESS are highly dependent on motivation, education and fatigue, which may lead to higher scores in some patient cohorts, while lower scores in other. The risk of motivational or recall bias concerning EDS is presumably lower in the men of 1943 cohort and the RICCADSA cohort than in the SAPIS cohort, which consisted of referred patients.

Statistical bias is avoided when the statistical analyses follow the hypothesis. For the included papers, we had a general statistical plan established, therefore hopefully avoiding statistical bias as well as type I errors. Observer bias was hopefully avoided since primary outcome variables were collected retrospectively, except in data concerning examination and ECG in "The Study of Men Born in 1943", where participants were examined at the clinic. However, ECG and thumb ECG were interpreted by experienced physicians, before definitive plans for future publications and analyses were made. The echocardiographic examination performed in connection with the study visit, was reassessed by the same observer one year later, and an inter-observer variation of 5% was reported.

Ethical considerations and approvals

The Study of Men Born in 1943

The study protocol was approved by the Regional Ethical Review Board in Gothenburg (approval number 886-13, date Jan 16, 2014), and this study complies with the Declaration of Helsinki[122]. The ethics application included information regarding responsible researchers, summary of the project, aims, working plan (including examinations and blood testing), included participants, consent, data gathering and the storing of the anonymized data files. In addition to receiving verbal information, all participants provided written informed consent at the study visit. The study is registered at clinicaltrial.gov, trial number NCT03138122.

Morbidities discovered at the study visit, including findings in the echocardiographic examinations and in blood testing, were dealt with by the study doctors. In cases of previously undetected OSA, participants were offered a referral to the sleep clinic at Sahlgrenska University Hospital.

The Sleep Apnea Patients in Skaraborg Study

The study protocol was approved by the Regional Ethical Review Board in Gothenburg (approval number 579-13, date Dec 8, 2013; amendment T779-18, date Sep 12, 2018).

The ethics application included information regarding responsible researchers, summary of the project, aims, working plan, data gathering and the storing of data files. The study was initiated in 2013, but the patients included in the study visited the sleep clinic in Skaraborg Hospital between 2005 and 2011. Therefore, no written consent could be given at the time of the sleep clinic visit. Due to the large number of included participants, it was judged to be practically and economically untenable to obtain informed consent from all included participants afterwards.

While the lack of informed consent is not a practical problem, this approach effectively eliminates the option for patients to request removal from the study. Whether patients with secret information, such as an ex-directory address, or with a hidden identity are included in the database is not known and is not discussed in the study protocol.

The Randomized Intervention with CPAP in CAD and OSA Study

The Study protocol was approved by the Regional Ethical Review Board in Gothenburg (ethical approval number 207-05, date Sep 13, 2005; amendment T744-10, date Nov 26, 2010, amendment T512-11, date Jun 16, 2011). This study complies with the Declaration of Helsinki[122]. The trial was registered at clinicaltrials.gov (trial number NCT 00519597) and at reasearchweb.org (FoU i Sverige – Research and development in Sweden, VGSKAS-4731, date Apr 29, 2005). The ethics application included information regarding responsible researchers, summary of the project, aims, working plan, included participants, consent, and data gathering. All patients provided written informed consent.

"What is right and what is wrong... We have to negotiate that, right?"
- Peter Wallenberg Sr.,
Swedish business leader, citing a comic strip

SUMMARY OF RESULTS

Paper I

In our cohort consisting of 71-year-old men from the general population, we found that AF is more common in participants with severe OSA than in compared to participants with no, mild, or moderate OSA. Adjusted analyses shows that severe OSA and heart failure, a powerful confounding factor, is associated with AF prevalence.

Paper II

Here, we showed that there was an independent association between OSA severity and LAE in 71-year-old men of the general population. LAE has previously been associated with both OSA and AF, and our findings may indicate a link between the two.

Paper III

In our sleep clinic cohort, there was an association between severe OSA without excessive daytime sleepiness and having AF at baseline. Since CPAP treatment may be less attractive for patients who do not experience daytime symptoms, these patients may be at risk of adverse outcomes in the future.

Paper IV

Here, we showed that the patients in our sleep clinic cohort with OSA had slightly shorter AF-free survival time compared to patients without OSA. Also, OSA severity is linearly associated with AF incidence. Unadjusted analyses indicated that moderate and severe OSA were associated with AF incidence. However, after adjusting for important confounders such as age and heart failure, this association was lost. Incident AF equally common in patients who were assigned to CPAP compared to those who were not. Allocation to CPAP treatment did not influence AF incidence.

Paper V

In the CAD patients of the RICCADSA study, severe OSA was associated with POAF. Here, 90% of the patients had beta blockers and 70% were allocated to CPAP when the study was initiated. None of the POAF patients required long-term hospitalization due to AF. It is unclear whether CPAP could be added on to beta blockers as POAF secondary prevention after CABG.

OSA and gender

The three cohorts included in this thesis are not easily compared, as the participants of the "Study of Men Born in 1943" are all men from the general population, whereas the men and women of SAPIS study are a sleep clinic cohort, and patients of the RICCADSA cohort all have CAD. As seen in Figure 4, before exclusion for the separate study purposes, the SAPIS study included 2825 (66.6%) men and 1414 (33.4%) wom-

en, while the RICCADSA study included 127 (86.4%) men and 20 (13.6%) women. In the "Study of Men Born in 1943" cohort, no, mild, moderate and severe OSA were found in 33.5%, 37.1%, 20,6% and 8,7%, respectively.

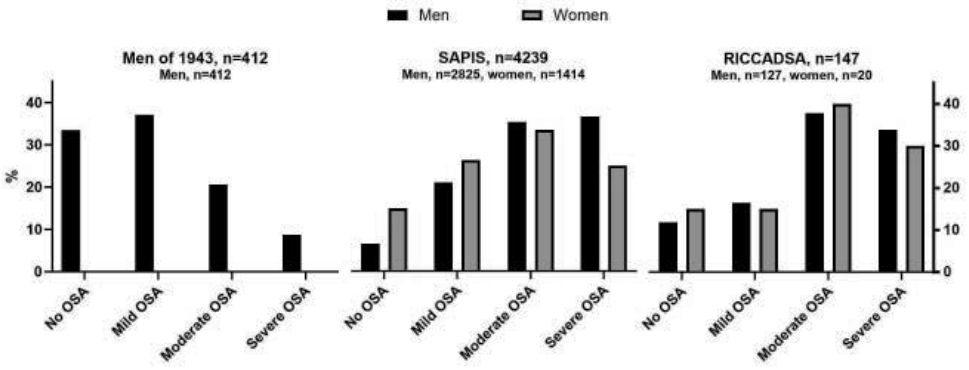

Figure 4. Obstructive sleep apnea severity in the study cohorts broken down by gender. OSA = obstructive sleep apnea, SAPIS = Sleep Apnea Patients In Skaraborg, RICCADSA = Randomized Intervention With CPAP in Coronary Artery Disease and OSA.

In the SAPIS cohort, no, mild, moderate and severe OSA were found in 6.5%, 21.1%, 35.5% and 36.8%, respectively, in men, with the following corresponding figures for the women: 14.9%, 26.4%, 33.6% and 25.1%. In the RICCADSA cohort, no, mild, moderate and severe OSA were found in 11.8%, 16.5%, 37.8%, and 33.9% of men respectively, and in 15.0%, 15.0%, 40.0% and 30.0% of women, respectively. While OSA is more common in men, it has been showed that women less frequently report EDS. Therefore, it is plausible that the women are less prone to be referred for OSA evaluation compared to men. In all, OSA severity show a similar distribution for both genders in the clinical SAPIS and RICCADSA studies, but not in the general population sample of men born in 1943. Notably, the RICCADSA substudy includes only 20 women.

"There is no sunrise so beautiful that it is worth waking me up to see it."
– Mindy Kaling, Is Everyone Hanging Out Without Me?

OSA severity in AF and POAF

For all cohorts and gender, there is a clear trend in which OSA severity is associated with AF (Figure 5).

EDS in OSA categories

It has been shown that EDS is not associated with OSA in women[120], whereas Figure 6 shows that in the SAPIS study, EDS prevalence in men and women are equally frequent. Data interpretation concerning EDS and gender in the RICCADSA substudy is limited due to the low number of women included.

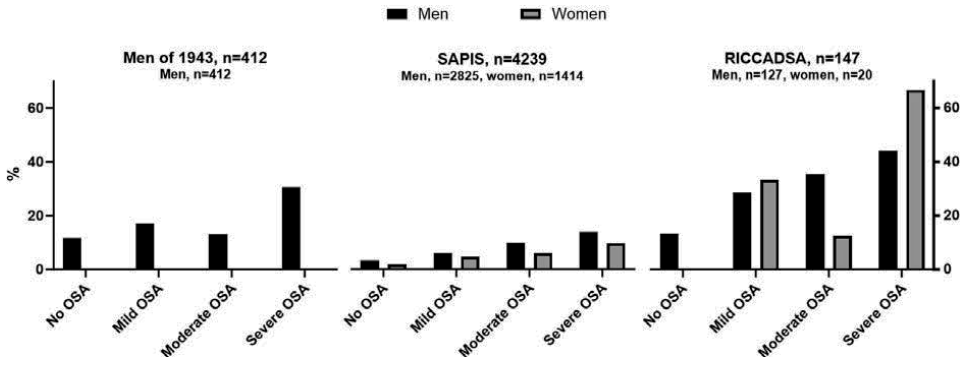

Figure 5. Atrial fibrillation prevalence in OSA categories divided by gender for the different cohorts. OSA = obstructive sleep apnea, SAPIS = Sleep Apnea Patients In Skaraborg, RICCADSA = Randomized Intervention With CPAP in Coronary Artery Disease and OSA.

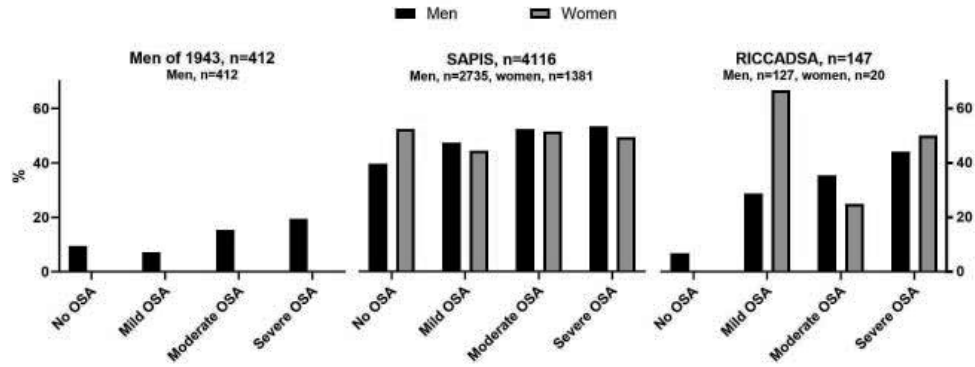

Figure 6. Excessive daytime sleepiness prevalence in OSA categories divided by gender for the different cohorts. OSA = obstructive sleep apnea, SAPIS = Sleep Apnea Patients In Skaraborg, RICCADSA = Randomized Intervention With CPAP in Coronary Artery Disease and OSA. In SAPIS, patients without ESS data were excluded.

DISCUSSION

There is a common thread in the results of the papers included in the thesis. Ther findings indicate that there seems to be an association between OSA severity and AF, as well as between OSA severity and and LAE:

- Severe OSA is associated with AF prevalence in a general population of 71-year-old men
- Moderate to severe OSA is associated with left atrial area in a general population of 71-year-old men
- Severe OSA is associated with AF prevalence in non-sleepy phenotype in a sleep clinic cohort
- OSA is linearly associated with AF incidence in a sleep clinic cohort
- Severe OSA is associated with POAF in a CAD cohort

Paper I

Here, it was shown that AF prevalence was more than twice as high in men with severe OSA than in to men with moderate OSA. AF was found in 11.6%, 17.0%, 12.9% and 30.6% of patients with no, mild, moderate and severe OSA, respectively. There was an association between AHI and AF, where each unit increase of apneic event per hour of sleep, was associated with a 2% higher risk of AF. Furthermore, we showed an association between severe OSA and AF prevalence as well as between AF and the established risk factors hypertension, CAD, and heart failure in unadjusted analyses. Severe OSA and heart failure remained significant in adjusted analyses. Since all participants were 71 years old, age was not a factor.

Participants with known OSA were not included (n = 16). Of the 412 participants included in paper I, 85 were found to have moderate OSA and 36 had severe OSA. Treatment for OSA (if EDS or other symptoms or comorbidities are not present) is often initiated in patients with an AHI of ≥15, making a total of 121 patients were eligible for treatment. These 121 patients were offered referral to the sleep clinic at Sahlgrenska University Hospital. Whether treatment for OSA lowers the risk of AF is not known, and existing studies show conflicting results. CPAP treatment in OSA is believed to reduce AF recurrence after catheter ablations[123-125]. There are however RCTs currently trying to address this matter, and one has shown that CPAP did not reduce AF morbidity in 109 patients with paroxysmal AF[126]. Another small study of 25 patients found no benefit of CPAP treatment for patients post cardioversion concerning AF recurrence[127].

Paper II

Of the 411 participants included, 121 (29.4%) had moderate to severe OSA. Unfortunately, during the echocardiographic examination, left atrial area was used for quantifying left atrial size instead of the more widely used left atrial volume index[128].

However, using a formula as described by Svedenhag which takes body surface area into account[129], we showed that OSA severity was linearly associated with LAE. LAE was present in 27.5%, 34.0%, 49.4% and 58.3% in participants with no, mild, moderate and severe OSA, respectively. In the multivariate regression model adjusting for important confounders (hypertension, atrial fibrillation, heart failure, overweight and mitral regurgitation), OSA severity was linearly associated with left atrial area and significant for both moderate and severe OSA. This supports previous findings that OSA is associated with LAE, which in turn is thought to be associated with AF prevalence and incidence.

OSA has previously been linked to diastolic dysfunction[130], ventricular hypertrophy and dilatation of the left atrium[131]. Paper II shows that OSA severity is linearly associated with LAE after adjusting for major confounders which supports the suggestion that OSA may be a risk factor for LAE in general populations. If there is indeed a causal relationship between the two conditions (a question which our cross-sectional design cannot address), then the discovery and treatment of OSA is important for reducing AF incidence as well as potentially reducing morbidity in patients with, for example, paroxysmal AF.

Limitations in paper I and II

Paper I and II have several limitations. "The Study of Men Born in 1943", as the name implies, does not include women. While the similar age of all participants can be viewed as a strength, the exclusion of women is an apparent and serious limitation. Men who chose to be included in the original study, and still are interested in participation, have been shown to be of higher socioeconomic status and lower mortality rates, and the participation itself creates a selection bias[119]. Furthermore, participants were mainly of Caucasian origin, limiting the geographical generalizability of our findings. Another limitation was the dropout rate: of the former 653 participants who were still alive and living in Sweden were invited to the re-examination in 2014, of whom 117 declined or did not answer the invitation. Furthermore, there was considerable problems regarding the HSAT, where 29 declined testing altogether, and a total of 79 were lost due to technical problems, short sleep observation time and language difficulties.

Additionally, 9.0% of participants had a history of stroke and/or TIA, and results from the HSAT did not take central sleep apneas into account. Another limitation of HSAT is that it is not recommended as a general screening tool[53]. Strengths of the studies presented in papers I and II includes our robust data concerning AF and other comorbidities due to not relying only on questionnaires and requisitioning of medical records, but also gathering data with 12-lead ECG as well as the two-week thumb ECG screening.

EDS prevalence in OSA cathegories is shown in Figure 6. As seen in paper I, Table 2, 10.6% of participants with no AF had EDS, while 10.9% of patients with AF had EDS. Since mainstay therapy for OSA is CPAP, which is for many a stressful and cumbersome treatment, those patients without EDS symptoms are likely to show much lower compliance with CPAP treatment.

Paper III

Previous studies have explored the association between OSA and AF[15], and OSA should be considered as a risk factor for AF according to the current guidelines[26]. The results from paper III support this, showing a linear association between OSA severity and AF prevalence in a sleep clinic cohort. Patients with heart failure, deemed to be a strong confounding factor, were excluded while we adjusted for other important confounding factors, namely: age, gender, obesity, smoking, diabetes, hypertension, CAD, and stroke. Adjusted analyses showed a 2.5-fold increased risk for having AF among patients with severe OSA compared to patients with no OSA.

Meta-analyses have indicated that CPAP treatment may lower the risk of recurrent AF in OSA[28,29], wheareas, a recent RCT did not show any protective effect of CPAP[126]. OSA and CVD often coexist, which suggests that CVD may lead to OSA, but it could equally mean that OSA lead to CVD or that there is a bidirectional relationship[71,132]. Several ways in which OSA may act as a modifiable risk factor have been suggested, including threshold for respiratory arousal, collapsibility of the upper airways. Patients with similar levels of OSA severity may show different patterns of respiratory arousal, hypoxia, cardiac response, and inflammation[71].

While several different OSA models for OSA phenotypes have been proposed[86], the ESS has been widely used ever since its introduction in the early 1990s[87]. By dichotomizing OSA patients into either with or without EDS, it has been suggested that EDS may be linked to CVD and compliance to CPAP treatment[133]. As stated above, although OSA is common in AF, OSA patients with AF often do not report EDS[134]. The problem of associating OSA with results from questionnaires is not limited to the ESS questionnaire, however; in a recent study of 100 patients with AF, none of the seven screening tools for OSA in AF patients showed good enough results in detecting clinically relevant OSA[135]. In paper III AF patients reported lower ESS scores, and the prevalence of EDS was therefore lower. This finding is similar to prior studies in the field[136].

Reported EDS symptoms are not closely correlated with OSA prevalence. It seems that AF patients experience fewer EDS symptoms, which may imply that AF patients are even less likely to seek health care for OSA. OSA is underdiagnosed in many patient groups as well as in the general population, but perhaps this is accentuated in AF patients. Recently, using data from the RICCADSA trial, colleagues showed that CPAP-compliant patients without EDS showed better cardiovascular outcomes when compared to CPAP-compliant patients with EDS[137]. Moreover, in a recent meta-analysis, it was concluded that CPAP adherence was associated with reduced risk of major adverse cardiac and cerebrovascular events[138].

Our results show that smoking was inversely associated with OSA. While it has been reported that both current smoking and former smoking are associated with OSA, whether a causal association exists is not clear[139]. In our sleep clinic cohort, this association may be attributed to active advice to AF patients to stop smoking. Current smokers were found to be younger, and as explained earlier, age is closely linked to AF.

Paper IV

Here, we found that there was an association between AF incidence and OSA. However, adjusted analyses show that this effect is mediated by age, obesity, stroke, and CAD. Hypertension, diabetes, CAD, and stroke were more prevalent in patients with AF. Also, AF patients were older, while current smoking was less prevalent. As in paper III, current smoking was inversely associated with this group. In the survival analysis, we showed that there was a small but significant reduction in AF-free survival time aligning linearly with OSA severity. In more crude analyses (as illustrated in Figure 2 of paper IV), there is a clear linear association between OSA severity and AF. There, we show that AF incidence was 2.9%, 3.8%, 5.7% and 7.9% (in no, mild, moderate and severe OSA, respectively) of patients. Furthermore, allocation to CPAP treatment did not affect AF incidence.

Unsurprisingly, patients with AF were found to be older, a factor which remained significant in adjusted analyses. This also applied to obesity, which in line with previous studies[72].

"Do you mind if I don't smoke?"
– Groucho Marx

Limitations in papers III and IV

There are some similar limitations in the SAPIS study to those in the men born in 1943 study. The design of paper III was cross-sectional; therefore, we cannot infer causality but only highlight associations. The total number of OSA examinations in the SAPIS study was 5450, and this volume of PSG examinations would not have been possible. Instead, patients were examined using HSAT, the only feasible examination option in this setting. Although HSAT is an alternative in uncomplicated adult cases where moderate to severe OSA is suspected, it is not recommended for general screening[53]. Another limitation is that information concerning central sleep apnea was not accessible in the database. In both papers III and IV we chose to include patients with a history of stroke, which in turn is associated with central sleep apnea. For all screenings, in line with the RICCADSA trial (recruiting at the same time), the Chicago criteria were used. Furthermore, screening for occult AF was not within the scope of this study. Unfortunately, the database did not include data concerning whether AF was paroxysmal, persistent, or permanent, what medication the patient was taking at the time of the HSAT, the type of heart failure, or levels of substance abuse and alcohol intake, and it did not discriminate between different types of lung disease (including only asthma and chronic obstructive lung disease, COPD). The patients in the SAPIS study represent a sleep clinic cohort in southwestern Sweden, and therefore the results from this cohort should be applied with caution in other patient groups.

We scrutinized the hospital records, in search for AF and comorbidities, and we acquired data from all patients from the regional VEGA registry containing ICD codes regarding AF, which greatly strengthens the reliability of our AF data. Furthermore, in cases where the patients had died, we noted date of death in the database. The total number of deaths was double checked against the data from the Swedish National Death Registry.

Paper V

A large study of 300 000 American patients have shown that 30.0% of patients develop POAF, the most common of postoperative complications[140], after CABG[141]. Similar numbers, 33%, have been reported in smaller and earlier studies[142]. Meta analyses in the field have suggested that OSA, despite the varying definitions, is an independent risk factor for POAF after CABG[143,144]. In another large American study including almost 400 000 patients on OSA in CABG patients and/or valve surgery patients, OSA was associated with a modestly increased risk of hospital readmission within 30 days postoperatively (19.6% vs 17.1%)[145]. However, a severe limitation in that study was the lack of a definition of OSA, and the lack of available data concerning OSA severity. Our study, on the other hand, suggested that severe OSA may be of importance, rather than OSA in general.

In paper V, we showed that severe OSA is independently associated with POAF. While POAF is often self-terminating, it has been shown that there is an increased risk of recurrent AF during five years postoperatively[146]. Our study showed that none of the included patients were admitted to a hospital due to AF during the follow-up period of 67 months. This can possibly be attributed to the fact that 70% were treated with beta blockers and that 70% were allocated to CPAP treatment within the parent RICCADSA study.

Limitations in study V

Since AF is often occult, AF screening after discharge would have been optimal, but this was not possible. Furthermore, this was a small post-hoc study of the CABG subgroup of the parent RICCADSA study, and results may not be applicable to other geographical regions and populations, nor to other types of cardiac surgery.

General limitations - night to night variability, central sleep apnea, OSA definitions and study design

There has been discussion as to whether OSA assessment for one night, which is stan- dard clinical practice in most sleep clinics, is adequate. It has been reported that night- to-night variability is relevant because AHI and ODI may differ between the first and second nights of screening[147]. Further, it has been proposed that there may be large variations in individual AHI between nights without any significant differences on the group levels, and as many as half of patients showed different OSA severity between four consecutive nights of screening[148]. In a relatively recent review, it was stated that significant intraindividual night-to-night variations may lead to misclassification of OSA as well as false negatives[149]. In the included papers in this thesis, all participants and patients were screened only once, except in cases of short sleeping time or technical malfunctions.

Another general limitation of “the Study of Men Born in 1943” and the SAPIS studies, is the lack of data concerning episodes of central sleep apneas. In the RICCADSA study, 21 (3.2%) of the 662 patients who underwent HSAT were found to have dominantly central sleep apneas and/or Cheyne-Stokes respiration.

Furthermore, the included studies used different OSA guidelines for scoring hypopneas. In "the Study of Men Born in 1943", the AASM 2012 scoring rules were used for scoring hypopneas. In the SAPIS and RICCADSA studies, the 1999 Chicago criteria were used. Moreover, the main design of the included papers is cross-sectional, and we therefore cannot address causality between OSA and AF prevalence and LAE.

"The best cure for insomnia is to get a lot of sleep."
– W.C. Fields

CONCLUSION

Main conclusion

OSA severity, and foremost severe OSA, is associated with AF prevalence as well as with LAE in a general male population. In our sleep clinic cohort, severe OSA without EDS is associated with AF, but in this patient group, compliance with CPAP treatment may be low. We also found that severe OSA is associated with AF in survival analyses. Furthermore, we found that severe OSA is associated with POAF after CABG .

Overall, patients with severe OSA have worse outcomes in comparison to patients with no, mild, and moderate OSA. AF or POAF was more prevalent in the severe OSA group in all cohorts.

In all, OSA may be both cause and comorbidity rather than one or the other.

Scientific relevance

The papers included in this thesis add a number of insights into the field of OSA and its association with AF. Primarily, this thesis shows that severe OSA is associated with worse outcomes and that LAE, associated with AF development, is associated with OSA severity in a general population. We have also shown that many patients with severe OSA are at risk of POAF after CABG.

Clinical relevance

Both OSA and AF are increasingly common conditions. The results of the papers included in this thesis hopefully contribute to confirming the general suspicion that OSA is a factor not only in AF but also in other comorbidities. EDS, perhaps the most generally known symptom of OSA, is not evident in many patients. This is of relevance to those patients with severe and even moderate OSA, who do not experience EDS but who may benefit from CPAP treatment.

Future perspectives

There is ongoing work concerning both the Men Born in 1943 study and the SAPIS study. The incidence of comorbidities in the “Study of Men Born in 1943” has been registered up to 2023, which makes follow-up of the incidence of AF and other comorbidities possible. We will also be able to follow up the development of AF in patients with enlarged atria. In the SAPIS study, there is ongoing work concerning other approaches to studying OSA and its association with, gender, AF and other comorbidities.

DEFINITIONS IN SHORT

Obstructive sleep apnea definitions

Adapted from AASM[46,49] and Thunström[150]:
Obstructive sleep apnea: Repetitive episodes of airflow reduction due to collapse of the upper airways during sleep. These episodes consist of reductions of airflow (hypopneas) and complete cessations of airflow (apneas). OSA is a laboratory diagnosis with three levels: mild (AHI 5–14.9/h), moderate (AHI 15–29.9/h), and severe (AHI ≥30/h).

OSAS: Obstructive sleep apnea syndrome is a clinical diagnosis of OSA with symptoms, mainly excessive daytime sleepiness but also morning headaches, nonrestorative sleep, fatigue, loud snoring and witnessed apneas.

Baseline: The mean amplitude of stable breathing and oxygenation in the two minutes preceding onset of the event (in stable breathing), or the mean amplitude of the three largest breaths in the two minutes preceding onset of the event (in unstable breathing).

Apnea: Two criteria must be fulfilled: (1) Amplitude reduction: there is a drop in the peak thermal sensor excursion by ≥90% of baseline. (2) the duration of the event is at least 10 seconds.

Hypopnea (1999 guidelines): Criterion (1) or (2) must be fulfilled in combination with criterion (3): (1) A clear decrease (≥50%) from baseline in the amplitude of a valid measure of breathing during sleep. (2) A clear amplitude of reduction on a validated measure of breathing during sleep that does not reach the 50% criterion but is associated with an oxygen desaturation of ≥4% and/or an arousal. (3) the events lasts 10 seconds or longer.

Hypopnea (2007 guidelines - recommended): A 30% of greater drop in flow for 10 seconds or longer, associated with at least 4% oxygen desaturation.

Hypopnea (2007 guidelines – alternative): At least 50% decreased flow for 10 seconds or longer, associated with at least 3% oxygen desaturation or an arousal.

Hypopnea (2012 guidelines): A 30% drop in the nasal pressure excursion for 10 seconds or longer, associated with at least 3% oxygen desaturation or an arousal.

AHI: The apnea-hypopnea index is based on the number of apneas and/or hypopneas per hour of registered sleep.

ODI: The oxygen desaturation index is based on the number of desaturations (≥4%) per hour of sleep time.

ODI, 2012 guidelines: The oxygen desaturation index is based on the number of desaturations (≥3%) per hour of sleep time.

RDI: An index created by adding RERA to the AHI.

RERA: Respiratory-effort-related arousal is a sequence of breaths characterized by increasing respiratory effort leading to an arousal from sleep, but which does not meet the criteria for an apnea or hypopnea. RERA events must fulfill both of the following criteria: (1) a pattern of progressively lower esophageal pressure, terminated by a sudden change in pressure to a higher level and arousal. (2) a duration of 10 seconds or longer.

Atrial fibrillation definitions

Adapted from Hindricks et al[39]:
Atrial fibrillation: A disorder characterized by an electrocardiographic finding of a supraventricular arrhythmia characterized by the replacement of consistent P waves by rapid oscillations or fibrillatory waves that vary in size, shape and timing and are accompanied by an irregular ventricular response.

First diagnosed: AF not diagnosed before, irrespective of its duration or the presence and severity of AF-related symptoms.

Paroxysmal: AF that terminates spontaneously or with intervention within 7 days of onset.

Persistent: AF that is continuously sustained beyond 7 days, including episodes terminated by cardioversion (drugs or electrical cardioversion) after ≥7 days.

Long-standing persistent: Continuous AF of >12 months' duration after adopting a rhythm control strategy.

Permanent: AF that is accepted by the patient and physician, and no further attempts to restore or maintain sinus rhythm will be undertaken. Permanent AF represents a therapeutic attitude of the patient and physician rather than an inherent pathophysiological attribute of AF, and the term should not be used in the context of a rhythm control strategy with antiarrhythmic drug therapy or AF ablation. Should a rhythm control strategy be adopted, the arrhythmia would be re-classified as 'long-standing persistent AF'.

Atrial flutter: A disorder characterized by an electrocardiographic finding of an organized, regular atrial rhythm with atrial rate of 240–340 beats per minute. Multiple P waves typically appear in the inferior leads in a saw tooth-like pattern between the QRS complexes.

NOTE: In this thesis, atrial flutter has been included in the AF (atrial fibrillation) variable because it is also a rhythmic disturbance of the heart (arrhythmia) and it has similar symptoms, causes and consequences. This matches the commonly used ICD-10 diagnosis code I48.9 ("Atrial fibrillation and atrial flutter, unspecified").

Prevalent AF: Patients with prevalent AF were those who already had a diagnosis of AF at study start.

Incident AF: Patients with incident AF were those who were first diagnosed with AF during the follow-up period of the study.

SAMMANFATTNING PÅ SVENSKA

BAKGRUND
Obstruktiv sömnapné (OSA) innebär upprepade andningsuppehåll under tiden man sover, vilket leder till störd nattsömn. Under sådana andningsuppehåll sjunker ofta syrenivåerna i blodet. Tidigare studier har visat att OSA är kopplat till ökad risk för hjärt- och kärlsjukdomar. OSA är vanligt och förekommer i alla åldrar. Bland vuxna och medelålders i Sverige har ca 20% av män och ca 10% av kvinnor mer än 15 andningsuppehåll per sömntimme. Riskfaktorer för sömnapné är ökad ålder, övervikt, manligt kön samt alkohol- och läkemedelsintag. Hos kvinnor ökar risken efter klimakteriet. Vanliga symptom är snarkningar och andningsuppehåll, orolig sömn, uppvaknanden, svettningar, koncentrationssvårigheter, morgonhuvudvärk sömnighet på dagtid. Dagtidssömninghet drabbar dock inte alla med sömnapné. OSA är behandlingsbart, exempelvis med andningsmask, som håller luftvägarna öppna när man sover.

Förmaksflimmer (FF) är en typ av hjärtrytmrubbning. När man har FF slår hjärtat oregelbundet och ofta för fort, vilket kan ge symtom som hjärtklappning, andfåddhet och trötthet. FF är förhållandevis vanligt, och drabbar ca 1% av 50-åringar och 10% av 80-åringar. FF ökar risken för stroke och för nedsatt pumpförmåga hos hjärtat. Riskfaktorer för FF är ökad ålder, högt blodtryck, hjärtsvikt och övervikt. Hjärtats förmak är ofta förstorade hos patienter med FF.

Både OSA och FF kan vara asymtomatiska, och kan därför vara svårupptäckta. OSA och FF har flera gemensamma riskfaktorer. Eftersom OSA är behandlingsbart, skulle mer kunskap kring OSA och eventuella följdsjukdomar leda till minskad risk att utveckla FF och andra tillstånd.

SYFTE
Syftet med avhandlingen är att studera kopplingen mellan svårighetsgrad av OSA och risk att ha eller utveckla FF.

METODER OCH RESULTAT
I avhandlingen studeras tre olika grupper i fem delarbeten: en grupp med slumpmässigt utvalda män bosatta i Göteborg födda 1943, en större grupp som sökt sig till sömnmottagningarna i Skaraborg på grund av misstanke om sömnapné och en mindre grupp patienter från Skaraborg som opererats på grund av kranskärlssjukdom (”bypass”-operation).

I artikel I och II studeras 412 män födda 1943 vid 71 års ålder. Delarbete I visar att svår sömnapné (30 eller fler andningsuppehåll på sömntimme) innebär en ökad risk för att ha FF. Delarbete II visar att medel till svår sömnapné (över 15 andningsuppehåll per sömntimme) ökar risken för att ha ett förstorat vänster förmak, vilket i sig är en riskfaktor för att utveckla FF.

I artikel III och IV studeras 4239 kvinnliga och manliga patienter som utretts för sömnapné. Delarbete III visar att patienter med svår OSA, men inte har dagtidssöm-

nighet har ökad risk för FF. Eftersom denna grupp inte har besvär kan det vara svårt att motivera dessa för behandling med andningsmask. Delarbete IV visar att OSA kan kopplas till risk för tidigare insjuknande i FF, men att denna koppling delvis kan bero på ålder och samsjuklighet i form av hjärtsvikt hos patienterna.

I artikel V studeras 147 män och kvinnor med kranskärlssjukdom som ”bypass”-opererats. Det visar sig att patienter med svår OSA löper större risk att utveckla FF inom 30 dagar efter sin operation jämfört med andra patienter.

SLUTSATSER
Sammanfattningsvis visar delarbetena i avhandlingen på att OSA, och då framförallt OSA med många andningsuppehåll per sömntimme, kan kopplas till:

- förstorat vänster förmak och ökad förekomst av FF hos 71-åriga män
- ökad risk för FF hos män och kvinnor som inte är dagtidssömniga och till en liten ökad risk för att utveckla FF hos patienter som utreds på sömnmottagning
- ökad risk att utveckla FF efter bypassoperation hos kranskärlssjuka

ACKNOWLEDGEMENTS

"Consciousness: That annoying time between naps"
– Steven Wright

Under åren har en hel del varit involverade på ett eller annat sätt. Stort tack till alla! Jag vill dock särskilt tacka:

Erik Thunström, allmänt ambitiös huvudhandledare, för möjligheten och för att ha hållit mig någotsånär på banan!

Yuksel Peker, bihandledare, för all förbättring av artiklar och ett häpnadsväckande tempo!

Per-Olof Hansson, bihandledare, för synpunkter, medförfattande och allmän blixtsnabb assistans när det behövts.

Michael Fu, bihandledare, för synpunkter och medförfattandeskap!

Eva Thydén, för allt arbete med SiS-studien och hjälp med avhandlingens färdigställande.

Ulrica Forslund Grenheden, för all hjälp med administrativa saker – annars hade ingenting blivit klart.

Catriona M Chaplin, CMC Scientific English, för väldigt värdefull och nödvändig granskning av text och sammanhang!

Maria Hedelin, *Ola Bratt*, kursledare respektive examinator för kliniska forskarskolan – för allt jobb med kursen för avgångsklassen 2021… Inte det lättaste på grund av alla restriktioner!

Medförfattare till alla delarbeten, för alla värdefulla tillägg och förbättringar till delarbetena.

Alla *tidigare kollegor* på Östra förstås!

Alla *klasskamrater* på Kliniska forskarskolan –väldigt trevligt, trots att mycket blev digitalt!

Malin :) ♥ - världens bästa Malin!

Erik och Per – världens bästa bröder!

Morsan (dativ) och *farsan* (adj. Hj)

Alla *vänner och bekanta* som hjälpt till på andra sätt!

The included papers, the production and presentation of this thesis was made possible by grants from the Swedish Heart-Lung Foundation, the Research fund at Skaraborg Hospital, the Swedish government under the ALF agreement between the Region Västra Götaland and the University of Gothenburg, The Health and Medical Care Committee of the Regional Executive Board, Region Västra Götaland and the ResMed foundation. ResMed Sweden provided the ApneaLink HSAT devices without having any influence on study design or interpretation of data.

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