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Everything will be okay in the end.
If it's not okay, it's not the end.
John Lennon

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Department of Pulmonary Diseases, Turku University Hospital
MINNA MYLLYLÄ: Long-term CPAP use in obstructive sleep apnea: Effects on cardiovascular outcomes, weight control and motor vehicle accidents
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ABSTRACT

Obstructive sleep apnea (OSA) is a common disorder associated with various adverse health effects, including an increased risk of cardiovascular disease (CVD) events, metabolic dysregulation, and motor vehicle accidents (MVA). This study evaluated the long-term effects of continuous positive airway pressure (CPAP), the primary treatment for OSA, in a large retrospective cohort of 1030 CPAP-adherent patients and 1030 controls matched for age, gender and apnea-hypopnea index (AHI). Controls had discontinued CPAP treatment despite their doctor's advice.

Approximately one half of the patients commencing CPAP had continued the treatment for ≥5 years, generally with good short- and long-term adherence. Only a weak positive correlation was found between AHI and long-term CPAP usage, while no association could be verified between AHI and the risk of CVDs or MVAs. CPAP-treated patients at the cohort level had a slight weight gain at a comparable rate to that observed in the general middle-aged Finnish population, while 10 % of the patients at the individual level had a significant weight gain. Those individuals, at baseline, were already more severely obese despite being younger than the rest of the cohort. An association between CPAP and a reduced risk of CVDs and all-cause mortality, in comparison to controls, was observed over a median follow-up of 9 years but only among those with CPAP use of >4–6 h/day. The incidence of MVAs did not change when compared 9 years before and after treatment or in CPAP-treated patients and controls regardless of the level of adherence.

The results of the present study emphasize that OSA is a heterogeneous disease, and the use of AHI alone is insufficient to assess OSA severity or to identify high-risk patients for adverse outcomes. The results further imply that CPAP use of >4–6 h/day is needed to achieve potential improvements in CVD risk. Patients are more likely to gain than lose weight during CPAP treatment, underlying the urge for lifestyle interventions. The incidence of MVAs did not change after CPAP use, suggesting that the MVA risk is likely to be multifactorial, and even longer observation periods may be needed to detect a significant difference.

KEYWORDS: adherence, cardiovascular disease, continuous positive airway pressure treatment, mortality, motor vehicle accident, obstructive sleep apnea syndrome, personalized medicine, real-world study, weight control

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TIIVISTELMÄ

Obstruktiivinen uniapnea on yleinen sairaus, johon liittyy vakavia terveysriskejä, kuten sydän- ja verisuonisairaudet, aineenvaihdunnan toimintahäiriöt ja suurentunut liikenneonnettomuusalttius. Tämä tutkimus kartoitti takautuvasti obstruktiivisen uniapnean ensisijaisen hoitomuodon, ylipaine- eli CPAP-hoidon vaikuttavuutta. Tutkimuksessa oli mukana 1030 pitkäaikaisesti hoitoon sitoutunutta potilasta ja 1030 iän, sukupuolen ja apnea-hypopneaindeksin (AHI) suhteen kaltaistettua verrokkia, jotka olivat lopettaneet CPAP-hoidon lääkärin suosituksesta huolimatta.

Keskimäärin puolet hoidon aloittaneista oli jatkanut hoitoa ≥5 vuotta. Hoitoon sitoutuminen oli hyvällä tasolla sekä lyhyt- että pitkäaikaisesti. Heikko tilastollinen vastaavuus havaittiin AHI:n ja pitkäaikaisten käyttötuntien välillä, mutta yhteyttä AHI:n ja sydän- ja verisuonitautisairastavuuden tai liikenneonnettomuusriskin välillä ei todettu. Ryhmätasolla havaittiin vähäinen painonnousu, joka oli vastaava kuin suomalaisessa keski-ikäisessä väestössä yleensä. Yksilötasolla 10 % potilaista lihoi merkittävästi. Nuoremmasta iästään huolimatta he olivat jo lähtötilanteessa vaikeammin lihavia kuin muut tutkimuspotilaat. Verrokkiryhmään verrattuna CPAP-hoidon käyttö >4–6 tuntia päivässä liittyi pienempään sydän- ja verisuonitautisairastavuuteen ja kokonaiskuolleisuuteen 9 vuoden seuranta-aikana. Liikenneonnettomuuksien esiintyvyys ei muuttunut, kun potilaita verrattiin 9 vuotta ennen ja jälkeen hoidon, käyttötuntien perusteella tai suhteessa verrokkipotilaisiin.

Tulosten perusteella obstruktiivinen uniapnea on monimuotoinen sairaus, jonka vaikeusastetta ei voida luotettavasti arvioida eikä suurimmassa terveysriskissä olevia tunnistaa pelkän AHI:n perusteella. Mahdollinen suotuisa vaikutus sydän- ja verisuonitautisairastavuuteen edellyttänee CPAP-hoidon käyttöä >4–6 tuntia päivässä. Lihominen hoidon aikana on todennäköisempää kuin laihtuminen painottaen elintapahoitojen tärkeyttä. Liikenneonnettomuuksien esiintyvyys ei muuttunut CPAP-hoidon myötä. Liikenneonnettomuuteen joutuminen on todennäköisesti monitekijäinen tapahtuma ja pidempi seuranta-aika saattaa olla tarpeen, jotta merkittävä ero voitaisiin havaita.

AVAINSANAT: CPAP-hoito, hoitoon sitoutuminen, kuolleisuus, liikenneonnettomuus, obstruktiivinen uniapnea, painonhallinta, reaalimaailman tutkimus, sydän- ja verisuonisairaus, yksilöllinen lääketiede

TABLE OF CONTENTS

ABBREVIATIONS

AASM	American Academy of Sleep Medicine
AF	Atrial fibrillation
AHI	Apnea-hypopnea index
ANOVA	One-way analysis of variance
BMI	Body mass index
BP	Blood pressure
CAD	Coronary artery disease
CI	Confidence interval
cmH_2O	Centimeter of water
CMV	Commercial motor vehicle
CO_2	Carbon dioxide
COPD	Chronic obstructive pulmonary disease
CPAP	Continuous positive airway pressure
CRP	C-reactive protein
CSA	Central sleep apnea
CVD	Cardiovascular disease
DEPS	Depression Scale
ECG	Electrocardiogram
EDS	Excessive daytime sleepiness
EEG	Electroencephalography
EOG	Electro-oculography
EMG	Electromyography
ESS	Epworth Sleepiness Scale
GHQ-12	General Health Questionnaire
HF	Heart failure
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HR	Hazard ratio
ICD-10	10th revision of the International Statistical Classification of Diseases and Related Health Problems
ICSD-3	The third edition of the International Classification of Sleep Disorders

IFG	Impaired fasting glucose
IL	Interleukin
IQR	Interquartile range
LVEF	Left ventricular ejection fraction
MAD	Mandibular advancement device
MRI	Magnetic resonance imaging
MSLT	Multiple Sleep Latency Test
MVA	Motor vehicle accident
MWT	Maintenance of wakefulness test
NF-$_K$B	Nuclear factor kappa B
NREM	Non-rapid eye movement sleep
ODI	Oxygen desaturation index
ODI4	Oxygen desaturation index of ≥4 %
OR	Odds ratio
OSA	Obstructive sleep apnea
OSAS	Obstructive sleep apnea syndrome
OSLER	Oxford Sleep Resistance Test
PAD	Peripheral artery disease
PALM	P_{crit}, arousal threshold, loop gain and muscle responsiveness
PCI	Percutaneous coronary intervention
pCO_2	Partial pressure of carbon dioxide
P_{crit}	Critical closing pressure of the airway
PLMS	Periodic limb movements of sleep
PSG	Polysomnography
RCT	Randomized controlled trial
RDI	Respiratory disturbance index
REI	Respiratory event index
REM	Rapid eye movement sleep
RERA	Respiratory effort-related arousals
ROS	Reactive oxygen species
RR	Risk ratio
SD	Standard deviation
SDB	Sleep-disordered breathing
SpO_2	Blood oxygen saturation level
T2D	Type 2 diabetes
TIA	Transient ischemic attack
TNF-α	Tumor necrosis factor-α

LIST OF ORIGINAL PUBLICATIONS

This dissertation is based on the following original publications, which are referred to in the text by their Roman numerals I–V. Some unpublished data are also presented.

I Myllylä M, Hammais A, Stepanov M, Anttalainen U, Saaresranta T, Laitinen T. Nonfatal and fatal cardiovascular disease events in CPAP compliant obstructive sleep apnea patients. *Sleep Breath.*, 2019; 4: 1209–1217.

II Myllylä M, Kurki S, Anttalainen U, Saaresranta T, Laitinen T. High adherence to CPAP treatment does not prevent the continuation of weight gain among severely obese OSAS patients. *J Clin Sleep Med*, 2016; 4: 519–528.

III Myllylä M, Anttalainen U, Saaresranta T, Laitinen T. Motor vehicle accidents in CPAP-compliant obstructive sleep apnea patients–a long-term observational study. *Sleep Breath.*, 2020; doi: 10.1007/s11325-020-02023-2. [Epub ahead of print]

IV Myllylä M, Hammais A, Stepanov M, Anttalainen U, Saaresranta T, Laitinen T. Response to letter entitled "CPAP adherence and cardiovascular disease: beware of the healthy adherer effect". *Sleep Breath.*, 2020; 2: 601–602.

V Myllylä M, Hammais A, Stepanov M, Anttalainen U, Saaresranta T, Laitinen T. Response to the letter entitled "COPD-and-smoking-induced 'down regulation' of CO2-related vasoconstriction in the brain during CPAP for sleep apnea may paradoxically reduce risk of cardiovascular events". *Sleep Breath.*, 2020; doi: 10.1007/s11325-020-02028-x. [Epub ahead of print]

1 INTRODUCTION

Obstructive sleep apnea (OSA) is a major public disorder with a range of adverse consequences to patients' health and is a heavy burden on health care systems (Kapur et al. 2017, Patil et al. 2019). It has been associated with various daytime and nocturnal symptoms, and it may increase the risk for weight gain, hypertension, other cardiovascular diseases (CVDs), metabolic dysregulation and motor vehicle accidents (MVAs) (Javaheri et al. 2017, Joosten et al. 2017, Pamidi & Tasali 2012, Patil et al. 2019, Tregear et al. 2009). A growing rate of obesity, in addition to an aging population, are expected to contribute to the increasing OSA prevalence (Qaseem et al. 2014).

The pathogenic significance of upper airway collapse during sleep and its potential connection with obesity was initially described in the 1960's (Gastaut et al. 1965). At first, tracheostomy was the only known effective treatment for OSA (Patil et al. 2019). The development of nasal continuous positive airway pressure (CPAP) treatment by Professor Sullivan and colleagues in 1981 completely changed the treatment of OSA (Sullivan et al. 1981). The CPAP device provides positive pressure throughout the respiratory cycle, thereby acting as a pneumatic splint that maintains the patency of the upper airway during sleep (Leech et al. 1992, Sullivan et al. 1981). It is still the primary treatment for OSA 40 years later (Chowdhuri et al. 2016, Gay et al. 2006, Sullivan 2018). However, adherence to CPAP has been challenging, even though technological advancements have enabled the development of auto-adjusting computer algorithms, modified pressure profiles, and the use of telemonitoring (Anttalainen et al. 2016a, Bakker et al. 2019, Patil et al. 2019). Inadequate adherence has hampered the evaluation of treatment effectiveness on different outcomes, particularly in randomized controlled trials (RCTs) assessing the risk of CVDs (McEvoy et al. 2016, Peker et al. 2016, Sánchez-de-la-Torre et al. 2020).

Our understanding of OSA heterogeneity has developed further during the past two decades, and recent studies have focused on identifying different symptom-, pathophysiological- and polysomnographic-based OSA phenotypes (Zinchuk & Yaggi 2020). Mounting evidence has shown that OSA development is dependent on several anatomic and non-anatomic factors and their varying combinations (Eckert et al. 2013). Advances in the knowledge of OSA and its pathogenesis provide an

opportunity towards more personalized medicine, since new targeted therapies could be developed (Eckert et al. 2013). Studies on OSA phenotypes have also suggested that the use of the apnea-hypopnea index (AHI) alone is insufficient for assessing OSA severity, since patients with a similar AHI may significantly differ in terms of symptoms and OSA-related outcomes (Keenan et al. 2018). New tools are needed to identify patients who are at the highest risk of encountering adverse outcomes and most likely to benefit from CPAP.

The aim of this thesis was to evaluate the impact of long-term CPAP treatment with adequate adherence on the incidence of CVD events, all-cause mortality and MVAs in comparison to untreated control patients matched for, age, gender and AHI. Another aim was to evaluate the effect of long-term CPAP treatment on weight maintenance, since the majority of previous studies have investigated these changes only in the short term (Drager et al. 2015). Finally, patient characteristics associated with an increased risk of adverse outcomes were determined, and the significance of the level of CPAP adherence on the incidence of CVDs and MVAs was evaluated. This work seeks to provide further data on OSA heterogeneity and to identify those patients who are either most likely to benefit from CPAP or who require additional support during treatment.

2 REVIEW OF THE LITERATURE

2.1 Obstructive sleep apnea (OSA)

2.1.1 Definition of OSA

OSA is characterized by recurrent episodes of complete (apnea) and partial (hypopnea) upper airway obstruction during sleep that results in repetitive interruption of ventilation (The Report of an American Academy of Sleep Medicine Task Force 1999). An obstructive apnea is defined as ≥90 % drop in airflow for ≥10 seconds in the presence of ongoing inspiratory efforts against the occluded airway (Berry et al. 2012). The 1999 guidelines of the American Academy of Sleep Medicine (AASM), known as the "Chicago Criteria", defined hypopnea as ≥50 % drop in airflow for ≥10 seconds with no requirement for oxygen desaturation, or alternatively, <50 % drop in airflow for ≥10 seconds associated with ≥4 % oxygen desaturation or an arousal (The Report of an American Academy of Sleep Medicine Task Force 1999). The 2007 AASM scoring manual provided two hypopnea definitions: the recommended hypopnea definition required ≥30 % drop in airflow for ≥10 seconds associated with ≥4 % oxygen desaturation, while the alternative hypopnea definition required ≥50 % drop in airflow for ≥10 seconds associated with ≥3 % oxygen desaturation or an arousal (Iber et al. 2007). Based on the current 2012 AASM criteria, a hypopnea is defined as ≥30 % drop in airflow for ≥10 seconds associated with ≥3 % oxygen desaturation or an arousal (Berry et al. 2012).

The number of apneas and hypopneas per hour of sleep is defined by AHI. An AHI of <5 /h is considered normal, whereas obstructive sleep apnea syndrome (OSAS) is characterized by an AHI of ≥5 /h in addition to OSA-related symptoms (The Report of an American Academy of Sleep Medicine Task Force 1999). Based on the third edition of the International Classification of Sleep Disorders (ICSD-3), OSA is defined as either 1) having an obstructive respiratory disturbance index (RDI) of ≥5 /h in polysomnography (PSG) in addition to typical OSA symptoms, or 2) having an obstructive RDI of ≥15 /h with or without OSA-related symptoms (American Academy of Sleep Medicine 2014). RDI, with a difference from AHI, also includes the number of respiratory effort-related arousals (RERAs), which can only be determined by PSG. RERA is defined as increasing respiratory effort or

flattening of the nasal airflow during inspiration, which lasts ≥10 seconds and results in arousal from sleep but does not fulfill the definition criteria of an apnea or a hypopnea (Berry et al. 2012).

2.1.2 Prevalence

A recent population-based study from Europe revealed that 50 % of middle-aged men and 23 % of women had moderate to severe OSA based on the current AASM definition for hypopnea (Heinzer et al. 2015). OSA may be overlooked, especially among women, since men are reported to be more likely to be referred for a sleep study and to receive treatment for OSA than are women, despite women having similar symptoms suggestive of sleep-disordered breathing (SDB) (Lindberg et al. 2017). The gender difference in OSA prevalence decreases after menopause (Heinzer et al. 2015). Mild or more severe OSA was found in 90 % of men and 78 % of women in the elderly population aged 60–85 years (Senaratna et al. 2017). The prevalence of OSA has been shown to be 2- to 3-fold higher among patients with than without CVD (Somers et al. 2008). A higher prevalence has also been reported among commercial vehicle (CMV) drivers, since mild OSA was found in 28 % and severe OSA in 5 % of the subjects in a study of 406 CMV drivers (Pack et al. 2006).

2.1.3 Pathophysiology

Obstruction of the upper airway during sleep with OSA may be induced by several anatomic and non-anatomic factors and their varying combinations (White 2005). The critical closing pressure (P_{crit}) that will cause it to collapse is used to define the required pressure level inside the airway (Eckert et al. 2013, White 2017). P_{crit} may be evaluated by reducing the CPAP pressure to a level at which the airway collapses (White 2017). Studies evaluating P_{crit} during sleep have shown an overlap between healthy controls, snorers and patients with apneas and hypopneas. One study reported that OSA was found in all subjects with a P_{crit} of -1 centimeter of water (cmH_2O) or more positive, while only healthy subjects had a P_{crit} of -6 cmH_2O or more negative; a P_{crit} between -5 and -2 cmH_2O was found in both groups. With the same P_{crit} value, patients may have OSA of different severities or they may not have OSA at all (Eckert et al. 2013, White 2017). Thus, abnormal anatomy does not entirely explain OSA's pathophysiology (White 2017).

2.1.3.1 Anatomic factors

The majority of the patients with OSA have an anatomically small pharyngeal airway due to alterations in craniofacial structures (e.g. small maxilla and mandible,

enlarged tonsils) or extra soft tissue around the airway (e.g. increase in fat tissue due to obesity). Peripheral edema may also accumulate to the neck area in supine position and construct the airway. Extra soft tissue or edema surrounding the airway increases extraluminal pressure, which, in turn, may exceed the elastance of the airway walls and partially or completely collapse the airway. Lung inflation generates longitudinal traction on the trachea and larynx, which stiffens the airway and decreases collapsibility. A reduction in lung volume during sleep or due to obesity results in a loss of longitudinal traction on the upper airway, predisposing it to collapse (Javaheri et al. 2017, White 2005). **Figure 1** summarizes the main forces that increase or decrease the collapsibility of the pharyngeal airway.

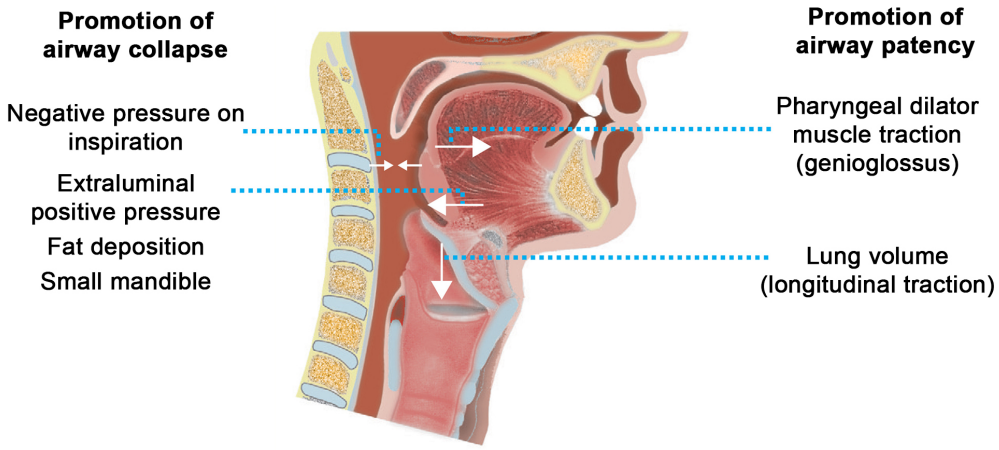


Figure 1. A sagittal section through the pharyngeal airway, and the main forces that increase or decrease the collapsibility of the airway. Reprinted from The Lancet (Malhotra & White 2002) with permission from Elsevier.

2.1.3.2 Non-anatomic factors

Non-anatomic factors include upper airway dilator muscle dysfunction (decreased muscle responsiveness during sleep), low arousal threshold and a high loop gain (Eckert et al. 2013, White 2005). The function of the pharyngeal dilator muscles, particularly genioglossus, primarily prevents the airway from collapsing. Genioglossus activation is mainly controlled by three neural inputs that respond to 1) negative pressure in the airway, 2) respiratory drive and 3) arousal state. Thus, pharyngeal muscle activity is elevated by increased negative airway pressure, hypoxia or hypercapnia, inspiration and wakefulness. The airway becomes more vulnerable to collapse during sleep due to diminished muscle responsiveness to negative airway pressure and carbon dioxide (CO_2), in addition to changes in arousal state (White 2005).

The arousal threshold as a response to respiratory stimulation has been shown to vary between individuals, since subjects with a low arousal threshold are likely to wake up in response to small increases in respiratory drive, while those with a higher arousal threshold demand clearly increased respiratory drive to wake up. A higher arousal threshold enables the activation of pharyngeal dilator muscles, revising the patency of the airway before arousal from sleep occurs. However, it may also lead to prolongation of apneas and hypopneas in subjects with decreased upper airway responsiveness (White 2017). Apneic or hypopneic events result in hypoxia and hypercapnia in OSA, which stimulates the respiratory drive and usually leads to arousal from sleep in order to stop the apneic event (Somers et al. 2008).

The respiratory system is regulated by feedback loops that enables it to become unstable. Loop gain, defined as the ratio of ventilatory response per ventilatory disturbance (apnea or hypopnea), may be used to represent the stability or instability of such system. A high loop gain (>1) stands for ventilatory instability, in which case a disturbance in the respiratory system will result in a large ventilatory response and unstable ventilatory control. Loop gain is influenced by controller gain (chemoreceptors reacting to the partial pressure of CO_2 (pCO_2): responsiveness to hypercapnia) and plant gain (lungs, respiratory muscles: change in ventilation). A high controller gain is generally caused by brisk responsiveness to hypercapnia, whereas a small change in ventilation induces a large change in pCO_2 in high plant gain (e.g. reduced cardiac output, low metabolic rate, hypercapnia). It has been suggested that high loop gain may contribute to OSA's pathogenesis, particularly in patients with a moderately collapsible airway, while it does not seem to increase the risk in those without other factors predisposing to OSA (White 2005, White 2017).

2.1.4 Risk factors

Obesity is the best-documented risk factor for OSA (Qaseem et al. 2014), although 20–40 % of OSA patients are not obese (Javaheri et al. 2017). OSA has been associated with a higher body-mass index (BMI), increased waist-to-hip ratio and neck girth (Heinzer et al. 2015, Qaseem et al. 2014). Fat deposited in lateral fat pads and tongue base decrease the patency of the upper airway, and abdominal fat tissue mechanically compresses the chest and abdominal wall, resulting in reduced lung volumes and longitudinal traction. Additionally, obesity-related leptin resistance may also lead to alterations in respiratory control (Joosten et al. 2017). In the population-based Wisconsin Sleep Cohort Study, a 10 % weight gain was associated with a 32 % increase in AHI in addition to a 6-fold greater risk of developing moderate to severe OSA over a 4-year follow-up (Peppard et al. 2000a).

Large population-based studies have also shown that the risk of having moderate to severe SDB was 1.7-fold greater among those aged ≥60 years compared to younger subjects (Young et al. 2002), and that every 10-year elevation in age increased the risk by 50 to 70 % (Heinzer et al. 2015). In addition to older age, a 2- to 3-fold greater risk for OSA has been reported among men compared to women (Heinzer et al. 2015, Young et al. 2002). This could be at least partly explained by the differences in upper airway anatomy, including longer pharyngeal airway length and increased pharyngeal soft tissue mass in the soft palate and tongue among men (Dempsey et al. 2010). The response to arousal, hormones, the distribution of fat tissue, and neurochemical mechanisms may also contribute to the gender difference. Menopause is a significant risk factor for OSA in women, and hormone replacement therapy has been associated with a lower prevalence of OSA, but a causal relationship has not been confirmed (Lin et al. 2008).

Patients with OSA were associated in a meta-analysis of 26 studies with craniofacial disharmony, such as decreased pharyngeal airway space, inferiorly located hyoid bone and increased anterior facial heights compared to controls. In the majority of the included studies, patients were mainly men and the average BMI was <30 kg/m^2 (Neelapu et al. 2017). Additionally, smoking, a positive family history for OSA, endocrine abnormalities, such as hypothyroidism and acromegaly, and the use of alcohol or benzodiazepines have been shown to increase the risk for apneas and OSA (Somers et al. 2008, The Report of an American Academy of Sleep Medicine Task Force 1999).

2.1.5 Diagnostic methods

Symptoms and clinical examination (signs and OSA risk factors) can suggest OSA, but the diagnostic standard is based on sleep studies (American Academy of Sleep Medicine 2014).

2.1.5.1 Clinical features

OSA patients may present with a number of different daytime and/ or nocturnal symptoms, which may have an adverse effect on quality of life (Patil et al. 2019). Excessive daytime sleepiness (EDS), defined as inability to stay awake during daytime resulting in increased need for sleep or unintentional dozing, is one of the most significant daytime symptoms (Berry et al. 2012, Kapur et al. 2017). However, <50 % of OSA patients have been shown to report on EDS (Saaresranta et al. 2016, Ye et al. 2014). Other symptoms suggestive for OSA include unrefreshing sleep, daytime fatigue, insomnia, witnessed apnea or gasping during sleep, frequent awakenings from sleep, loud snoring, sleep-related cardiac

dysrhythmias, morning headache, impaired concentration, nocturia and sexual dysfunction. None of these symptoms are specific to OSA, and symptoms may also differ between genders, since women are more likely to report on fatigue, insomnia, morning headaches and depression than men (American Academy of Sleep Medicine 2014, Lin et al. 2008, Qaseem et al. 2014, The Report of an American Academy of Sleep Medicine Task Force 1999). Patients with OSA may also be asymptomatic (Somers et al. 2008).

Different questionnaires may be used to identify patients for further evaluation (Kapur et al. 2017). The most common questionnaire is the self-reported Epworth Sleepiness Scale (ESS) **(Appendix 1)**, which includes eight questions that assess the level of daytime sleepiness and tendency to fall asleep during daytime. A score of ≤10 is considered normal, while mild to moderate EDS is defined as a score of 11–15 and severe EDS as a score of 16–24 (Johns 1991, Kapur et al. 2017). The risk for OSA is classified in the Berlin Questionnaire as high or low according to eleven questions that are divided into three categories (Netzer et al. 1999). The STOP-Bang questionnaire, a validated screening questionnaire for OSA, includes questions of symptoms (snoring, tiredness, observed apneas), age, gender, BMI, neck circumference and the history of high blood pressure (BP) (Chung et al. 2008).

Clinical signs suggestive for OSA include obesity, enlarged neck size, crowded-appearing pharyngeal airway, craniofacial disharmony, elevated BP in addition to other OSA-related comorbidities (Monderer et al. 2017, Neelapu et al. 2017). The physical examination should include the evaluation of throat, nose, neck, cervicofacial angle, lungs and heart. The measurement of weight, height, BMI, BP and the circumference of neck and waistline should also be included (Monderer et al. 2017). The accuracy of symptoms, clinical signs and questionnaires for the OSA diagnosis has been low compared to sleep studies, which underlines the need for differential diagnosis and further evaluation in patients suspected of having OSA (American Academy of Sleep Medicine 2014, Kapur et al. 2017).

2.1.5.2 Sleep studies

Sleep studies have been traditionally categorized into four groups: Type I (full attended PSG with ≥7 channels in a laboratory setting), Type II (full unattended portable PSG with ≥7 channels), Type III (limited number of sensors of 4–7), and Type IV (usually 1–2 sensors). Unattended studies that can be performed at a patient's home (home sleep apnea testing) belong to the categories of II–IV according to the number of monitoring sensors that are utilized. Type II studies have the same sensors as a full attended PSG, including electroencephalography (EEG), electro-oculography (EOG), chin electromyography (EMG), electrocardiogram

(ECG) or heart rate, airflow, respiratory effort (movement of the thorax and abdomen) and blood oxygen saturation level (SpO_2), but they can be performed outside the sleep laboratory. Type III studies measure at least two respiratory variables (at least two channels of respiratory movement, or respiratory movement and airflow), the level of SpO_2 and a cardiac variable (ECG or heart rate). Type IV studies usually measure only SpO_2 and heart rate (Kapur et al. 2017).

In-hospital, technician-attended PSG is considered the reference standard for OSA diagnosis (Kapur et al. 2017). However, it requires the patient to spend the night in a sleep laboratory, which increases the costs and limits the study's accessibility. The EEG, EOG and chin EMG that are measured in PSG are not utilized in cardiorespiratory polygraphy, a type III sleep study (Dingli et al. 2003); thus, the exact sleep time, stages of sleep or cortical arousals cannot be determined, and the AHI has been shown to be approximately 20 to 30 % higher in patients investigated with PSG than those studied by cardiorespiratory polygraphy (Escourrou et al. 2015, Hedner et al. 2011). According to the international standards, the term respiratory event index (REI) should actually be used instead of AHI when the OSA diagnosis is based on cardiorespiratory polygraphy (Kapur et al. 2017).

Cardiorespiratory polygraphy has been shown to be more accurate in the diagnosis of severe OSA and less accurate in mild OSA. Risk of technical failures is also increased if the study is performed unattended (Kapur et al. 2017). The use of cardiorespiratory polygraphy is particularly common in Europe, since it was used for OSA diagnosis in 67 % of 5103 subjects included in the European Sleep Apnea Database study (Hedner et al. 2011). Based on the clinical practice guideline from the AASM, either PSG or home sleep apnea testing may be used for OSA diagnosis in uncomplicated patients with suspected risk of moderate to severe OSA. The use of PSG is primarily recommended for patients with a significant cardiorespiratory disease, hypoventilation during wakefulness, long-term use of opioid medication, a history of stroke or severe insomnia, or suspected respiratory muscle weakness due to a neuromuscular condition or sleep-related hypoventilation (Kapur et al. 2017).

2.1.5.3 Other diagnostic methods

The Multiple Sleep Latency Test (MSLT) (Carskadon & Dement 1977) and the Maintenance of Wakefulness Test (MWT) (Mitler et al. 1982) have been used to objectively assess sleepiness and alertness. In the MSLT, patients are requested to fall asleep in a quiet, dark room, and sleepiness is measured by sleep latency during four registrations that occur at 2-hour intervals. The test is based on the assumption that the degree of sleepiness is associated with sleep latency (Carskadon & Dement 1977). The MWT measures ability to remain awake in a sleepy environment. The

test includes four 20- or 40-minutes registrations that occur at 2-hour intervals (Mitler et al. 1982). A significant, but a rather weak, correlation has been observed between the results of MSLT and MWT (Arand et al. 2005). Wide range in normal values and requirement for a laboratory environment, which differs significantly from workplace conditions, have been identified as limitations of MSLT, whereas motivation to stay awake may influence the MWT performance (Arand et al. 2005). Overall, the MSLT and MWT both have limitations in identifying OSA patients from the general population and should not be the main factors in assessing daytime sleepiness, verifying the OSA diagnosis, or in evaluating responsiveness to treatment (Arand et al. 2005).

The Oxford Sleep Resistance Test (OSLER) is a behavioral test that measures the ability to maintain wakefulness and daytime vigilance. Patients are requested not only to remain awake for four 40-minutes registrations but also to respond to a flash of light appearing every 3 seconds by hitting a button on a portable device. Seven subsequent misses are interpreted as falling asleep (Bennett et al. 1997). It has been shown to be a reliable tool for assessing daytime sleepiness compared to MWT. The main limitation of the OSLER test is its requirement for patient co-operation (Patil et al. 2019).

Driving simulation and real-life driving performance have been used to evaluate daytime sleepiness, especially in CMV drivers (Philip et al. 2008). However, the use of driving simulators has not accurately predicted real-life MVAs or near-miss accidents and it has actually been shown to artificially increase driving impairment compared to real-life driving performance (Dwarakanath & Elliott 2019, Philip et al. 2008). Subjects usually drive on a straight highway for 90 minutes in a real-life driving performance evaluation. They are instructed to maintain a constant speed while driving in the center of the lane without crossing the lanes. A professional driving instructor monitors the driving speed, inappropriate line crossings and subject's vigilance (Philip et al. 2008).

2.1.6 Severity

OSA severity can be determined by the level of daytime sleepiness, AHI and SpO_2 and it should be based on the most severe component (Current Care Guidelines for Adult Obstructive Sleep Apnea 2017, Institute for Clinical Systems Improvement (ICSI) 2005, The Report of an American Academy of Sleep Medicine Task Force 1999). **Table 1** summarizes the evaluation of OSA severity.

Table 1. The severity of obstructive sleep apnea determined by the level of daytime sleepiness, apnea-hypopnea index (AHI) and blood oxygen saturation level (SpO_2). Modified with permission from Current Care Guidelines for Adult Obstructive Sleep Apnea 2017. Based on the references: Institute for Clinical Systems Improvement (ICSI) 2005 and The Report of an American Academy of Sleep Medicine Task Force 1999.

Severity	Daytime sleepiness	SpO_2 (%)	AHI (/h)
Mild	Occurs only during activities that require little attention (e.g. reading or watching television) Only a minor effect on social or occupational function	Mean ≥90 AND Minimum ≥85	≥5 and <15
Moderate	Occurs during activities that require some attention (e.g. during meetings or concerts) A moderate effect on social or occupational function	Mean <90 AND Minimum ≥70	≥15 and <30
Severe	Occurs during activities that require more active attention (e.g. during conversation or driving) A significant effect on social or occupational function	Mean <90 AND Minimum <70	≥30

2.1.7 Differential diagnosis

Sleepiness may also be explained by numerous other factors than OSA: other sleep disorders, chronic hypoventilation syndromes, periodic limb movements of sleep (PLMS), narcolepsy, insomnia, idiopathic hypersomnia, insufficient sleep, personal stressors, shift working, circadian rhythm disorders, hypersomnia due to a medication or a psychiatric disorder, chronic fatigue syndrome, fibromyalgia, endocrine abnormalities (e.g. hypothyroidism, diabetes mellitus, excessive growth hormone), brain tumors or other malignancies, stroke, head trauma, epilepsy, the use of alcohol or illicit drugs, other basic diseases (e.g. chronic renal insufficiency, congestive heart failure (HF)) (Monderer et al. 2017), obesity (Vgontzas et al. 2006) or menopause in women (Lin et al. 2008).

Questionnaires may also be used in differential diagnosis for OSA, e.g. ESS (Johns 1991) and the STOP-Bang screening questionnaire (Chung et al. 2008). The 12-item General Health Questionnaire (GHQ-12) **(Appendix 2)** can also be used to assess psychological distress (a score of ≥3 of 12 indicates psychological distress) (Goldberg et al. 1997) and the Depression Scale (DEPS) to screen for depression (a score of ≥9 of 30 is associated with an increased likelihood of depression) (Salokangas et al. 1995). The laboratory tests are unspecific for OSA but are necessary in differential diagnosis and due to OSA-related comorbidities (The Report of an American Academy of Sleep Medicine Task Force 1999). Based on the

Finnish Current Care Guideline for obstructive sleep apnea in adults, the evaluation of at least basic blood count, glycated hemoglobin, serum lipid concentrations, thyroid-stimulating hormone and ECG are recommended for all patients. The need for chest or sinus X-ray, spirometry and the measurement of arterial or transcutaneous CO_2 is evaluated individually (Current Care Guidelines for Adult Obstructive Sleep Apnea 2017).

2.1.8 Other types of sleep apnea

Central sleep apnea (CSA) is defined by cessation of airflow without respiratory effort (American Academy of Sleep Medicine 2014). CSA generally results from the instability of the respiratory control system caused by a high loop gain (particularly a high controller gain). High loop gain predisposes to hyperventilation due to an elevated hypercapnic ventilatory response, which leads to a reduction in pCO_2. An apnea will occur when pCO_2 decreases below the apneic threshold and does not end until pCO_2 elevates above the threshold (Berry et al. 2012, Randerath et al. 2017, White 2005). Patients may have both obstructive and central apneas, since unstable respiratory control may also induce obstructive respiratory events (Randerath et al. 2017). Inclusion criteria have often required >50–80 % of the respiratory events to be central in studies involving patients with CSA (Somers et al. 2008).

CSA may be idiopathic (high controller gain) or induced by ambient hypoxia at high altitude, different comorbidities, including particularly HF but also acute stroke, other neurological diseases and end-stage renal disease, or the use of opioids. CSA has been estimated to affect 18 to 37 % of HF patients, being slightly more common among those with a reduced left ventricular ejection fraction (LVEF) (Randerath et al. 2017). Furthermore, Cheyne-Stokes respiration is commonly seen in HF patients due to a high controller gain, deceleration of circulation and hypocapnia resulting from increased filling pressures and lung edema. It is characterized by fluctuations in ventilation, which results in a crescendo-decrescendo pattern of breathing followed by central apneas (Randerath et al. 2017, White 2005).

Mixed sleep apnea is a combination of both central and obstructive apneas in which the interruption in ventilation begins with a central apnea and continues as an obstructive one (Berry et al. 2012). Dilating forces of the upper airway are sufficient enough to prevent the development of apneas and hypopneas but not to maintain the complete patency of the airway in prolonged partial upper airway obstruction. During these episodes, the upper airway is usually partially obstructed for several minutes, resulting in reduced inspiratory airflow and increased respiratory effort against the partially obstructed airway. The specific definition criteria include prolonged flow limitation for >20–30 % of total recording or sleep time, sustained flow limitation in nasal prongs, crescendo snoring, pCO_2 >6 kPa and absence of

repetitive arousals from sleep. It occurs particularly among women and is associated with daytime symptoms and increased risk of hypertension. It has been suggested as a clinically significant form of SDB. However, these patients may have a low AHI and are, thus, commonly interpreted incorrectly as having mild sleep apnea (Anttalainen et al. 2016b).

2.2 Comorbidities in OSA

2.2.1 Cardiovascular comorbidities and type 2 diabetes

The most compelling evidence supports an independent causal link between OSA and hypertension, since RCTs have demonstrated a reduction in BP after CPAP (Javaheri et al. 2017, Lurie 2011, Peker & Balcan 2018). OSA has been suggested to be a potential risk factor for atherosclerosis, since it has been associated with carotid intima-media thickness and an increased burden of noncalcified and calcified coronary plaques (Drager et al. 2011a, Hoyos et al. 2017, Yoshihisa et al. 2019, Zhou et al. 2017). Small studies have demonstrated an improvement in carotid intima-media thickness in OSA after CPAP, but however, CPAP has not been shown to decrease or stabilize plaques. Thus, causality between OSA and atherosclerosis has not been confirmed and further RCTs are needed to clarify whether CPAP could improve early signs of atherosclerosis and prevent the development of a clinically more severe form of CVD (Drager et al. 2007, Hoys et al. 2017, Hui et al. 2012).

OSA has been associated with an increased risk of CVDs, particularly stroke, but an association between coronary artery disease (CAD), HF, atrial fibrillation (AF), peripheral artery disease (PAD) and type 2 diabetes (T2D) has also been suggested in addition to a higher prevalence of OSA in pulmonary hypertension (Javaheri et al. 2013, Javaheri et al. 2017, Pamidi & Tasali 2012, Utriainen et al. 2013).

2.2.1.1 Mechanisms

The potential pathogenesis of CVDs in OSA is not completely understood, but it is likely multifactorial. **Figure 2** summarizes the main mechanisms and physiological effects that could contribute to the development of CVDs in OSA.

Intermittent hypoxemia. Intermittent hypoxemia is characterized by repetitive episodes of desaturation and re-oxygenation; it has been suggested to play a pivotal role in the pathogenesis of CVDs in OSA. The European Sleep Apnea Database study of over 11 000 subjects found an association between oxygen desaturation index (ODI) and prevalent hypertension independent of confounding factors (Tkacova et al. 2014), while a prospective study of patients with newly diagnosed OSA associated the severity of nocturnal oxygen desaturation with carotid artery

thickening and plaque occurrence (Baguet et al. 2005). Intermittent hypoxemia may trigger oxidative stress, systemic inflammation, endothelial dysfunction and sympathetic activation and it may promote glucose intolerance (Dewan et al. 2015). Treatment with CPAP has been shown to be effective in attenuating ODI (Iftikhar et al. 2017).

Inflammation. Systemic inflammation has been shown to crucially contribute to the progress of atherosclerosis at all stages of atheroma formation and its thrombotic complications (Dempsey et al. 2010, Dewan et al. 2015). Intermittent hypoxemia has been linked with the activation of pro-inflammatory transcription factors, particularly nuclear factor kappa B (NF-$_K$B), leading to the production of various inflammatory markers (Ryan et al. 2009). Tumor necrosis factor-α (TNF-α), interleukin (IL)-6, IL-8 and C-reactive protein (CRP) have been reported to be elevated in OSA patients. Observational studies have suggested that CPAP may reduce the levels of most of these markers (Xie et al. 2013, Peker & Balcan 2018). However, the association has not been confirmed in RCTs (Jullian-Desayes et al. 2015, Peker & Balcan 2018). OSA and obesity may also have synergistic effects, since intermittent hypoxemia may affect macrophages in adipose tissue leading to increases in inflammatory markers (Javaheri et al. 2017).

Vascular endothelial dysfunction. Endothelial dysfunction is characterized by increased adherence of inflammatory mediators to endothelial cells and imbalanced production of vasoactive hormones from the endothelium, including inhibition of nitric oxide (a vasodilator) and increased release of endothelin (a vasoconstrictor). Intermittent hypoxemia, oxidative stress and systemic inflammation, in addition to OSA-related obesity, hypertension and metabolic dysregulation, have been suggested to contribute to endothelial dysfunction. It may trigger vasoconstriction, hypercoagulability and the proliferation of vascular smooth muscle, predisposing to the development of CVDs (Budhiraja et al. 2007, Dempsey et al. 2010). Observational studies have suggested that CPAP could improve endothelial function, but however, the data of RCTs is scarce and not sufficient to support this conclusion (Peker & Balcan 2018).

Oxidative stress. Intermittent hypoxemia has been shown to result in increased production of reactive oxygen species (ROS). Cells adapt to lower oxygen levels, which leads to increased production of ROS at the end of apneas and hypopneas when the oxygen levels are restored (Butt et al. 2010, Dewan et al. 2015). ROS may oxidize cellular products, proteins and lipids and result in endothelial dysfunction by decreasing the level of nitric oxide and increasing the release of endothelin (Butt et al. 2010). Furthermore, it may activate the renin-angiotensin-aldosterone system, leading to elevated plasma aldosterone levels and the development of hypertension (Dempsey et al. 2010). CPAP has been suggested to potentially reduce oxidative stress in observational studies, but the data of RCTs is scarce and future RCTs are

needed to clarify whether the association between OSA and oxidative stress is causal (Hoyos et al. 2017, Peker & Balcan 2018).

Sympathetic nerve activity. Sympathetic nerve activity in OSA has been shown to also be elevated during the daytime by measurements of muscle sympathetic nerve activity and norepinephrine levels in plasma and urine. It has been shown to result in vasoconstriction with a consequent increase in BP and alterations in heart rate variability. Several etiological mechanisms have been suggested to be involved, including intermittent hypoxemia, increased activation of central and peripheral chemoreceptors, reduced baroreflex sensitivity and endothelial dysfunction (Butt et al. 2010, Dempsey et al. 2010). Several RCTs have shown that CPAP reduces muscle sympathetic nerve activity in addition to plasma and urinary catecholamines in OSA, indicating a causal relationship between OSA and sympathetic activation (Peker & Balcan 2018).

Thrombosis. Platelet dysfunction and hypercoagulability have been shown to contribute to the development of atherothrombotic events and CVDs. A potential association between OSA and hypercoagulability has been suggested, including increased plasma fibrinogen levels, excessive platelet activity and decreased fibrinolytic capacity (Dempsey et al. 2010, Somers et al. 2008). However, the data of both observational studies and RCTs on the effectiveness of CPAP in reducing coagulation factors in OSA have been conflicting, and it is not clear whether the association between OSA and hypercoagulability is causal (Peker & Balcan 2018).

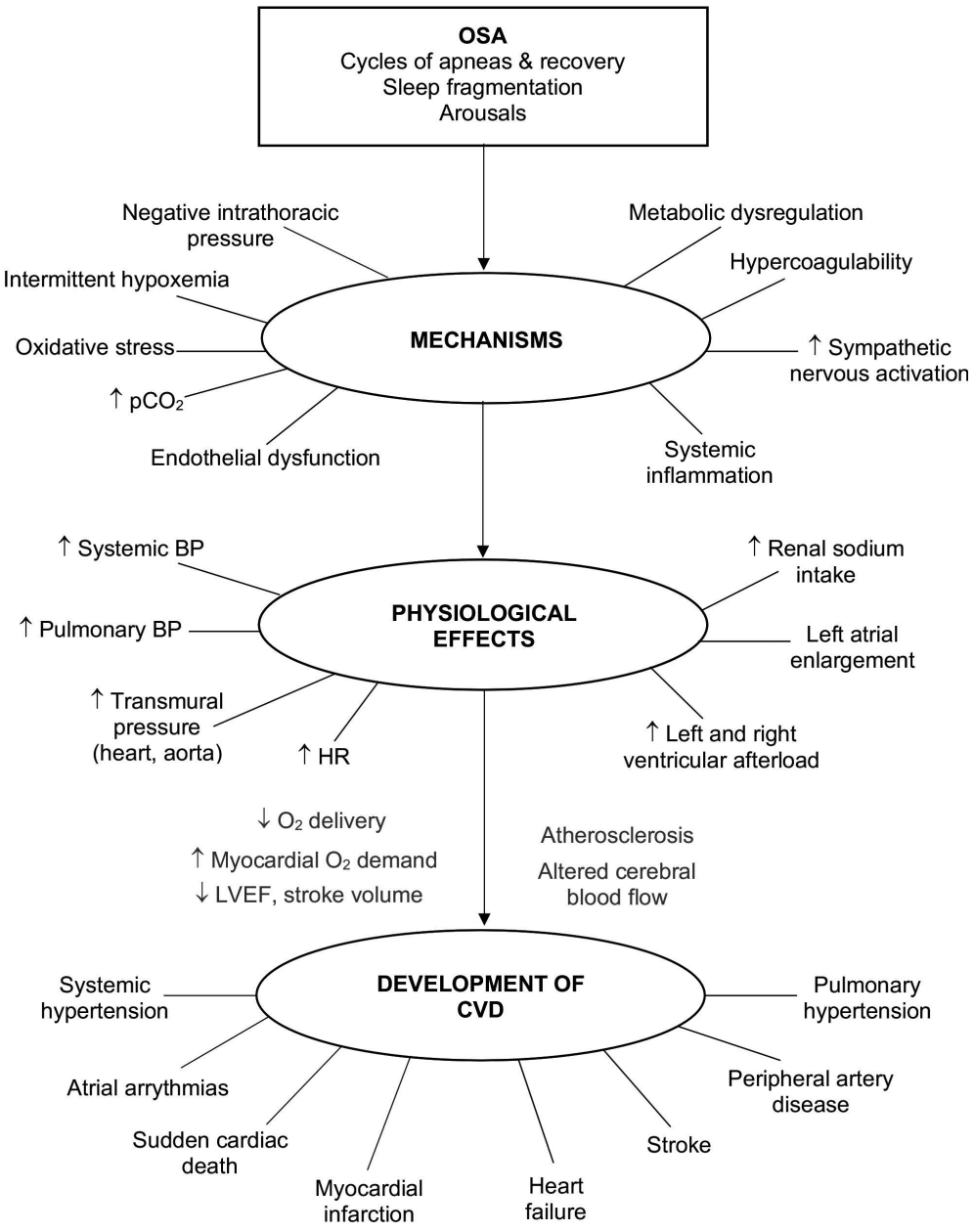
Intrathoracic pressure changes. Repetitive respiratory efforts against the closed upper airway in OSA result in major negative pressure swings in the chest cavity, which increases venous return to the heart and transmural pressure of all intrathoracic structures. Ventricular function may consequently be impaired due to increased cardiac afterload, decreased diastolic function and alterations in the function of the autonomic system (Somers et al. 2008). Thin-walled atriums stretch easily as a response to the surrounding negative pressure, which may lead to stimulation of atrial mechanoreceptors and activation of atrial ion channels and contribute to the development of atrial arrhythmias (Javaheri et al. 2017).

Insulin resistance. OSA has been suggested to associate with insulin resistance, a risk factor for atherosclerosis, potentially due to intermittent hypoxemia, sleep disruption and increased sympathetic nerve activity (Reutrakul & Mokhlesi 2017). The association appears to be at least partly independent of obesity and increasing OSA severity has been reported to correlate with an increasing level of insulin resistance (Hoyos et al. 2017, Kent et al. 2014a). Several RCTs have suggested that CPAP may improve insulin resistance in OSA patients without T2D (Lam et al. 2010, Patil et al. 2019, Weinstock et al. 2012), although the results are not entirely consistent. One RCT showed a reduction in insulin resistance only among those

treated with weight loss alone or weight loss plus CPAP, but not among those treated with CPAP alone (Chirinos et al. 2014).

Leptin. Leptin is an adipose tissue -derived hormone that regulates appetite, weight control and fat distribution and it may also act as a respiratory stimulant. Animal studies have demonstrated that chronic hyperleptinemia may increase BP, platelet aggregation and arterial thrombosis, but a causal link between leptin and CVDs has not been confirmed (Chen et al. 2015, Dempsey et al. 2010). OSA has been associated with leptin resistance, which is characterized by reduced anorexic effect of leptin despite having elevated leptin levels (Chen et al. 2015, Shechter 2017). Some prospective studies have reported decreased leptin levels after CPAP independent of weight changes, but importantly, RCTs have not. Thus, it is not clear whether the link between OSA and leptin is causal (Balcan et al. 2020, Chen et al. 2015, Shechter 2016).

Ghrelin. Ghrelin is a hormone that is predominantly secreted from the stomach. It has a broad range of physiological effects on almost every system; it stimulates appetite in an antagonist manner to leptin, has other impacts on gastric functions in addition to anabolic effects, and increases release of several hormones, including growth hormone. It has been suggested that ghrelin may have cardioprotective effects, such as improvement of LVEF, reduced BP and attenuation of causes of atherosclerosis, but a causal link has not been confirmed (Lilleness & Frishman 2016). Obesity is associated with decreased ghrelin levels, whereas most studies have shown increased ghrelin levels in OSA patients (Shechter 2017). The majority of prospective studies have suggested a reduction in ghrelin after CPAP (Shechter 2016). However, the effect of CPAP on ghrelin has been studied less than that on leptin, and data from RCTs are lacking (Shechter 2016).



BP, blood pressure; HR, heart rate; LVEF, left ventricular ejection fraction; O_2, oxygen; pCO_2, partial pressure of carbon dioxide.

Figure 2. The main mechanisms and physiological effects that could contribute to the development of cardiovascular diseases (CVD) in obstructive sleep apnea (OSA). Based on the references: Coniglio & Mentz 2020, Bradley & Floras 2003, Javaheri et al. 2017, Ryan et al. 2009, Sommers et al. 2008.

2.2.1.2 Hypertension

It has been estimated that ≥30 % of those with hypertension have an AHI of ≥15 /h (Floras 2015, Javaheri et al. 2017), while approximately 30 to 70 % of OSA patients are likely to have hypertension (Patel et al. 2019). OSA is the most common secondary cause of resistant hypertension, and an AHI of ≥15 /h has been found in ≥70 % of those with drug-resistant hypertension (Floras 2015, Patel et al. 2019). OSA may also result in unfavorable circadian pattern, since the prevalence of non-dippers (<10 % decrease in the mean nocturnal BP from the mean daytime BP) and risers (an increase in nocturnal BP) has been greater in OSA than in healthy subjects. Both may contribute to impaired CVD outcome (Torres et al. 2015).

Several population-based studies have shown an association between OSA and prevalent hypertension independent of other known CVD risk factors (Hou et al. 2018). The Wisconsin Sleep Cohort Study, the Sleep Heart Health Study and the more recent HypnoLaus Study involving together >9000 subjects showed an independent 1.3–1.8-fold increased risk of prevalent hypertension in moderate to severe SDB compared to healthy controls (Heinzer et al. 2015, Nieto et al. 2000, Young et al. 1997a). One large study also found that every 1 /h-unit increase in AHI increased the risk of prevalent hypertension by 1 %, whereas every 10 % decrease in nocturnal SpO_2 increased the risk by 13 % (Lavie et al. 2000). Furthermore, a few studies have suggested that OSA patients aged <60 years may be more likely to have prevalent hypertension than older patients (Bixler et al. 2000, Haas et al. 2005, Sjöström et al. 2002), potentially since the risk factors for OSA or physiological responses to upper-airway conclusion may differ according to age (Haas et al. 2005).

However, the results of population-based studies on incident hypertension have been rather conflicting, which may be at least partly explained by differences in cohort size, diagnostic methods for OSA and patient characteristics (Torres et al. 2015). The Wisconsin Sleep Cohort Study showed that patients with mild OSA had a 2-fold (95 % CI 1.3–3.2) and those with moderate to severe OSA a 2.9-fold (95 % CI 1.5–5.6) increased 4-year risk of incident hypertension independent of confounding factors (Peppard et al. 2000b). Conversely, the Sleep Heart Health Study and the Vitoria Sleep Cohort study of elderly patients failed to show an independent association over follow-ups of 5 to 7.5 years (Cano-Pumarega et al. 2011, O'Connor et al. 2009). A recent large meta-analysis further demonstrated that mild to moderate OSA was associated with a 1.2- to 1.3-fold and severe OSA with a 1.6-fold (95 % CI 1.3–1.9) increased risk of prevalent hypertension, while no significant results were found in terms of incident hypertension (Hou et al. 2018).

2.2.1.3 Ischemic heart disease

Mounting evidence from clinic- and population-based studies has suggested that OSA may be an independent risk factor for CAD (Hla et al. 2015, Marin et al. 2005, Peker et al. 2006). It has been estimated that approximately 38 % of patients with CAD have an AHI of ≥15 /h (Javaheri et al. 2017). The Sleep Heart Health Study found that the risk of prevalent CAD was 1.3-fold (95 % CI 1.0–1.6) greater among those with an AHI of >11 /h compared to controls (Shahar et al. 2001). Observational studies have suggested that OSA may be a trigger for nocturnal myocardial infarction (Kuniyoshi et al. 2008) or sudden cardiac death (Gami et al. 2013).

A clinic-based study of over 300 subjects found that mild OSA was associated with an adjusted 5-fold (95 % CI 1.8–11.6) increased 7-year risk of incident CAD compared to healthy subjects (Peker et al. 2006), while another study of over 1600 males found that severe OSA was associated with a 3-fold (95 % CI 1.2–7.5) higher 10-year risk of cerebrovascular and cardiac events compared to healthy controls (Marin et al. 2005). Population-based studies have generally shown an independent 1.1–2.6-fold greater risk of incident CAD in OSA or OSA subgroups. The Wisconsin Sleep Cohort Study showed a 3-fold (95 % CI 1.1–6.1) greater risk of CAD or HF in severe SDB over a follow-up of up to 24 years compared to healthy subjects (Hla et al. 2015), while the Sleep Heart Health Study found an increased 9-year risk of incident CAD in SDB only in males aged ≤70 years (Gottlieb et al. 2010). Another analysis of the same study population also found that moderate to severe SDB was associated with a 2-fold (95 % CI 1.1–2.5) increased risk of fatal CAD events only among males (Punjabi et al. 2009). However, a Finnish study of over 36 000 subjects did find a higher 15-year risk of CAD in females with OSA (Strausz et al. 2018).

OSA has also been suggested to worsen prognosis in CAD patients treated with percutaneous coronary intervention (PCI) (Lee et al. 2016, Qu et al. 2018). The Sleep and Stent Study of 1311 CAD patients treated with PCI found that those with an AHI of ≥15 /h had a 1.6-fold increased 2-year risk (95 % CI 1.1–2.2) of major adverse cardiac and cerebrovascular events (Lee et al. 2016). A meta-analysis of prospective studies including 2465 CAD patients treated with PCI confirmed that the risk of cardiac events was 1.6–2-fold higher among those with OSA (Qu et al. 2018).

2.2.1.4 Stroke

It has been estimated that approximately 57 % of patients with stroke have moderate to severe OSA (Javaheri et al. 2017). A recent Finnish study reported that up to 93 % of patients with acute ischemic stroke had at least mild sleep apnea and that the OSA severity actually progressed to moderate or severe in 69 % after a follow-up of 6 months (Huhtakangas et al. 2018). A large meta-analysis showed that OSA

prevalence was higher among those with recurrent rather than initial stroke (Johnson & Johnson 2010). Furthermore, a study of 161 patients with acute stroke or transient ischemic attack (TIA) found no correlation between the location of neurological lesions and OSA, suggesting that OSA had preceded the stroke onset (Parra et al. 2000). OSA patients with stroke have also shown to differ from those without stroke by being less sleepy and having a lower BMI (Arzt et al. 2005), and it has been suggested that sleep studies should be considered in all patients with acute stroke or TIA (Johnson & Johnson 2010, Kernan et al. 2014).

Compared to controls without OSA, the Sleep Heart Health Study showed a 1.6-fold (95 % CI 1.0–2.5) increased risk of prevalent stroke in patients with an AHI of >11 /h (Shahar et al. 2001), while the Wisconsin Sleep Cohort Study reported a 4-fold (95 % CI 1.3–14.2) greater risk among those with moderate to severe OSA (Arzt et al. 2005). The former also found a dose-response relationship between OSA and incident stroke over a follow-up of 9 years among women with an AHI of >25 /h and all men (Redline et al. 2015), while the latter did not find an independent association after a 4-year follow-up (Arzt et al. 2005). However, the Spanish Vitoria Sleep study of elderly patients found a 2.5-fold (95 % CI 1.0–6.0) higher 6-year risk of incident stroke (Munoz et al. 2006), and a clinic-based study of 1022 subjects also reported a 2-fold (95 % CI 1.1–3.5) increased 3-year risk of incident stroke or all-cause death compared to controls without OSA (Yaggi et al. 2005). Thus, the risk of stroke has been suggested to be approximately 2- to 4-fold higher in OSA. A large meta-analysis of prospective cohort studies further confirmed that the risk of incident stroke was 2.2-fold (95 % CI 1.4–3.2) higher among severe OSA compared to those without OSA (Wang et al. 2013).

OSA has also been associated with a worse prognosis in patients with stroke (Kaneko et al. 2003a, Martínez-García et al. 2009), including poorer functional outcomes, prolonged hospitalization and rehabilitation during the post-stroke period (Kaneko et al. 2003a), and potentially increased risk of death at least in those with moderate to severe OSA (Martínez-García et al. 2009).

2.2.1.5 Peripheral artery disease

PAD is a form of systemic atherosclerosis and it has been associated with an increased risk of CVD events and death (Hirsch et al. 2001). The prevalence of OSA has been unexpectedly high in patients with advanced PAD, since it was found in 50–85 % of PAD patients referred for revascularization (Szymanski et al. 2019, Utriainen et al. 2013). Furthermore, OSA may be associated with a worse prognosis in these patients, since an observational study of 84 patients with PAD referred for revascularization showed that those with moderate to severe OSA had an independent 5-fold (95 % CI 1.9–13.9) greater risk of major adverse

cardiovascular and cerebrovascular events than controls without OSA (Utriainen et al. 2014). However, the current data on the prevalence of PAD in OSA patients is scarce.

2.2.1.6 Heart failure

The relationship between OSA and HF is likely bidirectional. HF-related hypoxemia and venous congestion may result in unstable respiratory control particularly in obese subjects (Javaheri et al. 2020a). Peripheral edema may accumulate in the neck area in a supine position, predisposing to supine-predominant OSA (Wang et al. 2020). CSA and Cheyne-Stokes respiration may also lead to upper airway collapse (Javaheri et al. 2017). OSA may predispose to HF through negative intrathoracic pressure swings, intermittent hypoxemia, increased sympathetic nerve activity and endothelial dysfunction (Bradley & Floras 2003, Coniglio & Mentz 2020).

It has been estimated that the prevalence of moderate to severe OSA is approximately 20 % in HF with reduced (HFrEF) and 23 % in HF with preserved ejection fraction (HFpEF) (Javaheri et al. 2017). HF patients with OSA rarely report EDS, which likely leads to underdiagnosis of OSA (Bradley & Floras 2003, Javaheri et al. 2017). The Sleep Heart Health Study found that an AHI of >11 /h was associated with over a 2-fold (95 % CI 1.2–4.6) greater independent risk of prevalent HF compared to healthy controls (Shahar et al. 2001), while every 10 /h-unit increase in AHI increased the 9-year risk of incident HF by 13 % in men but not in women (Gottlieb et al. 2010). It has been recommended that all HF patients with New York Heart Association class II–IV should be screened for OSA (Yancy et al. 2017).

Observational studies have also suggested that the risk of death may be 2- to 3-fold higher in chronic HFrEF (Jilek et al. 2011, Wang et al. 2007) and 1.6-fold higher in acute HFrEF among those with moderate to severe OSA compared to a lower AHI (Khayat et al. 2015). This could be at least partly due to increased sympathetic nerve activity in the awake state, which may predispose to premature mortality and sudden death in HF (Floras 2003). Conversely, a smaller study did not find a difference in the 4-year mortality risk between HFrEF patients with or without OSA; however, those treated with CPAP were not examined separately (Roebuck et al. 2004).

2.2.1.7 Atrial fibrillation

OSA may predispose to AF particularly through intermittent hypoxemia and recurrent negative intrathoracic pressure swings, which may lead to increases in both pre- and afterload of the right side of the heart due to increased venous return and pulmonary vasoconstriction. Right atrial and ventricular enlargement and leftward septal displacement during diastole may impair left ventricular filling, leading to

increases in left atrial volume. Thin-walled left atrium also stretches easily due to intrathoracic pressure changes, which may activate catecholamine-sensitive ion channels and produce electrical impulse inducing AF (Javaheri et al. 2017, Linz et al. 2018). A large observational study also showed that obesity and nocturnal hypoxemia were both independently associated with AF over a follow-up of up to 15 years but only in patients aged <65 years (Gami et al. 2007).

The prevalence of OSA in patients with AF has been estimated to be in the range of 21 to 74 % (Linz et al. 2018). A large observational study found a higher prevalence of OSA (49 vs. 33 %) based on the Berlin questionnaire in patients with AF undergoing cardioversion compared to high-risk patients with multiple other CVDs (Gami et al. 2004). The Sleep Heart Health Study showed that severe SDB was associated with an independent 4-fold (95 % CI 1.0–15.7) greater risk of nocturnal AF compared to subjects without SDB (Mehra et al. 2006). Furthermore, nocturnal AF or non-sustained ventricular tachycardia occurred 18-times (95 % CI 5.3–58.4) more likely after a respiratory disturbance than normal breathing, although the absolute rate of observed arrhythmias was extremely low (Monahan et al. 2009). However, a smaller study found no significant association between OSA and AF when patients with AF were studied for OSA (Porthan et al 2004).

Observational studies have also suggested that untreated OSA is associated with an increased risk of AF recurrence after cardioversion and cardiac ablation compared to treated patients (Fein et al. 2013, Kanagala et al. 2003, Neilan et al. 2013) and a higher risk of hospitalization and worse symptoms. No significant differences were observed in the risk of all-cause mortality or CVD events (Holmqvist et al. 2015).

2.2.1.8 Pulmonary hypertension

The prevalence of OSA in patients with pulmonary hypertension, defined as a mean pulmonary artery pressure of >25 mmHg, appears to be much higher compared to that in the general population (Javaheri et al. 2013). All types of SDB may occur in 30–90 % of the patients (Wong et al. 2017). Particularly intermittent hypoxemia, negative intrathoracic pressure swings and endothelial dysfunction could result in the development of awake pulmonary hypertension directly by adverse remodeling of pulmonary arteries or myocardium or indirectly by e.g. systemic hypertension and left sided HF (Javaheri et al. 2013, Wong et al. 2017). The American College of Chest Physicians has recommended SDB to be assessed in all patients with established pulmonary hypertension (Atwood et al. 2004).

Conversely, the prevalence of pulmonary hypertension in OSA remains uncertain (Javaheri et al. 2013), particularly since the inclusion and exclusion criteria of patients have varied between studies (Wong et al. 2017). A combined analysis of 6 studies involving 519 OSA patients reported that pulmonary hypertension was

observed in 10 %, and its severity was mild in most cases (Javaheri et al. 2013). Severe pulmonary hypertension is not commonly met in OSA patients if other predisposing comorbidities, such as obesity or chronic obstructive pulmonary disease (COPD), do not exist (Javaheri et al. 2013, Wong et al. 2017).

2.2.1.9 Type 2 diabetes

The prevalence of T2D with OSA has been estimated to be up to 15–30 %, and 70 % vice versa (Kent et al. 2014b, Reutrakul & Mokhlesi 2017). It has been suggested that OSA may be independently associated with prediabetic conditions, although obesity has been an important confounding factor in these associations (Hoyos et al. 2017). T2D patients with OSA may also have worse glucose control than those without OSA (Pamidi & Tasali 2012). A few observational studies have suggested an association between increasing OSA severity and the risk of prevalent T2D (Kent et al. 2014b, Pamidi & Tasali 2012), although one study reported an increased risk only in those with severe OSA and EDS (Ronksley et al. 2009). Patients in the Wisconsin Sleep Cohort Study and the European Sleep Apnea Database study with moderate to severe OSA had an independent 2-fold increased risk of prevalent T2D compared to subjects without OSA (Kent et al. 2014b, Reichmuth et al. 2005).

The association between OSA and incident T2D has been more controversial (Pamidi & Tasali 2012). A cohort study of over 1200 subjects reported that OSA was associated with an adjusted 1.4-fold (95 % CI 1.1–1.9) higher 3-year risk of T2D (Botros et al. 2009). A similar result was found in the Australian Busselton Health Study (Marshall et al. 2009), while the Wisconsin Sleep Cohort Study did not report an increase in the 4-year T2D risk in moderate to severe OSA (Reichmuth et al. 2005). Two Swedish studies with >10-year follow-ups also showed mixed results, since one study found an increased risk only in women (Celen et al. 2010), while the other study showed a 4-fold (95 % CI 1.1–18.1) greater risk among males with an ODI of >5 /h (Lindberg et al. 2012). Overall, it is not clear whether OSA could predispose to T2D, and further large-scale studies are needed (Patil et al. 2019).

2.2.2 Other comorbidities

Depression and anxiety. OSA may be more prevalent in patients with depression, since its prevalence in this patient group has been approximately 50 % in clinic- and slightly over 7 % in population-based samples. However, the evidence regarding the prevalence of OSA in anxiety disorders other than posttraumatic stress disorder has been insufficient (Gupta et al. 2015). There are also data suggesting an increased prevalence of depression in OSA, which may contribute to EDS. A recent RCT of

CAD patients showed that depressive mood was more prevalent among those with OSA (29 vs. 19 %) and particularly in the present of sleepiness (Balcan et al. 2019).

COPD. The prevalence of COPD in OSA has been estimated to be 10–55 %, while the prevalence of OSA in COPD has varied in the range of 5–85 % (Khatri & Ioachimescu 2016). An overlap of OSA and COPD has been associated with more severe nocturnal hypoxemia, a higher prevalence of pulmonary hypertension and a 7-fold higher risk of all-cause mortality compared to OSA without COPD (Khatri et al. 2016, Lavie et al. 2007, McNicholas 2016). Furthermore, an observational study showed that the risk of all-cause mortality or hospitalization due to severe COPD exacerbation did not differ between CPAP-treated patients and those with COPD only (Marin et al. 2010). However, these findings remain to be confirmed in future RCTs (Khatri & Ioachimescu 2016, McNicholas 2016).

Asthma. It has been suggested that patients with asthma may have up to 2-fold increased OSA risk, while the prevalence of asthma in patients with OSA has been estimated to be approximately 35 %. Asthma and OSA share several risk factors and a causal relationship has not been confirmed. However, it has been reported that OSA may worsen asthma control (Khatri & Ioachimescu 2016).

Gastroesophageal reflux. A causal relationship between gastroesophageal reflux and OSA has not been confirmed, although OSA patients seem to have a higher prevalence of gastroesophageal reflux. Obesity has been the most important confounding factor in these associations (Zanation & Senior 2005).

Cancer. Observational studies have suggested an association between OSA and cancer incidence potentially due to intermittent hypoxemia and sleep fragmentation, but a causal relationship has not been confirmed (Patil et al. 2019). The Wisconsin Sleep Cohort study showed that the 22-year risk of cancer mortality increased independently with increasing AHI (Nieto et al. 2012). One study showed an increased risk of prevalent cancer in OSA only among women (Pataka et al. 2019), while the other study demonstrated a greater 4.5-year cancer incidence only among males aged <65 years (Campos-Rodriguez et al. 2013). An association between OSA and prevalent or incident cancer was not, however, observed in two other large studies, although nocturnal SpO_2 of <90 % did independently associate with smoking-related cancers (Christensen et al. 2013, Kendzerska et al. 2014). Overall, further studies on the subject are needed.

2.3 Risk of motor vehicle accidents (MVAs) in OSA

Several observational studies have suggested that patients with untreated OSA may have up to 2- to 7-fold greater risk of being involved in an MVA (Cassel et al. 1996, George 2001, Horstmann et al. 2000, Stoohs et al. 1994, Young et al. 1997b). Based on a meta-analysis of 10 studies with over 2200 subjects, the mean risk of MVAs

was estimated to be over 2-fold (95 % CI 1.2–4.9) greater in patients with than without OSA (Tregear et al. 2009). A Swedish observational study of 1478 subjects further confirmed that patients with OSA had a 2.5-fold (95 % CI) greater risk of objectively reported MVAs compared to control subjects from the general population (Karimi et al. 2015). It has been actually estimated that more than 800 000 drivers had an OSA-related MVA in the United States in the year 2000 resulting in 1400 deaths and a cost of 15.9 billion United States dollars (Sassani et al. 2004).

2.3.1 Potential predictors of MVAs

Daytime sleepiness. Several studies have reported that the MVA risk only tended to increase with increasing ESS score (Horstmann et al. 2000, Mulgrew et al. 2008, Young et al. 1997b), but however, a significant association has been observed in those with an ESS score of ≥16 (Karimi et al. 2015). Overall, daytime sleepiness from any cause has been associated with an increased MVA risk and is estimated to be responsible for approximately 20 % of highway accidents (Garbarino et al. 2001). Furthermore, experiencing sleepiness while driving rather than sleepiness in general may be one of the most important factors in addition to previous MVAs and near-miss accidents in the assessment of driving risk (Dwarakanath & Elliott 2019).

OSA severity. Only a few studies have suggested a significant association between more severe AHI and the risk of MVAs (Tregear et al. 2009), while the majority have not (Karimi et al. 2015, Mulgrew et al. 2008, Stoohs et al. 1994). Nocturnal hypoxemia may be a potential risk factor for MVAs, but a specific threshold level for SpO_2 has not been verified (Engleman et al. 1996, Tregear et al. 2009).

BMI. Several studies have found an association between a higher BMI and increased risk of MVAs (Tregear et al. 2009). Two observational studies reported that OSA patients with MVAs had a higher BMI 2 to 3 years before the accident compared to those without MVAs (Horstmann et al. 2000, Yamamoto et al. 2000). Another large observational study also showed a small but significant elevation in the risk of MVAs with increasing BMI (Mulgrew et al. 2008), and a study of 90 CMV drivers found that those with a BMI of ≥30 kg/m^2 had a higher MVA rate than leaner patients after adjustment for driving exposure (Stoohs et al. 1994).

Other risk factors. The MVA risk has also been shown to be elevated in patients with long annual driving distances, a short self-reported sleep time of ≤5 h/night and use of hypnotic medication, in addition to younger age and male gender (Gonçalves et al. 2015, Karimi et al. 2015). Furthermore, it has been suggested that OSA could potentially predispose to changes in brain morphology and neural activation leading to cognitive impairment and negative consequences on fitness to drive (Morrell et al. 2010). A study of 120 subjects found that OSA was independently associated with

focal loss of grey matter in magnetic resonance imaging (MRI) compared to those without OSA (Morrell et al. 2010). Working memory speed measured by functional MRI has also been shown to be significantly slower in OSA (Thomas et al. 2005). As a response to cognitive challenges, increased brain activation in several brain regions has been detected in functional MRI among OSA patients, which may represent an adaptive compensatory recruitment response (Ayalon et al. 2006).

2.4 Continuous positive airway pressure (CPAP) treatment of OSA

2.4.1 Mechanism and physiological effects

A CPAP device delivers a positive pressure to the airway throughout inspiration and expiration splinting the airways open and preventing them from collapsing. It reduces airway resistance and the work of breathing and consolidates sleep by decreasing the number of apnea-hypopnea episodes (Antonescu-Turcu & Parthasarathy 2010, Leech et al. 1992, Sullivan et al. 1981). A recent RCT meta-analysis observed an 86 % decrease in AHI with CPAP compared to before treatment, and CPAP was found to be efficient in reducing AHI/ RDI despite the severity of OSA at baseline (Patil et al. 2019). CPAP has been shown to be more effective in reducing AHI than a placebo, conservative treatment, positional therapy or oral appliances (Gay et al. 2006, Ramar et al. 2015). However, since OSA is a chronic condition that rarely resolves except with substantial weight loss or successful corrective surgery, long-term use of CPAP is usually required (Patil et al. 2019).

Positive airway pressure also increases intrathoracic pressure, which may result in reduced cardiac preload (by decreased venous return to heart) and reduced afterload (by reduced left ventricular transmural pressure), improving cardiac output (Antonescu-Turcu & Parthasarathy 2010). It improves end-expiratory lung volume, leading to increased oxygen stores and tracheal traction, which improves the patency of the upper airway (Antonescu-Turcu & Parthasarathy 2010). Several RCTs have shown CPAP to decrease BP and heart rate, particularly due to reductions in sympathetic activation, and small RCTs have suggested that CPAP may improve LVEF in HFrEF (Peker & Balcan 2018). **Figure 3** summarizes the main physiological effects of CPAP.

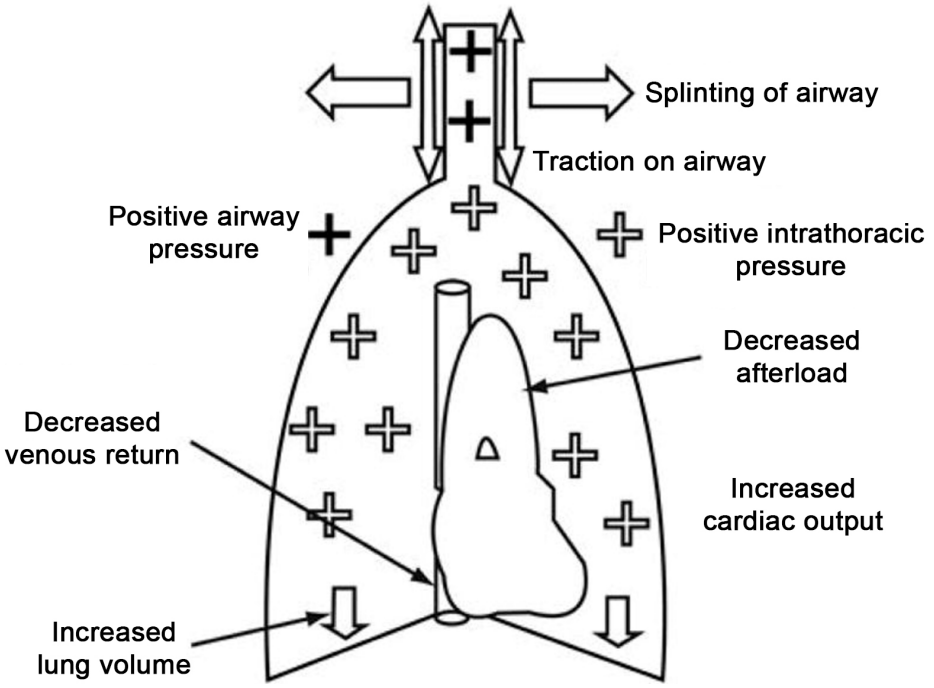


Figure 3. Physiological effects of continuous positive airway pressure (CPAP). Reprinted from Respiratory care: the official science journal of the American Association for Respiratory Care (Antonescu-Turcu & Parthasarathy 2010) with permission from the American Association for Respiratory Care.

However, CPAP may also result in ventilatory instability and the development of CSA during treatment in some OSA patients if the arterial pCO_2 is reduced below the apnea threshold level (Antonescu-Turcu & Parthasarathy 2010). The task force of the European Respiratory Society has defined two different phenotypes of patients developing CSA during CPAP. CSA disappears with continued CPAP use in treatment-emergent CSA, while it does not disappear in treatment-persistent CSA (Randerath et al. 2017). A study of 675 OSA patients found that CSA was present in 12 % during the first night with CPAP but declined to 7 % after 3 months of treatment (Cassel et al. 2011), suggesting disappearance of CSA in a significant proportion of patients. Sleep insufficiency, arousals, insomnia, adaptation of loop gain after resolution of upper airway obstruction, high CPAP pressure level and excessive mask leakage have been identified as factors that may predispose to the development of CSA during CPAP treatment (Randerath et al. 2017).

2.4.2 Evaluation of treatment

CPAP is the primary treatment for OSA, especially among patients with an AHI of ≥15 /h even in the absence of symptoms, but it is also recommended for milder OSA when the patient shows symptoms of EDS, has hypertension or other significant comorbidities, or impaired sleep-related quality of life (Chowdhuri et al. 2016, Gay et al. 2006, Loube et al. 1999, Patil et al. 2019, Sullivan et al. 1981).

2.4.3 Types of CPAP and the use of bilevel positive airway pressure for OSA treatment

A fixed pressure CPAP device delivers a constant air pressure (usually 4–20 cmH_2O) throughout the respiratory cycle, whereas an auto-adjusting device assesses breath-by-breath the minimum pressure required to maintain the patency of the airway. Thus, an auto-adjusting device increases or decreases the level of positive airway pressure in response to changes in airflow, circuit pressure or the resistance of the upper airway. Newer CPAP devices may also contain modified pressure profiles, which aim to reduce pressure during expiration to improve comfort of use (Bakker et al. 2019, Patil et al. 2019). **Figure 4** shows an example of a CPAP device.

According to a recent recommendation by the AASM, optimal CPAP pressure may be determined either by using an auto-adjusting device at home or by conventional in-laboratory titration, since no clinically relevant differences were found between the two strategies in terms of compliance, sleepiness or quality of life in OSA patients without significant comorbidities. Either auto-adjusting or fixed CPAP device may be used for ongoing treatment, although auto-adjusting device is often preferred due to cost-effectiveness, faster initiation of treatment and greater access to care, since laboratory environment is not required. It also enables the continuation of effective treatment without the guidance of health-care personnel, since it automatically adjusts the pressure to a required level in response to e.g. changes in body position or weight. However, treatment-related problems may not be identified as effectively as during an in-laboratory titration (Patil et al. 2019).

As a difference to CPAP, a bilevel positive airway pressure device delivers a higher positive airway pressure during inspiration than expiration. It has not been recommended to be used instead of CPAP for routine OSA treatment due to a higher cost with no clinically relevant differences observed in compliance, residual AHI, sleepiness or sleep-related quality of life. However, it may be used in special cases, particularly if high pressure levels (>20 cmH_2O) are required. A trial with bilevel positive airway pressure or modified pressure profile CPAP may also be suitable for some of those patients who do not adapt to CPAP due to its high pressure demands. Overall, SDB-related hypercapnia remains to be the most common indication for the use of bilevel positive airway pressure instead of CPAP (Patil et al. 2019).

Figure 4. An example of a continuous positive airway pressure (CPAP) device with a humidifier. Reprinted with permission from ResMed Finland Oy.

2.4.4 Compliance

Adherence to CPAP has been shown to be comparable to adherence to other medical treatments (Bakker et al. 2019). An observational study of 639 OSA patients reported that 81 % had continued CPAP after 5 years and 70 % after 10 years (Kohler et al. 2010). However, it has been estimated that 30 to 80 % of patients are not compliant with CPAP if a threshold of ≥4 h/day is used to define compliance (Sawyer et al. 2011, Weaver & Grunstein 2008). The mean use of CPAP has been reported to be approximately 3 h/day among non-compliant patients and 6 h/day among those who are compliant (Sawyer et al. 2011). Patients with mild OSA have been reported to adhere to CPAP similar to those with a more severe disease (Bakker et al. 2019). A study of 77 mild OSA patients found that 62 % had continued CPAP for 6 months with a mean compliance of 5 h/day (Monasterio et al. 2001). Prolonged partial upper airway obstruction has also been shown to be treatable with CPAP with good adherence to treatment (Anttalainen et al. 2016b).

2.4.4.1 Criteria for adequate compliance

Adequate compliance with CPAP has usually been defined as CPAP use of ≥4 h/day, since several studies have shown that sleepiness and other OSA-related symptoms are generally improved by this level of adherence (Patil et al. 2019, Weaver et al. 2007). Studies have traditionally accepted a patient to be compliant with CPAP if the device has been used ≥4 h/day for ≥70 % of the days monitored (Gay et al. 2006). However, patients are considered to benefit from CPAP in a dose-response manner and even a one-night withdrawal may reverse achieved improvements in daytime sleepiness and increase AHI (Weaver et al. 2007). The adequate use of CPAP may also vary between different clinical outcomes (Antic et al. 2011, Weaver et al. 2007). A study of 149 patients with severe OSA reported that sufficient treatment responses to self-reported sleepiness, objective sleepiness and functional status were achieved

with a CPAP use of 4, 6 and 7.5 h/day, respectively (Weaver et al. 2007), although improvement or normalization of these symptoms may still not be observed in all patients (Bakker et al. 2019). Overall, the majority of clinicians recommend CPAP to be used regularly for the entire night (Patil et al. 2019).

2.4.4.2 Factors affecting and methods to improve compliance

OSA and patient characteristics. CPAP adherence has not been consistently associated with age or gender (Kohler et al 2010, Weaver et al. 2007) and its association between subjective sleepiness or OSA severity has been relatively weak (Weaver & Grunstein 2008, Sawyer et al. 2011). A large observational study did, however, report that ODI was the only clinical variable independently linked to long-term adherence (Kohler et al. 2010). Nasal anatomy or existence of comorbidities may also affect CPAP use (Sawyer et al. 2011). A smaller nasal cross-sectional area has been associated with poorer adherence (Sawyer et al. 2011). Psychiatric disorders have been suggested to affect a patient's perception of OSA symptoms and CPAP-related side effects, although e.g. depression and anxiety may affect adherence differently. Tendencies to claustrophobia may preclude some patients from initiating CPAP, although they may not result in nonadherence. Future studies on the effects of psychiatric disorders and personality types on CPAP adherence are still needed (Sawyer et al. 2011).

Remote monitoring. Compliance during the first few weeks has been shown to predict compliance in the long term, emphasizing the importance of patient follow-up after the initiation of CPAP (Patil et al. 2019, Weaver & Grunstein 2008). An RCT of CAD patients showed that poor CPAP use at 1 month was an independent predictor of inadequate usage at 12 months (Chai-Coetzer et al. 2013). Patients have also been reported to overestimate their CPAP usage by approximately 1 h/day (Sawyer et al. 2011). The AASM has recommended objective telemonitoring of CPAP compliance in addition to subjective assessment, while routine re-evaluation of patients by sleep studies is not required. Patients with repetitive treatment-related difficulties can be identified through telemonitoring and are recommended to be followed more frequently than those who have been compliant. Adjustments to the device can be made, since data on residual AHI, potential mask leak and other CPAP settings are received (Patil et al. 2019). Overall, telemonitoring has been linked to improved or similar adherence to CPAP (Anttalainen et al. 2016a, Patil et al. 2019).

CPAP-related side effects. Side effects have been estimated to occur in two-thirds of patients (Sawyer et al. 2011). They may be mask-related (e.g. leak, facial irritation, sore eyes/ conjunctivitis), pressure-related (e.g. rhinitis, dryness of mouth or nose, rhinorrhea, headache, ear pain, pressure intolerance), equipment-related

(e.g. noise, spousal intolerance, equipment maintenance and cleaning) and other side effects (e.g. anxiety, insomnia, nocturnal awakenings) (Gay et al. 2006, Patil et al. 2019). Side effects may result in sleep disruption and decreased quality of sleep, and their existence at 1 month has been shown to independently predict CPAP adherence at 12 months. Proper treatment of side effects during early-on treatment may, thus, improve long-term adherence (Chai-Coetzer et al. 2013, Patil et al. 2019). A recent meta-analysis showed that a nasal mask was associated with an increased treatment compliance compared to oronasal mask due to fewer side effects. The use of humidification was also associated with a reduction in side effects, although no significant difference was observed in CPAP adherence (Patil et al. 2019).

Psychological factors and interventions. Behavioral determinants have actually been suggested to account for up to 20 % of the total variance in CPAP compliance (Bakker et al. 2019, Patil et al. 2019). A recent RCT meta-analysis reported that the use of different types of interventions soon after the initiation of CPAP was associated with improved compliance (Patil et al. 2019). Educational intervention has focused on providing general information on OSA, its harmful consequences and CPAP's beneficial effects. Behavioral intervention has usually included cognitive behavioral therapy or motivational enhancement, whereas the identification of problems related to CPAP and their potential resolutions have been emphasized in troubleshooting intervention (Patil et al. 2019).

2.5 Effects of CPAP treatment for OSA

2.5.1 OSA symptoms and quality of life

Several RCTs have shown a decrease in ESS score of 2–7 points after a 4- to 6-week treatment with CPAP, in addition to an improvement in objective sleepiness and functional outcomes compared to oral placebo treatment, subtherapeutic or sham CPAP (Batool-Anwar et al. 2016, Faccenda et al. 2001, Montserrat et al. 2001). An improvement in ESS has been reported also to remain over the long term (Batool-Anwar et al. 2016, McEvoy et al. 2016). A recent RCT meta-analysis by the AASM confirmed a mean reduction of 2.4 scores in ESS after CPAP in addition to improved capacity to maintain wakefulness, particularly in sleepy OSA patients compared to no treatment. A reduction of ≥2 points in ESS with CPAP was demonstrated to fulfil the criteria of clinical significance (Patil et al. 2019). However, patients with other signs of sleepiness, tiredness or fatigue may also benefit from a trial with CPAP, despite having a low ESS score at baseline (Patil et al. 2019).

The results of RCTs evaluating the effectiveness of CPAP on mood, neurocognitive functions and quality of life in moderate to severe OSA have been controversial (Batool-Anwar et al. 2016, Martínez-García et al. 2015, McEvoy et al.

2016). A recent RCT meta-analysis by the AASM confirmed a clinically significant association between CPAP and sleep-related quality of life but not on overall quality of life. No significant improvements were observed in neurocognitive functions and mood, although none of the studies specifically enrolled patients with depression, anxiety or deficits in neurocognitive functions. However, CPAP may have beneficial effects on depression in different OSA subgroups, since an RCT of CAD patients showed that a 3- to 12-month treatment with CPAP independently improved mood in sleepy and non-sleepy patients (Balcan et al. 2019). This finding was confirmed in a recent RCT meta-analysis of 4255 patients with CVD (Zheng et al. 2019).

Emerging evidence has suggested that treatment of mild OSA with CPAP is likely to improve subjective sleepiness, whereas the data on neurocognition, mood and quality of life have been more controversial (Barnes et al. 2002, Batool-Anwar et al. 2016, Chowdhuri et al. 2016, Monasterio et al. 2001, Patil et al. 2019). Overall, further studies on the effectiveness of CPAP on symptoms in mild OSA are needed. A need also exists for studies on other OSA-related symptoms, such as nocturia, sexual dysfunction or insomnia, in all OSA patients (Patil et al. 2019).

2.5.2 Weight management and metabolic outcomes

Untreated OSA has been suggested to predispose to weight gain, even though increased attempts to breath against the closed airway during sleep have been associated with elevated nocturnal energy expenditure levels (Stenlöf et al. 1996). A study of 53 OSA patients reported that weight gain of 7–8 kg was observed in both genders over the year preceding OSA diagnosis compared to controls matched for age, gender, BMI and percent body fat (Phillips et al. 1999). Daytime fatigue, sleep fragmentation and hypoxemia may predispose to weight gain by decreased physical activity, increased caloric intake potentially due to changes in leptin and ghrelin levels, and alterations in the gut microbiome (Drager et al. 2015, Joosten et al. 2017). Thus, CPAP could have beneficial effects on weight maintenance.

Conversely, a large RCT showed that each 1 h/day increase in CPAP adherence was actually associated with an increase of 0.4 kg in weight over a 6-month follow-up (Quan et al. 2013). A meta-analysis of 25 RCTs involving 3181 OSA patients further confirmed a significant albeit a modest increase in weight among CPAP-treated patients compared to controls (+0.4 vs. -0.1 kg) over a follow-up of 3 months. The BMI outcome was predicted only by baseline weight, while age, gender, OSA severity or CPAP adherence did not affect the results. However, most of the studies were not specifically designed to evaluate the effect of CPAP on BMI. Long-term RCTs are still needed, but overall, lifestyle interventions should be recommended for all overweight OSA patients initiating CPAP (Drager et al. 2015, Joosten et al.

2017). **Table 2** summarizes the characteristics and results of the main studies investigating the association between CPAP treatment and weight changes.

The mechanisms by which CPAP could contribute to weight gain are not entirely clear. CPAP reduces airway resistance and the work of breathing, which results in reduced nocturnal energy expenditure levels. A study of 63 patients with newly diagnosed OSA observed a small reduction in basal metabolic rate after a 3-month treatment with CPAP, even though energy intake levels and physical activity remained unchanged (Tachikawa et al. 2016). CPAP may also contribute to weight gain due to reduced sympathetic activation (Drager et al. 2015, Quan et al. 2013). Furthermore, it appears that CPAP has only minimal effect on increasing physical activity despite the improvements in fatigue and daytime sleepiness (Shechter 2017).

Most RCTs have failed to show any significant improvement in fasting glucose or glycated hemoglobin by 2- to 6-month treatment with CPAP in patients with or without established T2D (Hoyos et al. 2012, Patil et al. 2019, Shaw et al. 2016, Sivam et al. 2012). The majority of the studies have involved mainly obese male patients with moderate to severe OSA and CPAP use of 3.3–4.3 h/day. It is not clear whether a better outcome could be observed in other patient groups or with higher adherence (Patil et al. 2019). RCTs are still needed to evaluate whether benefits in glucose metabolism could potentially occur during long-term treatment with CPAP (Hoyos et al. 2017).

Table 2. Selected RCTs and observational studies investigating the association between CPAP treatment and weight changes in OSA patients.

RANDOMIZED CONTROLLED TRIALS (RCTS)

Author	Subjects	**Age** (y), **AHI** (/h), **BMI** (kg/m^2) (mean values in groups)	**CPAP use** (h/d) (mean)	**Study duration** (months)	**Adjustments**	**Findings** (Δ in BMI in kg/m^2)	**Comments**
Ou et al. 2019 (SAVE)	N=2483 M: 2006 F: 477	Age: 61–63 AHI: 27–30 BMI: 28–30	M: 3.3 F: 3.2	45	Age, sex, weight, country, duration in study, PCI	CPAP+UC vs. UC: Δ in BMI NS	Baseline: 45–75 y, ODI4 ≥12, CVD, ESS ≤15, SpO_2 ≥80%; M: CPAP ≥4 h/d ↑ weight (0.4 kg) vs. control
Shaw et al. 2016	N=298 M: 192 F: 106	Age: 62 AHI: 26–28 BMI: 33	4.9	6	Weight change (HbA1c analysis)	CPAP+UC: ↔BMI (Δ -0.3); UC: ↓ BMI (Δ -1.2)	Baseline: ≥18 y, ODI ≥15, AHI <70, T2D; CPAP+UC vs. UC: Δ in BMI, HbA1c NS
Chirinos et al. 2014	N=181 M: 104 F: 77	Age: 48–49 AHI: 40–47 BMI: 38–40	4.0	6	No adjustments	CPAP+WL or WL: ↓ weight (both: -7 kg); CPAP: weight ↔	Baseline: AHI ≥15, BMI ≥30; IR, trigly, CRP: ↓ in CPAP+WL, ↓ in WL, ↔in CPAP
Kritikou et al. 2013	N=81 M: 41 F: 40	Age: 52–58 AHI: 32–42 (OSA) BMI: 27–31	6.0	2	Age, BMI; M and F analyzed separately	CPAP or sham CPAP: ↔BMI, abdominal and intra-hepatic adiposity	Groups: 1) OSA: F: AHI >10 + menopausal, M: AHI >15 + middle-aged, 2) Control: AHI <5
Pedrosa et al. 2013	N=35 M: 77% F: 33%	Age: 56 AHI: 29 (median) BMI: 32 (median)	6.0	6	No adjustments	CPAP vs. UC: Δ in BMI NS (0.4 vs. 0.5)	Baseline: 30–65 y, AHI ≥15, RHTN; Baseline BMI higher in CPAP
Quan et al. 2013 (APPLES)	N=812 M: 65% F: 35%	Age: 53 AHI: 41 BMI: 32	4.8	6	No adjustments	CPAP: ↑ weight vs. sham CPAP (0.4 vs. -0.7 kg)	Baseline: >18 y, AHI ≥10; 1 h/d ↑ in CPAP use ↑ weight by 0.4 kg

RANDOMIZED CONTROLLED TRIALS (RCTS)

Author	Subjects	**Age** (y), **AHI** (/h), **BMI** (kg/m^2) (mean values in groups)	**CPAP use** (h/d) (mean)	**Study duration** (months)	**Adjustments**	**Findings** (Δ in BMI in kg/m^2)	**Comments**
Barbé et al. 2012	N=723 M: 619 F: 104	Age: 52 AHI: 35-42 (median) BMI: 31	5.0 (median)	48	No adjustments	CPAP: ↔ BMI (Δ 0.08); UC: ↓ BMI (Δ -0.3)	18-70 y, AHI ≥20, ESS ≤10; UC vs. CPAP: Δ in BMI significant
Craig et al. 2012 (MOSAIC)	N=391 M: 305 F: 86	Age: 58 AHI: N/A BMI: 32–33	2.4	6	BMI, participating center, ODI, CV risk score	CPAP: ↑ BMI (Δ 0.1) UC: ↓ BMI (Δ -0.2)	Baseline: 45–75 y, ODI4 >7.5, minimally symptomatic; CPAP vs. UC: ↑ BMI
Hoyos et al. 2012	N=65 M: 65 F: 0	Age: 49 AHI: 40 BMI: 31	3.6	3	No adjustments	CPAP: ↔ BMI (Δ 0.1) Sham CPAP: ↔ BMI (Δ 0.1)	Baseline: ≥18 y, AHI ≥20 (<80), ODI3 ≥15, SpO_2 ≥65% CPAP vs. sham CPAP: ↔ FG, visceral abdominal/ liver fat
Sivam et al. 2012	N=27 M: 26 F: 1	Age: 47 AHI: 37 BMI: 31	4.6	2	No adjustments	CPAP vs. sham CPAP: Δ in BMI NS (Δ 0.3)	Baseline: >21 y, AHI ≥25, ODI ≥20, BMI ≤35; CPAP vs. sham CPAP: ↔ FG, liver/ SC/ visceral abdominal
Weinstock et al. 2012	N=50 M: 21 F: 29	Age: 54 AHI: 44 BMI: 39	4.8	2	AHI, BMI, sex, race, 2-h OGTT glucose level	CPAP vs. sham CPAP: Δ in BMI NS	Baseline: 18–75 y, AHÍ ≥15, IGT; CPAP + AHI ≥30 vs. sham CPAP: ↑ ISI, ↓ 2-h OGTT
Drager et al. 2011b	N=36 M: 36 F: 0	Age: 43 AHI: 56 BMI: 29	5.2	3	No adjustments	CPAP vs. no CPAP: Δ in BMI NS (0 vs. 0.1)	Baseline: ≤60 y, AHI >30, BMI ≤40, masked/ pre-HTN

RANDOMIZED CONTROLLED TRIALS (RCTS)

Author	Subjects	**Age** (y), **AHI** (/h), **BMI** (kg/m^2) (mean values in groups)	**CPAP use** (h/d) (mean)	**Study duration** (months)	**Adjustments**	**Findings** (Δ in BMI in kg/m^2)	**Comments**
Sharma et al. 2011	N=86 M: 77 F: 9	Age: 46 AHI: 48 BMI: 32–34	5.1	3	No adjustments	CPAP vs. sham CPAP: $\downarrow$ BMI (Δ -0.3), MBS, SC/ visceral fat, HbA1c, trigly, cholesterol, LDL	Baseline: 30–65 y, AHI ≥15, ESS >10
Lozano et al. 2010	N=64 M: 44 F: 20	Age: 59 AHI: 53 BMI: 31	5.6	3	No adjustments	CPAP+UC vs. UC: Δ in BMI NS	Baseline: 18–80 y, AHI ≥15, RHTN
Lam et al. 2007	N= 101 M: 79 F: 22	Age: 45–47 AHI: 19–24 BMI: 27–28	4.2	2.5	No adjustments	CPAP+UC: $\downarrow$ weight (Δ -1.2 kg), BMI (Δ -0.4) UC/ OA: $\leftrightarrow$weight	Baseline: AHI ≥5–40, ESS >9 for those with AHI 5–20
Hui et al. 2006	N=46 M: 37 F: 9	Age: 50–51 AHI: 29–31 BMI: 27	5.1	3	No adjustments	CPAP: $\leftrightarrow$BMI (Δ 0.3); Sub-therapeutic CPAP: $\leftrightarrow$BMI (Δ 0.5)	Baseline: AHI ≥5 + EDS or two other OSA-related symptoms
Montserrat et al. 2001	N=45 M: 91% F: 9%	Age: 54 AHI: 54 BMI: 32	4.3	1.5	Smoking, BMI	CPAP vs. sham CPAP: Δ in BMI NS (0.2 vs. -0.3)	Baseline: AHI >10, EDS
OBSERVATIONAL STUDIES							
Diamanti et al. 2013	N=41 M: 35 F: 6	Age: 52 AHI: 34–38 BMI: 32–34	6.3	9	No adjustments	CPAP: $\leftrightarrow$BMI, energy expenditure, physical activity (1 week)	Baseline: AHI ≥15; Age/ AHI/ BMI for compliant and non-compliant

OBSERVATIONAL STUDIES

Author	**Subjects**	**Age** (y), **AHI** (/h), **BMI** (kg/m^2) (mean values in groups)	**CPAP use** (h/d) (mean)	**Study duration** (months)	**Adjustments**	**Findings** (Δ in BMI in kg/m^2)	**Comments**
Garcia et al. 2011	N=20 M: 17 F: 3	Age: 60 AHI: 50 BMI: 37	5.3	6	No adjustments	CPAP: ↑ weight (Δ 1.6 kg), ↔ BMI (Δ 0.6) CPAP: 40% gained ≥2% of initial weight	Baseline: AHI ≥15; CPAP: ↑ insulin, IR, ↓ ghrelin, ↔ leptin; Δ in weight correlated with Δ in insulin, IR
Münzer et al. 2010	N=78 M: 67 F: 11	Age: 51 AHI: 46–49 BMI: 30–31	5.9	8	No adjustments	CPAP in M: ↑ BMI (Δ 0.5), WC, LBM, SC fat, IGF-1 CPAP in F: ↔ BMI, SC fat, IGF-1, ↑ WC, LBM	Baseline: >18 y, AHI ≥5; Age/ AHI/ BMI for M and F; CPAP in M: ↑ LBM only in <60 y, ↑ IGF-1 only in 40–60 y
Cuhadaroğlu et al. 2009	N=44 M: 27 F: 17	Age: 54 AHI: 43 BMI: 32	N/A	2	No adjustments	CPAP ≥4 h/d (n=31): ↔ BMI (Δ 0.1), ↓ leptin, cholesterol, LDL	Baseline: AHI <15, symptoms; CPAP ≥4 h/d: ↑ insulin secretion capacity
Redenius et al. 2008	N=228 M: 64% F: 36%	Age: 55 AHI: N/A BMI: 34–36	N/A	12	No adjustments	CPAP vs. control: Δ in BMI NS; CPAP: ↑ BMI in F (Δ 0.6) or if initial BMI <30 (Δ 0.4)	Baseline: ≥18 y, AHI ≥5; Groups: 1) CPAP: ≥4 h/d ≥70% of nights, 2) control: lower CPAP use; CPAP: none lost weight
Chin et al. 1999	N=31 M: 29 F: 2	Age: 46–51 AHI: 53–64 BMI: 29–31	N/A	6	No adjustments	CPAP + ↔ BMI: ↓ visceral fat, ↔ SC fat CPAP + ↓ BMI: ↓ SC, visceral fat	Baseline: AHI >20; CPAP: ↓ leptin (after 3–4 days); No CPAP: ↔ visceral/ SC fat (follow-up 36 days)

OBSERVATIONAL STUDIES

Author	Subjects	**Age** (y), **AHI** (/h), **BMI** (kg/m^2) (mean values in groups)	**CPAP use** (h/d) (mean)	**Study duration** (months)	Adjustments	**Findings** (Δ in BMI in kg/m^2)	Comments
Loube et al. 1997	N=32 M: 22 F: 10	Age: 54–58 AHI/ BMI: N/A	N/A	6	No adjustments	CPAP >4 h/d: $\leftrightarrow$ BMI (Δ -1.6); <4 h/d: $\leftrightarrow$ BMI (Δ 0.2)	Baseline: OSA, BMI ≥25; CPAP >4 vs. <4 h/d: more likely to $\downarrow$ weight >4.5 kg (43 vs. 0 %)

$\leftrightarrow$, unchanged; Δ , difference; AHI, apnea-hypopnea index; APPLES, the Apnea Positive Pressure Long-Term Efficacy Study; BMI, body mass index; CRP, C-reactive protein; CV, cardiovascular; CVD, cardiovascular disease; F, female; FG, fasting glucose; HbA1c, glycated hemoglobin; HTN, hypertension; IGF-1, serum insulin-like growth factor 1; IGT, impaired glucose tolerance; IR, insulin resistance; ISI, insulin sensitivity index; LBM, lean body mass; LDL, low-density lipoprotein; M, male; MBS, metabolic syndrome; N/A, not available; NS, not significant; OA, oral appliance; ODI, oxygen desaturation index; ODI3, oxygen desaturation index of ≥3%; ODI4, oxygen desaturation index of ≥4%; OGTT, oral glucose tolerance test; PCI, percutaneous coronary intervention, RHTN, resistant hypertension; SAVE, the Sleep Apnea Cardiovascular Endpoints study; SpO_2, blood oxygen saturation level; SC, subcutaneous; T2D, type 2 diabetes; trigly, triglycerides; UC, usual care; WC, waist circumference; WL, weight loss.

2.5.3 Cardiovascular outcomes

2.5.3.1 Hypertension and fatal and nonfatal cardiovascular disease events

Most RCTs have shown a 2–3 mmHg reduction in mean 24-h systolic, diastolic and mean arterial BP after CPAP compared to sham CPAP or usual care (Patil et al. 2019, Peker & Balcan 2018). Long-term reductions in BP of this magnitude may reduce the risk of stroke and CAD by 4 to 8 %, having potential public health importance (Javaheri et al. 2017). CPAP may also normalize the nocturnal dipping pressure pattern, since ≥10 % decrease in the average BP has been reported during night compared to that during daytime (Javaheri et al. 2017, Peker & Balcan 2018). The effect of CPAP on BP may be reduced if the primary cause of hypertension is other than OSA or if consequent remodeling of the vascular structures has occurred in the long term (Javaheri et al. 2017). An RCT meta-analysis actually found that the decrease in BP after CPAP was greater in those aged <60 years (Pengo et al. 2020).

Reductions of up to 4–5 mmHg in BP levels have been observed by CPAP in resistant hypertension (Javaheri et al. 2017, Peker & Balcan 2018). Patients with more severe OSA or higher treatment compliance may also particularly benefit from CPAP. The level of adherence needed to achieve significant antihypertensive response is not unequivocal; it has been recommended to be ≥4 h/day, but optimally >5–6 h/day (Javaheri et al. 2017). Non-sleepy or mildly sleepy patients have been suggested to benefit less from CPAP than those with sleepiness. A meta-analysis of 4 RCTs involving 1206 patients with minimally symptomatic OSA showed a slight but clinically significant decrease of 1.4 mmHg in diastolic BP only among those who had used CPAP >4 h/day (Bratton et al. 2014, Patil et al. 2019). The data on the effect of CPAP on BP in mild to moderate OSA are scarce and controversial (Barnes et al. 2002, Lam et al. 2007, Patil et al. 2019).

Long-term observational studies have independently associated CPAP with a reduced risk of CVDs (Patil et al. 2019, Peker & Balcan 2018). Conversely, RCTs have failed to confirm a significant association (Patil et al. 2019). The largest RTC in the field, the Sleep Apnea Cardiovascular Endpoints study, found no beneficial effect of CPAP on the secondary prevention of CVDs compared to usual care (McEvoy et al. 2016). However, subgroup analyses of RCTs involving non-sleepy OSA patients have found that CPAP use of ≥4 h/day may reduce the risk of stroke and cerebral events (McEvoy et al. 2016) or composite CVD events (Barbé et al. 2012, Peker et al. 2016). A meta-analysis of 10 RCTs, of which one included CSA patients, did not find a difference in CVD outcome between the untreated and treated patients (Yu et al. 2017). A few RCT meta-analyses have shown an association between CPAP use of ≥4 h/day and a reduced risk of composite CVD events

(Abuzaid et al. 2017, Javaheri et al. 2020b, Khan et al. 2018). Since then, another RCT of non-sleepy OSA patients did not find a significant effect of CPAP on the secondary prevention of CVDs compared to usual care, even when those with CPAP use of ≥4 h/day were analyzed separately (Sánchez-de-la-Torre et al. 2020).

Overall, RCTs have confirmed that CPAP is associated with a modest but clinically significant reduction in BP levels in moderate to severe OSA. Future RCTs are needed to clarify whether CPAP could reduce BP also in mild OSA. No recommendation was presented in a recent guideline of the AASM, on whether or not non-symptomatic OSA patients should be treated with CPAP to solely improve CVD outcome, since RCTs have failed to show a beneficial effect of CPAP as secondary prevention (McEvoy et al. 2016, Patil et al. 2019, Sánchez-de-la-Torre et al. 2020). Subgroup analyses of RCTs have suggested that CPAP use of ≥4 h/day may improve CVD outcome, particularly stroke (Javaheri et al. 2020b). Future RCTs of CVDs, with particular emphasis on adequate CPAP adherence and well-defined targeted outcomes, are needed before final conclusions can be made. **Table 3** summarizes the characteristics and results of the main studies investigating the associations between CPAP treatment, hypertension and CVD events.

2.5.3.2 Heart failure, atrial fibrillation, peripheral artery disease and pulmonary hypertension

Small RCTs of HFrEF patients have demonstrated that a 4- to 12-week treatment with CPAP may improve LVEF, myocardial sympathetic nerve function, heart rate and systolic BP in OSA (Egea et al. 2008, Hall et al. 2014, Kaneko et al. 2003b, Usui et al. 2005) and potentially myocardial energetics in those with an AHI of >20 /h (Hall et al. 2014). Only few RCTs have investigated the effect of CPAP in HFpEF patients with OSA (Peker & Balcan 2018). One RCT found an improvement in diastolic function after a 12-week treatment with CPAP (Arias et al. 2005), while the other RCT only found an association between CPAP use of ≥4 h/day and improved diastolic relaxation velocity after 12 months (Glantz et al. 2017).

A few observational studies have suggested that CPAP may be associated with a better CVD outcome in patients with HF and OSA (Peker & Balcan 2018). One study showed a 50 % greater 2-year survival rate among HF patients whose OSA was treated (Javaheri et al. 2011), while the other study found an independent 2-fold (95 % CI 1.1–3.7) increased risk of death or hospitalization in HFrEF patients with untreated OSA compared to CPAP treatment (Kasai et al. 2008). Recent RCTs have not shown a beneficial effect of CPAP on the incidence of hospitalization for HF, although the mean use of CPAP has been <4 h/day (McEvoy et al. 2016, Sánchez-de-la-Torre et al. 2020). Overall, observational studies and small RCTs have

suggested that CPAP may have some beneficial effects in HFrEF patients with OSA but larger RCTs and data on patients with HFpEF are needed (Peker & Balcan 2018).

In patients with AF and OSA, observational studies have suggested that those treated with CPAP may be more likely to achieve a higher therapeutic success of cardioversion and cardiac ablation (Peker & Balcan 2018) and less likely to develop more permanent forms of AF compared to patients without CPAP (Holmqvist et al. 2015). One study reported that the AF recurrence rate one year after cardioversion did not differ between CPAP-treated patients and those without OSA (Kanagala et al. 2003). Three observational studies of AF patients also found that a 12- to 42-month treatment with CPAP after pulmonary vein isolation, a type of cardiac ablation, was associated with a reduced risk of AF recurrence in OSA compared to those without CPAP (Naruse et al. 2013), while the risk did not differ from subjects without OSA (Fein et al. 2013, Neilan et al. 2013). CPAP has been actually recommended in all AF patients with OSA undergoing surgical or catheter ablation (Calkins et al. 2012). However, RCT data are lacking and definite conclusions of the effectiveness of CPAP in AF cannot be made (Peker & Balcan 2018).

The current data investigating the effect of CPAP on progression and prognosis of PAD in conventionally and surgically treated patients is scarce and remains to be evaluated in further studies (Utriainen et al. 2013).

It has been suggested that CPAP could reduce pulmonary artery pressure by decreasing left-sided filling pressures and improving left ventricle diastolic function and altered blood gases (Javaheri et al. 2013). However, studies evaluating the effect of CPAP on pulmonary hypertension have usually lacked invasive hemodynamic assessment, and the number of patients with significant pulmonary hypertension at baseline has been low. Two small RCTs involving patients without significant heart and lung diseases showed a significant reduction of 3–6 mmHg in pulmonary artery pressure after a 4- to 12-week treatment with CPAP. In both studies, pulmonary artery pressure was measured by echocardiography, and those who had pulmonary hypertension at baseline were shown to benefit the most from CPAP (Arias et al. 2006, Javaheri et al. 2013, Sajkov et al. 2002). Overall, the data of RCTs is scarce and further RCTs evaluating the effect of CPAP on pulmonary hypertension with OSA are needed.

Table 3. Selected randomized controlled trials (RCTs) and observational studies investigating the association between continuous positive airway pressure (CPAP) treatment, hypertension (HTN) and cardiovascular disease (CVD) events in obstructive sleep apnea (OSA) patients.

RANDOMIZED CONTROLLED TRIALS (RCTS)

Author	**Outcome**	**Subjects**	**Age** (y), **AHI** (/h), **BMI** (kg/m^2) (mean values in groups)	**CPAP use** (h/d) (mean)	**Study duration** (months)	**Adjustments**	**Findings** (Δ in BP in mmHg)	**Comments**
Muxfeldt et al. 2015	HTN	N=117 M: 40% F: 60%	Age: 61 AHI: 41 BMI: 33	4.8	6	No adjustments	CPAP vs. no CPAP Δ in ambulatory/ clinic BP levels NS	Baseline: AHI ≥15, RHTN
Gottlieb et al. 2014	HTN	N=281 M: 209 F: 72	Age: 63–64 AHI: 24–26 BMI: 33–35	3.5	3	CAD, BP, study site	CPAP vs. UC: ↓ 24h MAP (Δ -2.4), DBP (Δ -2.8), Δ in SBP NS	Baseline: 45–75 y, AHI ≥15 (≤50), SpO_2 ≥85%; CPAP vs. oxygen at night: ↓ 24h MAP, DBP
Martínez-García et al. 2013 (HIPARCO)	HTN	N=194 M: 133 F: 61	Age: 56 AHI: 40 BMI: 34	5.0	3	BP, AHI, ESS, CVD events, nocturnal BP dipper*/ riser	CPAP vs. UC: ↓ 24h MAP (Δ -3.1), DBP (Δ -3.2), Δ in SBP NS, ↑ nocturnal BP dippers (36 vs. 22%)*	Baseline: 18–75 y, AHI ≥15, ESS <18, RHTN; ↑ CPAP use: ↓ 24h MAP, SBP, DBP
Pedrosa et al. 2013	HTN	N=35 M: 77% F: 33%	Age: 56 AHI: 29 (median) BMI: 32 (median)	6.0	6	No adjustments	CPAP vs. UC: ↓ awake DBP (Δ -7.2), SBP (Δ -9.6), Δ in nocturnal BP NS	Baseline: 30–65 y, AHI ≥15, RHTN; CPAP: ↔ nocturnal BP dipping*
Drager et al. 2011b	HTN	N=36 M: 36 F: 0	Age: 43 AHI: 56 BMI: 29	5.2	3	No adjustments	CPAP: ↓ 24h DBP, SBP (both: Δ -5); CPAP vs. no CPAP: ↓ 24h DBP, SBP	Baseline: ≤60 y, AHI >30, BMI ≤40, masked/ pre-HTN; CPAP: ↓ masked (-34%)/ pre-HTN (-39%)

RANDOMIZED CONTROLLED TRIALS (RCTS)

Author	**Outcome**	**Subjects**	**Age** (y), **AHI** (/h), **BMI** (kg/m^2) (mean values in groups)	**CPAP use** (h/d) (mean)	**Study duration** (months)	**Adjustments**	**Findings** (Δ in BP in mmHg)	**Comments**
Barbé et al. 2010	HTN	N=359 M: 299 F: 60	Age: 56 AHI: 45 BMI: 32	4.7	36	AHI, T90, BMI, Δ in BMI, BP, follow-up time	CPAP: ↓ DBP, SBP (both: -2), best effect with CPAP >5.6 h/d	Baseline: 18–70 y, AHI ≥20, ESS ≤10 (non-sleepy), HTN
Durán-Cantolla et al. 2010	HTN	N=340 M: 277 F: 63	Age: 52 AHI: 44 BMI: 32	4.4	3	No adjustments	CPAP vs. sham CPAP: ↓ 24h DBP (Δ -1.3), SBD (Δ -2.1)	Baseline: 18–75 y, AHI >15, HTN; CPAP: ↓ 24h BP, ↑ nocturnal BP dippers*
Lozano et al. 2010	HTN	N=64 M: 44 F: 20	Age: 59 AHI: 53 BMI: 31	5.6	3	No adjustments	CPAP vs. UC: ↓ 24h DBP (-4.9 vs. 0.1), Δ in 24h SBP NS; CPAP: ↑ nocturnal BP dippers*	Baseline: 18–80 y, AHI ≥15, RHTN; CPAP >5.8 h/d vs. UC: ↓ 24h DBP (-7 mmHg), SDB (-10 mmHg)
Lam et al. 2007	HTN	N= 101 M: 79 F: 22	Age: 45–47 AHI: 19–24 BMI: 27–28	4.2	2.5	No adjustments	Morning DBP: ↓ by CPAP (Δ -5.2), OA (Δ -2.8); other BPs ↔	Baseline: AHI ≥5–40, ESS >9 if AHI 5–20
Campos-Rodriguez et al. 2006	HTN	N=68 M: 41 F: 27	Age: 55–58 AHI: 58–60 BMI: 34–36	5.0	1	No adjustments	Therapeutic CPAP vs. sub-: Δ in 24h DBP/ SBP, nocturnal BP dippers* NS	Baseline: 30–70 y, AHI ≥10, HTN; CPAP use/ AHI did not correlate with Δ in BP
Hui et al. 2006	HTN	N=46 M: 37 F: 9	Age: 50–51 AHI: 29–31 BMI: 27	5.1	3	No adjustments	Therapeutic CPAP vs. sub-: ↓ 24h MAP (Δ -3.8), DBP (Δ -3.5), Δ in SBP NS	Baseline: AHI ≥5+EDS or two other symptoms; Therapeutic CPAP vs. sub-: ↓ nocturnal SBD

RANDOMIZED CONTROLLED TRIALS (RCTS)

Author	Outcome	Subjects	**Age** (y), **AHI** (/h), **BMI** (kg/m^2) (mean values in groups)	**CPAP use** (h/d) (mean)	**Study duration** (months)	**Adjustments**	**Findings** (Δ in BP in mmHg)	**Comments**
Robinson et al. 2006	HTN	N=35 M: 31 F: 4	Age: 54 AHI: N/A BMI: 33	5.2	1	No adjustments	Therapeutic CPAP vs. sub-: Δ in 24h DBP, SBP NS	Baseline: ODI4 >10, ESS <10 (non-sleepy), HTN
Pepperell et al. 2002	HTN	N=118 M: 118 F: 0	Age: 50–51 AHI: N/A BMI: 35	4.9	1	No adjustments	Therapeutic CPAP vs. sub-: ↓ 24h MAP, DBP, SBP (Δ >-3)	Baseline: 30–75 y, ODI4 >10, ESS >9
Barbé et al. 2001	HTN	N=54 M: 49 F: 5	Age: 52–54 AHI: 54–57 BMI: 29	5.0	1.5	No adjustments	CPAP vs. sham CPAP: Δ in 24h DBP, SBP NS	Baseline: AHI ≥30, ESS ≤10 (non-sleepy); CPAP: ↔BP non-dippers*
Sánchez-de-la-Torre et al. 2020 (ISAACC)	HTN; CVD death/ event (in-hospital UAP/ TIA/ HF, MI, stroke)	N=1255 M: 1058 F: 197	Age: 60–61 AHI: 36 BMI: 29–30	2.8	40	Age, sex, ESS; obesity, DM, smoking, AHI, HTN, first episode of ACS	CPAP+UC vs. UC: Δ in CVDs NS (16 vs. 17%, HR 0.9), ↓ DBP (Δ >-3 after 24 to 48 months)	Baseline: AHI ≥15, ESS ≤10, ACS; CPAP ≥4 h/d vs. PS-matched UC: Δ in CVDs NS (HR 0.8)
McEvoy et al. 2016 (SAVE)	HTN; CVD death/ event (TIA, stroke, MI, in-hospital HF/ UAP)	N=2687 M: 2174 F: 513	Age: 61 AHI: 29–30 BMI: 29	3.3	44	Age, sex, ODI, BMI, ESS, CVD, DM, country	CPAP+UC vs. UC: Δ in CVDs (17 vs. 15%, HR 1.1), SBP, DBP NS	Baseline: ODI4 ≥12, ESS ≤15, cerebral CVD/ CAD; CPAP ≥4 h/d vs. PS-matched UC: ↓ cerebral CVD, stroke (HR 0.5-0.6)
Peker et al. 2016 (RICCADSA)	CVD death/ event (RVN, MI, stroke)	N=144 M: 105 F: 39	Age: 66–67 AHI: 28–29 BMI: 28–29	At 0.5 y: 5.5; At 4 y: 6.2	57	Age, sex, AHI, BMI, smoking, LVEF, MI, HTN, DM, RVN, lung disease	CPAP vs. no CPAP: Δ in outcome NS (18 vs. 22%, HR 0.8)	Baseline: AHI ≥15, ESS <10 (non-sleepy), CAD +newly RVN; CPAP ≥4 vs. <4 h/d or no CPAP: ↓ CVDs (HR 0.3)

RANDOMIZED CONTROLLED TRIALS (RCTS)

Author	Outcome	Subjects	**Age** (y), **AHI** (/h), **BMI** (kg/m^2) (mean values in groups)	**CPAP use** (h/d) (mean)	**Study duration** (months)	Adjustments	**Findings** (Δ in BP in mmHg)	Comments
Huang et al. 2015	HTN; CVD death/ event (MI, stroke, RVN, in-hospital HF)	N=73 M: 60 F: 13	Age: 62–63 AHI: 28–29 BMI: 28	4.5	36	No adjustments	CPAP vs. no CPAP: ↓ SBP (-8 vs. -3), Δ in CVD death/ event NS (2.8 vs. 13.5%)	Baseline: 45–75 y, AHI ≥15, HTN, CAD, ESS <15; CPAP vs. no CPAP: improved HTN control
Parra et al. 2015	CVD death/ event (CAD event, stroke)	N=126 M: 89 F: 37	Age: 64–66 AHI: N/A BMI: 29–30	5.3	68	No adjustments	CPAP+UC vs. UC: ↓ fatal CVDs (0 vs. 10%), Δ in all CVDs NS (11 vs. 25%)	Baseline: <75 y, AHI ≥20, first-ever stroke
McMillan et al 2014 (PREDICT)	HTN; CVD event (AP, stroke, MI, AF, PAD)	N=278 M: 229 F: 49	Age: 71 AHI: 28–29 (median) BMI: 34	2.2 (n=102)	12	Study center, ESS, functionality	CPAP+UC vs. UC: Δ in outcome NS; CPAP: ↔ DBP, SBP; UC: ↓ SBP	Baseline: ≥65 y, ODI4 >7.5, ESS ≥9
Barbé et al. 2012	HTN; CVD death/ event (TIA, stroke, MI, AR, in-hospital HF/ UAP)	N=723 M: 619 F: 104	Age: 52 AHI: 35–42 (median) BMI: 31	5.0 (median)	48	Hospital site	CPAP vs. UC: Δ in HTN, CVD outcome NS	Baseline: 18–70 y, AHI ≥20, ESS ≤10 (non-sleepy); CPAP≥4 h/d vs. UC: ↓ HTN, CVD outcome
Craig et al. 2012 (MOSAIC)	HTN; Calculated 5-y risk of CVD death	N=391 M: 305 F: 86	Age: 58 AHI: N/A BMI: 32–33	2.4	6	BMI, participating center, ODI, CVD risk score	CPAP vs. UC: Δ in HTN, risk of CVD death NS	Baseline: 45–75 y, ODI4 >7.5, minimal symptoms; CPAP ≥4 vs. <4 h/d: Δ in risk of CVD death NS

RANDOMIZED CONTROLLED TRIALS (RCTS)

Author	Outcome	Subjects	**Age** (y), **AHI** (/h), **BMI** (kg/m^2) (mean values in groups)	**CPAP use** (h/d) (mean)	**Study duration** (months)	**Adjustments**	**Findings** (Δ in BP in mmHg)	**Comments**
Kushida et al. 2012 (APPLES)	Adverse and serious adverse CVD events	N=1098 M: 719 F: 379	Age: 51–52 AHI: N/A BMI: 32	4.2	6	No adjustments	CPAP vs. sham CPAP: Δ in outcome NS	Baseline: ≥18 y, AHI ≥10
OBSERVATIONAL STUDIES								
Peker et al. 2017 (RICCADSA)	CVD death/ event (MI, RVN, stoke)	N=267 M: 221 F: 46	Age: 62–63 AHI: 32 (No OSA: 3) BMI: 26–30	At 0.5 y: 5.5; At 4y: 6.0	57	Age, sex, LVEF AHI, BMI, HTN, MI, lung disease, DM, RVN, smoking	CPAP vs. no OSA: Δ in outcome NS (23 vs. 16%; no effect of level of CPAP use)	Baseline: CAD+RVN; Groups: 1) CPAP (AHI ≥15, ESS ≥10), 2) No OSA (AHI <5)
Ou et al. 2015	CVD death/ event (MI, stroke, ACS +RVN)	N=130 M: 104 F: 26	Age: 71–73 AHI: 36–45 BMI: 31	N/A	60	No adjustments	CPAP vs. no CPAP: ↓ outcome (14 vs. 56%)	Baseline: ≥60 y, AHI ≥20; CPAP ≥4 (n=24) vs. <4 h/d (n=12): ↓ outcome (4 vs. 17%)
Wu et al. 2015	CVD death/ event (RVN, stroke, stent clot, MI)	N=390 M: 328 F: 62	Age: 54–56 AHI: 10–46 BMI: 28–30	N/A	58	Age, sex, BMI, CVD, smoking, HTN, DM, PCI, DLP	CPAP vs. no CPAP: Δ in outcome NS	Baseline: AHI ≥5, CAD +PCI; AHI ≥15 vs. CPAP: 2-fold ↑ risk of RVN (adjusted)
Campos-Rodriguez et al. 2014	CVD event (stroke, CAD)	N=967 M: 0 F: 967	Age: 52–59 AHI: 24–43 (Control: 4) BMI: 32–38	N/A	82	Age, BMI, HTN, DM, AF	CPAP vs. control: Δ in outcome NS; Untreated vs. control: 2.8-fold ↑ risk	Groups: 1) control: AHI <10, 2) OSA: AHI ≥10 (CPAP: ≥4, untreated: <4 h/d or no CPAP)

OBSERVATIONAL STUDIES

Author	Outcome	Subjects	**Age** (y), **AHI** (/h), **BMI** (kg/m^2) (mean values in groups)	**CPAP use** (h/d) (mean)	**Study duration** (months)	Adjustments	**Findings** (Δ in BP in mmHg)	Comments
Campos-Rodriguez et al. 2012	CVD death (stroke, MI, HF, AR)	N=1116 M: 0 F: 1116	Age: 52–64 AHI: 17–61 (Control: 4) BMI: 33–39	6.0	72	Age, BMI, HTN, CVD, DM	CPAP vs. control: Δ in outcome NS	Groups: 1) control: AHI <10, 2) OSA: AHI ≥10 (CPAP: ≥4, untreated: <4 h/d or no CPAP)
Garcia-Rio et al. 2012	CVD event (MI, RVN)	N=186 M: 160 F: 26	Age: 58–59 AHI: 21–22 (No OSA) BMI: 26–27	6.1	72	Age, sex, BMI, DM, packs-year, DLP	CPAP vs. no OSA: Δ in outcome NS; No CPAP vs. no OSA: ↑ CVD event	Baseline: ≥18 y, MI; Groups: 1) OSA: AHI ≥5 (CPAP vs. no CPAP), 2) no OSA: AHI <5
Martínez-García et al. 2012	CVD death (MI, HF, stroke)	N=939 M: 601 F: 338	Age: 70–72 AHI: 21–59 (Control: 7) BMI: 32–35	6.4	69	Age, sex, BMI, CVD, DM, ESS, smoking, sleep study, clinic, DLP	CPAP vs. control: Δ in outcome NS; Untreated AHI ≥30 vs. control: 2.3-fold ↑ risk (whereas AHI 15–29: NS)	Baseline: ≥65 y; Groups: 1) Control: AHI <15, 2) OSA: AHI ≥15 (CPAP: ≥4, untreated: <4 h/d or no CPAP); ↑ CPAP use: ↓ outcome
Buchner et al. 2007	CVD death (MI, stroke)/ event (MI, stroke, ACS +RVN)	N=449 M: 384 F: 65	Age: 55–58 AHI: 15–31 BMI: 29–31	N/A	72	Age, sex, BMI, CVD, malignant disorders, HTN, COPD, nicotine use, DM, DLP	CPAP vs. untreated: ↓ risk of outcome, also in mild OSA (both: HR 0.36)	Baseline: AHI ≥5; CPAP: AHI ≥5+EDS/ AHI ≥15
Cassar et al. 2007	CVD death/ event (MI, RVN, severe AP, stroke)	N=371 M: 325 F: 46	Age: 64 AHI: 39–50 BMI: 33–35	N/A	60	No adjustments	CPAP vs. untreated: ↓ CVD death (3 vs. 10%), Δ in CVD event NS	Baseline: AHI ≥5, CAD+PCI

OBSERVATIONAL STUDIES

Author	Outcome	Subjects	**Age** (y), **AHI** (/h), **BMI** (kg/m^2) (mean values in groups)	**CPAP use** (h/d) (mean)	**Study duration** (months)	Adjustments	**Findings** (Δ in BP in mmHg)	**Comments**
Doherty et al. 2005	CVD death/ event (HTN, stroke, heart event)	N=168 M: 155 F: 13	Age: 50–53 AHI: 37–48 BMI: 30–31	N/A	90	Age, sex, BMI, AHI, smoking, alcohol use, CVD	CPAP ≥5y vs. untreated: ↓ CVD deaths (2 vs. 15%), Δ in CVD events NS	Baseline: AHI >15; CPAP ≥5 y vs. untreated: ↓ all CVD deaths+ events (18 vs. 31%)
Marin et al. 2005	CVD death/ event (MI, stroke, ACS +RVN)	N=1274 M: 1274 F: 0	Age: 50 AHI: 18–43 (Healthy: 1) BMI: 28–31	N/A	120	Age, CVD, HTN, DLP, smoking, alcohol use, BP, medication, DM	CPAP vs. healthy: Δ in CVD death/ event NS	Groups: 1) Healthy, 2) Untreated OSA (AHI ≥5), 3) CPAP (AHI >30 or ≥5+EDS, usage >4 h/d)
Martínez-García et al. 2005	CVD event (AP, MI, stroke)	N=51 M: 63% F: 37%	Age: 73 AHI: 37 BMI: 27	5.7	18	AF, HTN, ICS, BMI, smoking, DM, cognition, DLP, CAD, FGN	Untreated vs. CPAP: ↑ CVD event (36 vs. 7%; 5-fold ↑ risk)	Baseline: AHI ≥20, TIA/ stroke
Milleron et al. 2004	CVD death/ event (ACS, RVN, HF)	N=54 M: 53 F: 1	Age: 57 AHI: 29–34 BMI: 28	5.7	87	Age, AHI, DLP, BMI, smoking, HTN, LVEF, DM	Treated vs. not treated: ↓ outcome (24 vs. 58%, HR 0.2)	Baseline: CAD, AHI ≥15 Groups: 1) Not treated, 2) Treated (CPAP/ UAS)

↔, unchanged; Δ, difference; ACS, acute coronary syndrome; AF, atrial fibrillation; AHI, apnea-hypopnea index; AP, angina pectoris; APPLES, the Apnea Positive Pressure Long-Term Efficacy Study; AR, arrhythmia; BMI, body mass index; BP, blood pressure; CAD, coronary artery disease; DBP, diastolic BP; DM, diabetes mellitus; DLP, dyslipidemia; F, female; FGN, fibrinogen; HF, heart failure; ICS, internal carotid stenosis; ISAACC, Impact of Sleep Apnea syndrome in the evolution of Acute Coronary syndrome, Effect of intervention with CPAP; LVEF, left ventricular ejection fraction; M, male; MAP, mean arterial BP; MI, myocardial infarction; N/A, not available; NS, not significant; OA, oral appliance; ODI, oxygen desaturation index; ODI4, oxygen desaturation index of ≥4%; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; PS, propensity score matched; RHTN, resistant hypertension; RVN, revascularization; SAVE, the Sleep Apnea Cardiovascular Endpoints study; SBP, systolic BP; SpO_2, blood oxygen saturation level; T90, percentage of time spent under SpO_2 of 90 %; TIA, transient ischemic attack; UAP, unstable angina pectoris; UAS, upper airway surgery; UC, usual care.

* Nocturnal BP dippers: ≥10 % decrease in the average BP during night compared to that during daytime.

2.5.4 All-cause mortality

Observational studies have suggested a beneficial effect of CPAP on all-cause mortality, particularly CVD deaths (Patil et al. 2019). A large observational study of 1010 male OSA patients found no difference in the 10-year risk of CVD death between CPAP use of >4 h/day and subjects without OSA (Marin et al. 2005). A similar result was shown in a smaller study of males over a follow-up of 7.5 years (Doherty et al. 2005). A beneficial effect of CPAP on preventing CVD deaths in females was reported in a large, long-term study (Campos-Rodriguez et al. 2012), while another study showed reduced all-cause mortality in middle-aged and elderly males, but not at all in females (Jennum et al. 2015). It has also been suggested that OSA patients with CPAP use of >6 h/day may have a higher 5-year survival rate compared to those with lower CPAP usage (Campos-Rodriguez et al. 2005).

Conversely, RCTs have not confirmed a significant association between CPAP and all-cause mortality (Patil et al. 2019). Two large RCTs of OSA patients with established CVD and minimal sleepiness at baseline found no significant difference in all-cause mortality over follow-ups of 3 to 4 years between patients treated with CPAP or usual care, although the mean use of CPAP was <4 h/day (McEvoy et al. 2016, Sánchez-de-la-Torre et al. 2020). Similar results were found in two other RCTs involving non-sleepy patients, although in both of these studies the number of deaths was only <10 per group (Barbé et al 2012, Peker et al. 2016).

Overall, a meta-analysis of observational studies involving 2340 patients found a 60 % lower risk of all-cause mortality in CPAP-treated patients compared to controls (Patil et al. 2019). However, since RCTs have failed to confirm a significant association, the existing data is insufficient to support a beneficial effect of CPAP on all-cause mortality. Further RCTs with adequate CPAP compliance are needed.

2.5.5 MVAs

A reduced risk of MVAs after CPAP has been shown in several observational studies (Barbé et al. 2006, Karimi et al. 2015, Walia et al. 2019). Most of the studies have involved middle-aged, obese male patients with moderate to severe OSA. A meta-analysis of nine studies involving 1976 patients reported that MVA risk was reduced by 65–78 % after CPAP in observation periods of 6 months to 5 years before and after treatment (Tregear et al. 2010), although one study found a decrease in MVAs also in healthy controls (Barbé et al. 2006). However, only a minority of studies have provided objective data on MVAs (Tregear et al. 2010). One study actually found that patients subjectively reported only one-third of their objectively measured MVAs, implying their reluctance to disclose their MVA history (Findley et al. 2000). **Table 4** summarizes the characteristics and results of the main studies investigating the association between CPAP treatment and risk of MVAs.

Table 4. Selected studies investigating the association between continuous positive airway pressure (CPAP) treatment and risk of motor vehicle accidents (MVAs) in obstructive sleep apnea (OSA) patients. Studies with subjective and objective MVA data are categorized separately.

OBJECTIVE DATA ON MVAS

Author	**Study design**	**Subjects**	**Age** (y), **AHI** (/h), **BMI** (kg/m^2) (mean values in groups)	**CPAP use** (h/d) (mean)	**Study duration** (months)	**Factors controlled for** (if compared to controls)	**Findings**	**Comments**
Catalá et al. 2016	OBS Study; B-A	N=373 M: 315 F: 58	Age: 56 AHI: 54 BMI: 31	5.3	B: 12 A: 12	N/A	CPAP: ↔ MVAs (Δ -0.8%), usage ≥4 vs. <4 h/d did not affect	Baseline: AHI ≥15; MVAs: medical costs from clinical records
Karimi et al. 2015	OBS Study; B-A	N=567 * M: 425 F: 142	Age: 56–57 AHI: 22–30 BMI: 30–31	≥4 h/d: 5.8 <4 h/d: 1.4	B: 60 A: 42	Groups: Δ in driving exposure NS	CPAP ≥4 h/d: ↓ MVAs (Δ -5.1 /1000 person years); CPAP <4 h/d: ↑ MVAs (Δ 5.6 /1000 person years)	Baseline: DL; MVAs: police-reported; Groups: 1) CPAP ≥4 h/d, 2) CPAP <4 h/d
George 2001	OBS Study; B-A + Case-control	N=420 M: N/A F: N/A	Age: 52 AHI: 54 BMI: 36 (Controls: N/A)	5.9 †	B: 36 A: 36	Matched for age, sex, DL class	CPAP: ↓ MVAs (Δ -0.14 /driver /year), Δ from controls NS; No CPAP vs. control: ↑ MVAs (Δ 0.14 /driver /year)	Baseline: AHI ≥10 (no OSA in controls); MVAs: definition N/A, from the database of the Ministry of Transportation of Ontario
Findley et al. 2000	OBS Study; B-A + Case-control	N=50 M: 43 F: 7	Age: 54–60 AHI: 38 BMI: N/A	7.2 †	B: 24 A: 24	Matched for age, sex; Δ in weight NS	CPAP: ↓ MVAs (Δ -0.07 /driver /year); No CPAP: ↔ MVAs (both 0.07 /driver /year)	Baseline: OSA MVAs: property damage >$500/ personal injury, from State DMV records

SUBJECTIVE DATA ON MVAS

Author	Study design	Subjects	Age (y), AHI (/h), BMI (kg/m^2) (mean values in groups)	CPAP use (h/d) (mean)	Study duration (months)	Factors controlled for (if compared to controls)	Findings	Comments
Walia et al. 2019	OBS Study; B-A	N=2059 M: 1124 F: 935	Age: 56 AHI: 23 BMI: 33	N/A	10	N/A	Drowsy driving: ↓ by 8.8% in PAP ≥4 h/d, by 6% in lower usage (usage not predictive)	Baseline: OSA; MVAs/ near-misses due to drowsy driving; 1-point ↓ in ESS ↓ drowsy driving by 14%
McEvoy et al. 2016 (SAVE)	Randomized controlled trial	N=2687 M: 2174 F: 513	Age: 61 AHI: 29–30 BMI: 29	3.3	44	N/A	CPAP+UC vs. UC: Δ in MVAs NS (RR 0.8)	Baseline: ODI4 ≥12, ESS ≤15, cerebrovascular disease/ CAD; MVA/ near-miss: drowsy driving/ personal injury
McMillan et al. 2014 (PREDICT	Randomized controlled trial	N=278 M: 229 F: 49	Age: 71 AHI: 28–29 (median) BMI: 34	2.2 (n=102)	12	N/A	CPAP+UC vs. UC: Δ in MVAs NS (MVA data for n=150)	Baseline: ≥65 y, ODI4 >7.5, ESS ≥9 MVAs: definition N/A
Komada et al. 2009	OBS Study; B-A + Case-control	N=1216 M: 1216 F: 0	Age: 46 AHI: 44 (OSA) BMI: 23–27	N/A	B: 60 A: 60	Matched for age	CPAP: ↓ MVAs by 14%, Δ from no OSA NS; Untreated vs. no OSA: ↑ MVAs (12 vs. 5%)	Baseline: DL; Groups: 1) AHI ≥5 (n=291 with CPAP), 2) no OSA; ↑ MVAs in untreated OSA: ESS ≥11, AHI ≥40
Barbé et al. 2006	OBS Study; B-A + Case-control	N=160 M: 156 F: 4	Age: 46–49 AHI: 60 (OSA) BMI: 27–33	5.9	B: 24 A: 24	BMI, alcohol intake, ESS; Matched for age, sex	↓ MVAs in CPAP (RR 0.41) and in no OSA (RR 0.49), Δ in MVAs NS	Baseline: DL; Groups: 1) AHI >20 + CPAP, 2) no OSA; MVAs: damage >$500/ personal injury

SUBJECTIVE DATA ON MVAS

Author	Study design	Subjects	**Age** (y), **AHI** (/h), **BMI** (kg/m^2) (mean values in groups)	**CPAP use** (h/d) (mean)	**Study duration** (months)	**Factors controlled for** (if compared to controls)	Findings	Comments
Horstmann et al. 2000	OBS Study; B-A	N=160 M: 90% F: 10%	Age: 57 AHI: N/A BMI: 32	N/A	B: 36 A: 15	Driving exposure; Matched for age, sex	CPAP: ↓ MVAs (Δ -7.9 /million km); Untreated vs. no OSA: ↑ MVAs (12 vs. 3%);	Groups: 1) OSA: AHI ≥10 (n=85 with CPAP), 2) no OSA; MVAs: material damage/ personal injury
Yamamoto et al. 2000	OBS Study; B-A	N=39 M: 39 F: 0	Age: 50 AHI: N/A (>50) BMI: 29	N/A	B: 24 A: 24	N/A	CPAP: ↓ MVAs (82 vs. 10%), near-misses (33 vs. 0%)	Baseline: DL; MVA: definition N/A
Scharf et al. 1999	OBS Study; B-A	N=316 M: 234 F: 82	Age: 49 AHI: 43 BMI: N/A	N/A	B: 6 A: 6	N/A	CPAP: ↓ MVAs, near-misses	MVA: definition N/A
Krieger et al. 2000	OBS Study; B-A	N=893 M: 87% F: 13%	Age: 57 AHI: 35 BMI: 34	6.0	B: 12 A: 12	N/A	CPAP: ↓ MVAs, near-misses (data for n=547)	MVA: definition N/A
Cassel et al. 1996	OBS Study; B-A	N=59 M: 59 F: 0	Age: 49 AHI: 39 BMI: 32	6.1 (n=37)	B: 60 A: 12	Driving exposure	CPAP: ↓ MVAs (Δ -7 /million km)	Baseline: 25–65 y, DL, EDS, CPAP indicated; MVAs: definition N/A
Engleman et al. 1996	OBS Study; B-A	N=215 Sex: N/A	Age: 53 AHI: 47 BMI: N/A	5.1 (n=62)	B: 60 A: 24	Driving exposure	CPAP: ↓ near-misses (Δ -0.8/ 10 000 miles), ↔ major, minor MVAs	Baseline: AHI >5, symptoms; Sleep-related MVAs with (major)/ without (minor) injury, near-misses

SUBJECTIVE DATA ON MVAS

Author	Study design	Subjects	**Age** (y), **AHI** (/h), **BMI** (kg/m^2) (mean values in groups)	**CPAP use** (h/d) (mean)	**Study duration** (months)	**Factors controlled for** (if compared to controls)	Findings	Comments
Minemura et al. 1993	OBS Study; B-A	N=14 M: 14 F: 0	Age: 46 AHI: N/A BMI: N/A	N/A	B: 36 A: 11	N/A	CPAP: ↓ MVAs (42 vs 0%), near-misses (64 vs. 0%)	MVAs: definition N/A

↔, unchanged; Δ , difference; A, after; AHI, apnea-hypopnea index; B, before; BMI, body mass index; CVD, cardiovascular disease; DL, driver' s license; ESS, Epworth Sleepiness Scale; F, female; HTN, hypertension; M, male; N/A, not available; ODI4, oxygen desaturation index of ≥4%; PAP, positive airway pressure; RR, risk ratio; SpO_2, blood oxygen saturation level; UC, usual care.

***** Only patients treated with CPAP included.

† The level of CPAP usage subjectively measured.

2.5.5.1 Evaluation of fitness to drive

The American Thoracic Society has defined a high-risk driver as a subject with moderate to severe daytime sleepiness (e.g. falling asleep unintentionally during daily activities) in addition to a recent MVA or near-miss MVA related to sleepiness, fatigue or inattention. Driving risk and possible non-OSA causes of EDS (e.g. use of alcohol or sedatives, sleep restriction, neurological disorders) should be evaluated in all patients with suspected or confirmed OSA. High-risk drivers should be warned about the potential risk associated with driving. A sleep study and further initiation of CPAP in confirmed OSA should be performed in less than one month to reduce driving risk. Patients should be followed after the initiation of CPAP to reassess the risk of driving and to ensure compliance with treatment (Strohl et al. 2013).

A revision of Annex III of the European Union Directive on Driving Licenses was established in 2014 based on the recommendations from a Working Group established by the Transport and Mobility Directorate of the European Commission (Commission Directive 2014/85/EU, McNicholas et al. 2013). The new Directive was subjected to mandatory implementation by all Member States starting in December 2015. It states that moderate to severe OSAS as an AHI of ≥15 /h is a risk of driving due to its association with EDS. Drivers with suspected moderate to severe OSAS shall be referred for further authorized medical advice before a driving license may be issued and they may be advised not to drive until the diagnosis is confirmed. Driving licenses may be issued to drivers with confirmed moderate to severe OSAS if sleepiness is improved and an authorized medical practitioner has confirmed that the control of OSAS and compliance with appropriate treatment is adequate. During treatment, drivers with moderate to severe OSAS shall be subject to medical review at intervals not exceeding 3 years for group 1 drivers and 1 year for group 2 drivers to ensure treatment compliance, continuation of good vigilance and to reassess the need for continuing treatment (Commission Directive 2014/85/EU).

Additional recommendations from the Working Group defined EDS as ESS of ≥15 scores. A driving license may be recovered by drivers advised not to drive in the absence of EDS after a 2- to 4-week treatment with CPAP with adequate compliance, defined as CPAP use of ≥4 h/day on ≥70 % of days. Residual AHI for professional drivers should be <10 /h. Driving may be authorized for drivers with untreated, mild OSA if the driver does not report on EDS or recent MVAs, has no hypertension requiring ≥2 medications and if BMI is <35 kg/m^2 (McNicholas et al. 2013).

However, the assessment of sleepiness by ESS has been insufficient for identifying high-risk drivers, since it is prone to bias and patients may underrate their sleepiness. Objective tests are not well suited to be performed on a large scale, although they may be particularly useful if sleepiness continues during treatment. The use of MSLT in the assessment of driving ability has been criticized, since patients do not aim to fall asleep while driving, and the reliability of MWT to match

real-life driving performance has also been questioned (Bonsignore et al. 2016, Dwarakanath & Elliott 2019, McNicholas et al. 2013, Strohl et al. 2013). Furthermore, the use of AHI or BMI alone in the assessment of fitness to drive is not recommended, since patients with similar AHI may differ regarding the severity of EDS, and the specificity of BMI to predict MVAs has been poor (McNicholas et al. 2013, Strohl et al. 2013). It is also not clear how moderate or severe OSA should be suspected or how good compliance, treatment effectiveness or good vigilance should be determined. The European Respiratory Society has established a task force to provide practical recommendations considering these issues. Overall, new tools to assess fitness to drive are needed (Bonsignore et al. 2016).

2.5.6 Economic impact

Untreated OSA has been associated with increased healthcare utilization and costs (Kapur et al. 2017). Based on cost-effectiveness analyses, CPAP has been shown to be cost-effective in OSA treatment compared to no treatment (Patil et al. 2019). A study of 373 OSA patients reported CPAP to be cost-effective as of the second year in patients with CPAP use of ≥4 h/day but not in those with lower usage (3357 vs. 5959 €). Costs related to the OSA diagnosis and the initiation of CPAP, particularly if in-laboratory titration was required, are likely to explain why CPAP was not cost-effective right from the beginning. Total costs included in the analysis consisted of direct health-care costs (treatment for diseases and MVAs), direct non-health-care costs (patient transport costs, costs of medical care covered by private health insurance schemes) and indirect costs (loss of work productivity) (Català et al. 2016). The main result was consistent with a previously published study of the British National Health Service (Guest et al. 2008). However, there are no studies evaluating the cost-effectiveness of CPAP and outcomes on BP levels, suggesting that CPAP might be even more cost-effective than previously estimated (Patil et al. 2019).

2.6 Alternative treatment options for OSA

2.6.1 Lifestyle interventions

The clinical practice guideline from the American Thoracic Society has recommended that overweight and obese OSA patients should be treated with conventional lifestyle intervention such as a reduced-calorie diet, increased physical activity and/ or behavioral guidance (Hudgel et al. 2018). The Wisconsin Sleep Cohort Study reported that a 10 % weight loss resulted in a 26 % reduction in AHI over a follow-up of 4 years (Peppard et al. 2000a), and an RCT meta-analysis of 410 patients with mild to moderate OSA further confirmed that lifestyle interventions

reduced weight by 14 kg and AHI by 16 /h (Mitchell et al. 2014). Weight loss has been shown to affect non-supine AHI to a greater extent than supine AHI; thus, non-positional OSA may be converted to positional OSA (Joosten et al. 2017).

The combination of weight loss and CPAP has been more effective than CPAP treatment alone (Joosten et al. 2017). An RCT of 146 obese patients with moderate to severe OSA found that weight loss and weight loss plus CPAP were associated with significant reduction in weight (both -7 kg) over 6 months, while CPAP alone was not (Chirinos et al. 2014). In a 2-year study of 31 obese males with OSA, CPAP plus weight loss similarly did not contribute to greater results than weight loss alone (Kajaste et al. 2004). Exercise has been shown to reduce AHI regardless of weight changes in mild to moderate OSA (Peppard & Young 2004). An RCT meta-analysis found that reduction in AHI did not differ between exercise training or CPAP in comparison to controls (mean change in AHI -17 /h vs. -25 /h) (Iftikhar et al. 2017).

However, only a minority of OSA patients have achieved a normal AHI of <5 /h by conventional lifestyle interventions (Joosten et al. 2017). An RCT of 63 obese males with moderate to severe OSA found that a normal AHI was achieved only in 17 % after a 9-week very low-calorie diet (Johansson et al. 2009). Another RCT of 72 overweight patients with mild OSA showed that 63 % had achieved a normal AHI after a 12-month very low-calorie diet with supervised lifestyle counseling, but the prevalence had decreased to 32 % at 60 months and did not differ from controls treated with usual care (17 %) (Tuomilehto et al. 2009, Tuomilehto et al. 2013).

2.6.2 Positional therapy for positional OSA

It has been suggested that 50 to 60 % of OSA patients have positional OSA, usually defined as an AHI of ≥5 /h with ≥50 % increase in AHI in supine position compared to non-supine positions. The non-supine AHI may be either <5 /h (supine-isolated OSA) or ≥5 /h (supine-predominant OSA). Patients with positional OSA have been reported to be more likely younger, male and have a lower BMI than those with non-positional OSA (Joosten et al. 2012, Kim et al. 2016, Srijithesh et al. 2019).

Positional therapy aims to avoid sleeping in a supine position, e.g. by tennis ball sewn onto the back of a shirt, waistband or positional alarms (Srijithesh et al. 2019). The AASM has recommended positional therapy as an effective secondary treatment for positional OSA. It may also be a supplement to primary therapies if non-supine AHI is low, and the correction of OSA by position has been verified in a sleep study (Epstein et al. 2009). An RCT meta-analysis of 323 patients with mainly moderate OSA reported that CPAP was more effective in reducing AHI than positional therapy, while no difference was found in ESS. Positional therapy reduced both AHI and ESS more effectively compared to no treatment. Common side effects included

sleep disturbances and back and chest pain. However, RCTs on long-term adherence are needed, since most of the RCTs have been short-term (Srijithesh et al. 2019).

2.6.3 Oral appliances

A majority of the oral appliances, termed mandibular advancement devices (MADs), aim to enlarge the pharyngeal airway by pulling the lower jaw forward (Ramar et al. 2015, Sutherland et al. 2014). Based on the AASM and American Academy of Dental Sleep Medicine, CPAP should generally be the first-line treatment alternative for OSA. MADs have been used as a first-line treatment option in patients with mild to moderate OSA who prefer MADs over CPAP or as a secondary alternative in those with more severe OSA who do not tolerate CPAP (Epstein et al. 2009, Ramar et al. 2015). A combination of CPAP and MAD may be beneficial in selected patients to improve CPAP compliance, since MAD may prevent mouth opening, leaks and chin retrusions and reduce CPAP's pressure requirements (Sutherland et al. 2014).

MADs have been shown to improve daytime sleepiness and sleep parameters compared to a placebo or inactive devices (Ramar et al. 2015). The impact of MADs on AHI appears to be similar to CPAP in mild OSA, whereas CPAP is more effective in reducing AHI in moderate to severe OSA (Ramar et al. 2015). The effect of CPAP on BP has been studied in more detail, although mounting evidence suggests that MADs may reduce BP, at least in selected patients (Lam et al. 2007, Ramar et al. 2015). Compliance with MAD appears to be greater than that with CPAP and it appears to remain in the long term. Side effects may also lead to discontinuation of treatment less frequently (de Almeida et al. 2005, Ramar et al. 2015).

Custom-prepared titratable devices that allow the anterior repositioning to be increased over weeks are preferred over non-custom devices (Ramar et al. 2015). Patient follow-up during treatment is recommended to identify potential side effects and to reassure treatment response with a sleep study (Ramar et al. 2015), since an AHI of <10 /h may be achieved only in 52 % of the patients (Ferguson et al. 2006). Younger age, lower BMI and female gender may result in better treatment outcome. MAD-related side effects are usually transient: mouth dryness, excessive salivation, tooth pain, gum irritation, pain in temporomandibular joint and headaches. Long-term use of MADs may result in small but significant dental changes, such as decreases in overbite and overjet, changes in anterior-posterior occlusion and reduced number of occlusal contacts, compared to CPAP (Ramar et al. 2015).

2.6.3.1 Bariatric surgery

Bariatric surgical procedures, which aim to increase malabsorption and/ or caloric restriction, have been associated with greater weight loss and reductions in AHI

compared to conventional weight loss interventions (Joosten et al. 2017). Bariatric surgery is generally recommended to be considered in those who have failed to lose weight by conventional interventions and have a BMI of ≥40 kg/m^2 without complications or a BMI of ≥35 kg/m^2 with obesity-related comorbidities (e.g. OSA, T2D, hypertension) (Mechanick et al. 2008).

A meta-analysis of 12 uncontrolled trials involving 342 patients showed that BMI was reduced by 18 kg/m^2 and AHI by 38 /h after 17 months of bariatric surgery, but only 38 % had achieved an AHI of ≤15 /h. These patients were younger and had a lower BMI than those with a higher residual AHI (Greenburg et al. 2009). An RCT of 60 obese patients with moderate to severe OSA found that bariatric surgery was more likely to result in an AHI of <15 /h compared to those treated with conventional weight loss program (27 vs. 7 %), while no differences were observed in pressure requirements or adherence in patients continuing CPAP (Dixon et al. 2012).

Overall, only a minority of patients have been shown to be cured of OSA after bariatric surgery; thus, most of the patients will require continued treatment for OSA. The possible attenuation of the disease should always be verified by a postoperative sleep study (Mechanick et al. 2008). One study showed that 45 % of the patients had achieved an AHI of <5 /h 1-year after bariatric surgery (Peromaa-Haavisto et al. 2017), while the prevalence has been approximately 40 % two years after bariatric surgery depending on the amount of achieved weight loss (Mechanick et al. 2008).

2.6.3.2 Upper airway surgery

Reconstructive upper airway surgery includes a variety of different procedures regarding the nasal (e.g. septoplasty, nasal polypectomy, nasal valve surgery), oral/ oro-/ nasopharyngeal (e.g. tonsillectomy, adenoidectomy, uvulopalatoplasty), hypopharyngeal (e.g. tongue reduction, tongue advancement) and laryngeal (e.g. epiglottoplasty, hyoid suspension) areas. Maxillary and mandibular advancement, in which the patency of the upper airway is enhanced in several areas, may improve OSA similarly to CPAP. Bypassing the upper airway with a tracheostomy naturally leads to elimination of OSA. The majority of other upper airway surgical procedures rarely cure OSA but may improve symptoms and other outcomes. Laser-assisted uvulopalatoplasty is not recommended for OSA treatment (Epstein et al. 2009).

As a primary treatment for OSA, evaluation of upper airway surgery may be considered in mild OSA with severe obstructing anatomy that could be corrected by a surgical procedure. As a secondary treatment for OSA, it may be considered in patients with residual OSA during CPAP or MAD treatment, patients who do not tolerate CPAP or MAD, or as an adjunct therapy if obstructive anatomy is likely to reduce the adherence to OSA treatment. A follow-up sleep study is recommended to reassure adequate treatment response after surgical treatment (Epstein et al. 2009).

3 AIMS

The aims of the present study were to evaluate:

1) whether CPAP treatment is associated with a reduced risk of nonfatal and fatal CVD outcomes compared to untreated controls in order to comprehend at which level of adherence this could be achieved and to further investigate whether the results differ in terms of specific outcomes
2) the impact of CPAP treatment on weight changes at the cohort and individual levels and to identify patient characteristics associated with significant weight change, particularly those at high risk for significant weight gain
3) the impact of CPAP on the incidence of police-reported MVAs compared between before and after treatment and between the CPAP-treated patients and untreated controls and to determine the potential effect of the level of CPAP adherence on the results
4) the level of long-term adherence to CPAP at the cohort and individual levels and to identify patient characteristics associated with significant change in adherence
5) the potential changes in the self-administered ESS and GHQ-12 questionnaires during long-term CPAP treatment
6) the effectiveness of AHI in the assessment of high-risk patients for adverse outcomes

4 MATERIALS AND METHODS

Original publications I, IV and V present the data from study I, original publication II the data from study II, and original publication III the data from study III.

4.1 Study subjects

4.1.1 CPAP-treated patients (studies I–III)

From the discharge database of the Turku University Hospital (Turku, Finland), 2489 patients who had commenced CPAP treatment for OSAS during the years 2002–2006 were identified. Of these patients, 1116 had continued the treatment for ≥5 years. Patients without available cardiorespiratory polygraphy data (N=52) or with <4 follow-up visits (N=34) were excluded. These remaining 1030 patients formed the group of CPAP-treated patients without any further selection in studies I and III. Those who had engaged in bariatric surgery before or during CPAP treatment (N=7) were additionally excluded in study II in order to more reliably evaluate the association between CPAP and weight changes **(Figure 5)**.

4.1.2 Control patients (studies I, III)

The control group was identified among 2359 OSAS patients who had commenced CPAP treatment at the Turku University Hospital (Turku, Finland) during 2002–2009 but who discontinued the treatment within 5 years despite their doctor's advice **(Figure 5)**. Patients without available cardiorespiratory polygraphy data were excluded (N=83). The remaining 2276 patients had used CPAP for a median of 8.9 (IQR 28.6) months. Among these patients, the best-matched control for each CPAP-treated patient was determined according to gender, age and AHI. The pairwise-matched control patients (N=1030) had used CPAP for a median of 4.0 (IQR 16.0) months prior to the study's initiation.

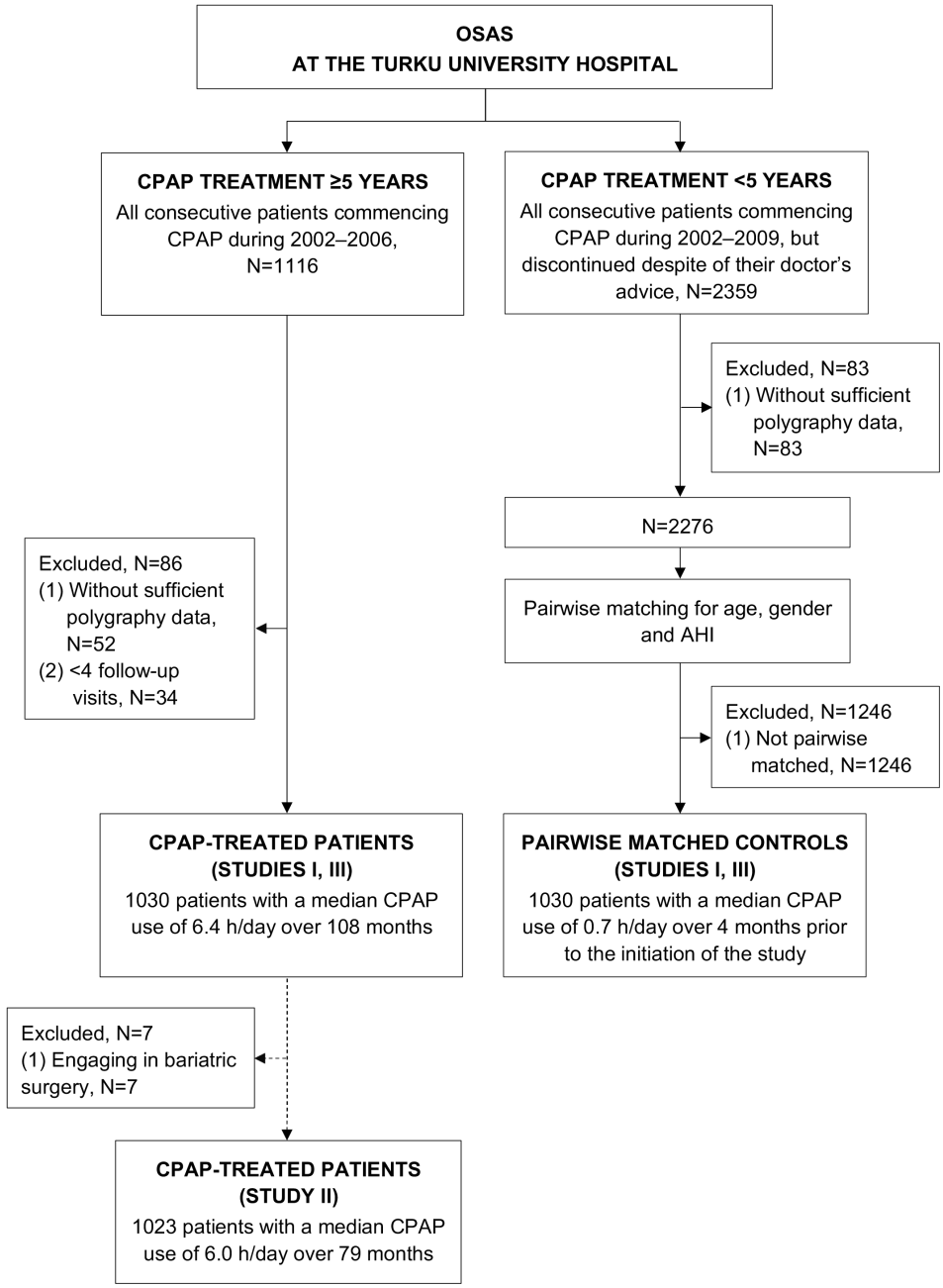


Figure 5. Flowchart of the recruitment of the continuous positive airway pressure (CPAP) treated obstructive sleep apnea syndrome (OSAS) patients in studies I–III and their controls matched for age, gender and apnea-hypopnea index (AHI) in studies I and III. Modified with permission from original publications I–II.

4.2 Methods

4.2.1 Study designs (studies I–III)

All the studies consisted of a retrospective, observational, single-center cohort of CPAP-treated patients (studies I–III) and their pairwise-matched controls (studies I and III). Study I used a matched case-control study design to compare the incidence of nonfatal and fatal CVD events between CPAP-treated patients and controls. Study II explored the development of BMI and adherence during CPAP treatment and studied them at the cohort and the individual levels. Study III determined the incidence of MVAs in CPAP-treated patients by using both before-after and case-control study designs.

4.2.2 Sleep studies (studies I–III)

All included patients underwent cardiorespiratory polygraphy prior to the initiation of CPAP treatment. OSAS was diagnosed either by a cardiorespiratory polygraphy in the hospital (Embla, Somnologica Software, Flaga hf. Medical Devices, Reykjavik, Iceland) or by an ambulatory device at home (Embletta, Somnologica Software, Flaga hf. Medical Devices, Reykjavik, Iceland). Electroencephalography was not recorded during polygraphy. OSAS diagnosis was based on the Chicago criteria in the majority of the patients, while the 2007 AASM criteria were used for those patients diagnosed with OSAS during 2007 to 2009 (Iber et al. 2007, The Report of an American Academy of Sleep Medicine Task Force 1999). The sleep studies were scored by a pulmonologist or a clinical neurophysiologist.

Categories of OSAS severity were defined according to the AHI: an AHI of <5 /h (normal), an AHI of ≥5 but <15 /h (mild OSAS), an AHI of ≥15 but <30 /h (moderate OSAS), and an AHI of ≥30 /h (severe OSAS) (The Report of an American Academy of Sleep Medicine Task Force 1999). CPAP treatment was generally recommended for patients with an AHI of ≥15 /h (Chowdhuri et al. 2016, Gay et al. 2006, Loube et al. 1999, Patil et al. 2019, Sullivan et al. 1981). The need for treatment was assessed individually in patients with a lower AHI, according to the patients' symptoms and clinical findings strongly suggestive for OSAS.

During the data collection of the studies I and III, AHI was confirmed to be measured during treatment among 3 of the patients with an AHI of <5 /h reported in study II and was corrected in studies I and III. The prevalence of moderate and severe disease among CPAP-treated patients was slightly higher in studies I and III compared to study II for the same reason. Study III additionally determined the following characteristics for those CPAP-treated patients and controls who had an MVA from the electronic medical records, if available: oxygen desaturation index

of ≥4 % (ODI4), or alternatively of ≥5 % if ODI4 was not reported, mean and minimum SpO_2 and the percentage of time spent under SpO2 of 90 %.

4.2.3 Questionnaires (studies I–III)

The scores of the self-administered ESS (Johns 1991) **(Appendix 1)** and GHQ-12 (Goldberg et al. 1997) **(Appendix 2)** questionnaires were generally evaluated both at the commencement of CPAP and at follow-up visits and entered into the electronic medical records. Data on baseline ESS and GHQ-12 scores were determined for the patients from the electronic medical records, if available. Study II determined the individual trends (slopes) of ESS and GHQ-12 development over time for those patients who had ≥3 available measurements during CPAP treatment. Study III evaluated the mean change in ESS during treatment for those CPAP-treated patients who had an MVA by comparing the first and last available values.

4.2.4 Baseline comorbidity (studies I–III) and cardiovascular disease risk factors (study I)

The following baseline variables were examined from the electronic medical records: age, gender, BMI and smoking status (defined as current smoker, ex-smoker or never smoker). Diagnoses of asthma, COPD, T2D (fasting glucose of ≥7.0 mmol/l, use of insulin and/ or oral antidiabetics), IFG (fasting glucose of 6.1–6.9 mmol/l), AF and psychiatric disorders, including depression, anxiety and psychotic disorder, were gathered from a diagnosis database of the Turku University Hospital. All diagnoses of the patients recorded during hospital visits are preserved in this database. The diagnoses of the patients were also verified from the electronic medical records during the manual collection of other patient data (studies I–III).

Data on lipid concentrations in serum (including triglycerides, total cholesterol, low-density lipoprotein and high-density lipoprotein cholesterol) and the history of hypertension and CVD were determined in order to more reliably evaluate the association between CPAP treatment and CVD risk (study I). The patients' laboratory test results were derived from a separate database of the Turku University Hospital, which includes all patient laboratory tests performed during hospital visits. Among those patients who did not have available values, data on serum lipid concentrations were examined manually from the electronic medical records, since the tests may have been ordered by general practitioners prior to the referral to a pulmonologist. Only serum lipid concentrations measured within 6 months before or after the initiation of CPAP treatment were included. Hypertension was defined as BP >140/90 mmHg and/ or use of antihypertensive medication. CVD included coronary, cerebral or peripheral artery diseases. An internist diagnosed CAD by

clinical symptoms and findings and/ or exercise testing or coronary angiography. A neurologist confirmed the diagnosis of stroke by computerized tomography or MRI. PAD was assessed by ankle-brachial index. The history of hypertension and CVD was also included in studies II and III.

4.2.5 Study follow-up

4.2.5.1 CPAP-treated patients (studies I–III)

The follow-up of the CPAP-treated patients started from the commencement of CPAP treatment in all the studies. CPAP follow-up visits occurred approximately three times during the first year and after habituation every second year.

Study I followed the CPAP-treated patients until the first nonfatal or fatal CVD event, all-cause death, CPAP withdrawal or the last CPAP follow-up visit before the end of 2014. The median follow-up time was 8.7 (IQR 2.8) years with a mean number of follow-up visits of 8.4 ± 2.2 per patient. The follow-up of the CPAP-treated patients in study II ended with CPAP withdrawal, or the last CPAP follow-up visit before the end of 2011. The mean follow-up period was 6.6 ± 1.2 years with a mean number of follow-up visits of 7.4 ± 2.1 per patient. Study III followed the CPAP-treated patients until CPAP withdrawal, or the last follow-up visit before the end of 2014. The median follow-up time was 9.0 (IQR 2.5) years with a mean number of follow-up visits of 8.4 ± 2.2 per patient. CPAP-treated patients were also screened for MVAs for 9 years prior to CPAP to compare MVAs before and after treatment.

4.2.5.2 Control patients (studies I, III)

Studies I and III started the follow-up of controls from the last CPAP follow-up visit. Study I followed control patients until the first nonfatal or fatal CVD event, all-cause death or until the end of 2014. The median follow-up time was 6.2 (IQR 4.1) years. In study III, control patients were followed until all-cause death or the end of 2014. The median follow-up time was 6.5 (IQR 3.9) years. Controls were also screened for MVAs for 6.5 years prior to CPAP in order to determine whether the incidence had changed over time.

4.2.6 CPAP adherence and other treatment options for OSA (studies I–III)

All patients were treated with a fixed pressure CPAP device. An auto-adjusting device may have been used at the beginning of the treatment in the assessment of

optimal treatment pressure (cmH_2O). Treatment pressure and CPAP usage (h/day) were recorded by an inbuilt counter clock on the CPAP device. The CPAP use was determined from the device at every follow-up visit undertaken during the study and entered into the electronic medical records. The data on CPAP treatment were derived from a sleep database of the Department of Pulmonary Diseases at the Turku University Hospital. The database was updated at every follow-up visit. The mean usage hours across the whole CPAP treatment period (including missed days of use) were determined for each patient to evaluate long-term adherence. Those with a mean CPAP usage of ≥4 h/day were considered compliant with the treatment. Study II additionally determined short-term adherence by calculating the mean usage hours from the initiation of treatment either until the first follow-up visit or, alternatively, the 6-month follow-up visit when the habituation to treatment took longer period of time.

CPAP-treated patients who had engaged in bariatric surgery before or during CPAP treatment (studies I–III) and controls who had been submitted to bariatric surgery or commenced MAD treatment during the study follow-up (studies I and III) were identified from the electronic medical records. A physician and a trained nurse gave overweight patients instructions for weight loss at the commencement of treatment in all the studies. According to the patient's motivation, further diet and lifestyle counseling by a dietician were arranged but were not systematically offered to all patients.

4.2.7 Follow-up data on body mass index (studies II–III)

BMI was calculated by dividing weight in kilograms by the square of height in meters (kg/m^2). The patients' weight was measured during visits by a nurse. BMI was generally determined both at the commencement of CPAP treatment and at follow-up visits and entered into the electronic medical records. Study II determined the individual trends (slopes) of BMI development during treatment for each CPAP-treated patient based on the BMI measurements recorded at baseline and follow-up visits. Study III evaluated the mean change in BMI during treatment for those CPAP-treated patients who had an MVA by comparing the first and last available values.

4.2.8 The definition of cardiovascular disease events (study I) and the data on deaths (studies I, III)

A composite CVD event consisted of nonfatal and fatal CVD events. A nonfatal CVD event included angina pectoris (stable or unstable), CAD diagnosed by angiography and invasively treated, nonfatal myocardial infarction and nonfatal stroke. CVD events were diagnosed in special health care by a cardiologist or an

internist according to international guidelines. Coronary angiography data of the patients were gathered from a cardiological angiography database of the Turku University Hospital with a cardiologist's guidance. The database included the following data on performed coronary angiographies: date, indication (elective vs. acute angiography), number of occluded coronary arteries, treatment decision (invasively vs. conservatively treated) and the type of procedure if invasively treated (PCI, coronary artery bypass grafting or heart valve procedure). All acutely performed angiographies with ≥1 occluded coronary artery (myocardial infarction, unstable angina pectoris) were included regardless of the treatment decision (either invasively or conservatively treated). Those electively performed angiographies with ≥1 occluded coronary artery in addition to a need for invasive treatment procedure were also included as a nonfatal CVD event (CAD diagnosed and invasively treated). The Turku University Hospital is the only hospital in the region performing surgical and interventional cardiology procedures with an emergency department and an intensive cardiac care unit.

Fatal CVD events were based on the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10), a medical classification list by the World Health Organization (World Health Organization, 2004). Diseases of the circulatory system as determined by the ICD-10 (diagnoses I00–I99) that had led to death were included as fatal CVD events. The underlying cause of death was confirmed by an autopsy or documented disease history. All nonfatal and fatal strokes and nonfatal cardiac (CAD diagnosed by angiography and invasively treated, nonfatal angina pectoris or myocardial infarction) and fatal cardiac (death from ischemic heart disease) events were analyzed separately in additional analyses. Data on all-cause deaths before the end of 2014 were derived from the national registry maintained by Statistics Finland and were acknowledged in the follow-up durations of controls. All-cause mortality, death from CVD and death from cancer were analyzed separately in additional analyses.

4.2.9 Data on MVAs (study III)

All MVAs reported to the police and notified to the national registry maintained by Statistics Finland during the study follow-up were identified. Only accidents resulting in personal injury and involving the study subject as the actual driver were included. Data on accident conditions were provided. According to the data protection practices of Statistics Finland, small groups consisting of a few individuals may not be utilized; thus, the number of patients was either reported as approximate values or referred to as being 'low' in these cases.

4.3 Statistical analyses

Data analyses were performed using IBM SPSS Statistics version 22.0 or 25.0 (IBM Corporation, Armonk, NY, USA) (studies I–III), R Core Team 2013 (R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria) (study II) or SAS 9.4 (SAS Institute Inc., Cary, NC, USA) (study III) software packages. Normally distributed continuous variables were presented as mean values and standard deviations (SD), and not normally distributed variables as median values and interquartile ranges (IQR). Means and medians were compared by the independent-samples T test or the one-way analysis of variance (ANOVA) and the Mann–Whitney U test, respectively, and categorical variables by the χ^2 test. The linear relationship between two continuous random variables was assessed by the Spearman correlation coefficient (study II). P values of <0.05 were considered statistically significant.

4.3.1 Study I

The Cox regression model was used to evaluate the association between CPAP and the risk of CVD events, all-cause mortality and death from cancer by comparing CPAP-treated patients to untreated controls. For the basic Cox regression models, individual follow-up time was always calculated from the initiation of CPAP in CPAP-treated patients and from the last CPAP follow-up visit in controls. Time to the endpoint was determined in patients who had a specific endpoint (CVD event/ death from all-cause or cancer). In case of multiple CVD events, only the first event was considered. CPAP-treated patients who did not have an endpoint were followed until CPAP withdrawal or the last CPAP follow-up visit before the end of 2014. Controls who did not have a CVD event as an endpoint were followed until all-cause death or the end of 2014, while those who did not have all-cause death as an endpoint were followed until the end of 2014. Similarly, those controls who did not have death from cancer as an endpoint were followed until death from other causes or the end of 2014.

Additional analyses were performed by using a modified Cox regression model to more reliably compare the incidence of CVD death, all-cause death and death from cancer between the CPAP-treated patients and controls. The main inclusion criterion for the CPAP-treated patients was continuation of treatment for ≥5 years, which naturally favors CPAP-treated patients over controls in terms of death survival rates, since they were followed from the initiation of treatment. Thus, in those analyses where a composite CVD event or death was the endpoint, follow-up duration of controls was modified from that of the basic Cox regression models. Individual follow-ups of those controls who had a fatal endpoint were increased by 5 years in the modified Cox regression analyses where a composite CVD event was the

endpoint, whereas in the analyses of CVD death, all-cause death or death from cancer, individual follow-ups of all the 1030 controls were increased by 5 years.

The adjusted basic/ modified models were generally adjusted for the following confounding covariates, in addition to CPAP treatment: gender, age, AHI, BMI, IFG/ T2D, COPD, hypertension and CVD at baseline. As an exception, the adjusted model for stroke also included AF (all diagnoses of AF before the end of 2014) and the model for all-cause mortality the prevalence of psychiatric disorders at baseline. In further analyses, the adjusted model of the effect of smoking on the risk of CVDs included data on active/ former smoking and/ or a history of COPD instead of COPD alone. Data on serum cholesterol concentrations and the ESS score at baseline did not affect the hazard ratios (HR) of the CPAP-treated patients and were thus omitted from the final adjusted basic/ modified models. In unadjusted models, each covariate was computed separately in the model. HRs and 95 % CIs were used to determine the associations between the studied covariates and time to the endpoint. In terms of continuous covariates, HRs represented the risk associated with every one-unit increase in the studied covariate (e.g. one-year increase in age or one kg/m^2 increase in BMI).

Additional analyses by Cox regression model were performed to evaluate the association between the level of CPAP use and the risk of CVD events, all-cause mortality and death from cancer. These analyses compared CPAP-treated patients with CPAP use of >6 h/day, >4 but ≤6 h/day, or ≤4 h/day to controls. Furthermore, the effect of the level of CPAP adherence on the risk of having a composite CVD event or a nonfatal cardiac event was analyzed separately for those who had (secondary prevention) or did not have established CVD at baseline (primary prevention). Additional analyses were also performed separately for CPAP-treated patients and controls. In terms of composite CVD events, CPAP-treated patients with CPAP use of >6 h/day were compared to those with ≤6 h/day. Among controls, an AHI of ≥15 /h was compared to a lower AHI regarding the risk of a composite CVD event, CVD death or all-cause mortality.

Unadjusted Kaplan–Meier curves with data censored at the time of the end of follow-up were used to visually compare the risk of having a composite CVD event, nonfatal stroke or nonfatal cardiac event between CPAP-treated patients and controls. Among controls, survival free time from all-cause mortality was shown in unadjusted Kaplan-Meier curves for those with an AHI of ≥15 /h or less.

4.3.2 Study II

The patients' measurements of BMI and CPAP usage were assessed in relation to time starting from the initiation of CPAP. Based on these consecutive measurements, individual slopes of both BMI (kg/m^2/year) and CPAP usage (h/day/year) were

determined for each patient by using the linear mixed model. Ascending slopes of BMI or CPAP usage were associated with gaining weight or increasing use of CPAP, respectively, whereas descending slopes were associated with the opposite. The accuracy of a single slope is dependent on the number of measurements available and the within-patient variation between the sequential measurements. The mean number of measurements were 7.4 ± 1.7 measurements of BMI and 6.5 ± 1.8 measurements of CPAP usage during treatment for each CPAP-treated patient.

The Bayesian hierarchical model for linear trend and the Markov Chain Monte Carlo simulation were used to account for the uncertainty related to individual trends, including the effect of within-patient variation, and to identify those individuals who had a significant constant change in BMI or CPAP adherence. For each patient, 5000 lines were simulated through the measurement points, and the trend of these lines was evaluated individually at the posterior probability level of >90 %. These 5000 lines thus represented the possible trends of development in each patient (the posterior distribution of trends) based on real data. Patients with >4500 ascending or descending slopes of the total simulated 5000 slopes (>90 %) were defined as having a significant increase or decrease, respectively, in BMI or CPAP adherence during treatment. Patients with fewer ascending or descending slopes did not have a significant change. Due to the model uncertainty and the within-patient variation, patients with a similar slope value may have been divided either into the subgroups of 'significant change' or 'no significant change' according to the Bayesian Hierarchical model and Monte Carlo simulation **(Figure 6)**.

Patients with a significant change in BMI or CPAP adherence were further profiled by the multivariate logistic regression analysis to evaluate potential predictors of change. These models were always adjusted for age, gender, AHI, BMI, ESS and GHQ-12 scores, the prevalence of IFG/ T2D, hypertension, CVD, psychiatric disorders and current smoking at baseline in addition to the ESS and GHQ-12 slopes. The models regarding significant changes in adherence were additionally adjusted for the prevalence of asthma at baseline, short-term CPAP usage and the BMI slope, whereas the models regarding significant changes in BMI were additionally adjusted for the CPAP adherence slope. The results were reported as ORs and 95 % CIs.

The individual slope values of BMI and CPAP usage in addition to ESS and GHQ-12 scores (change of score/ year) determined by the linear mixed model, were used to evaluate the annual change in these variables. The average annual change at the cohort level was reported for all the CPAP-treated patients with available data. Additionally, the slope values of BMI and CPAP usage were also reported at the individual level for the following subgroups: patients with no significant change, patients with a significant increase and patients with a significant decrease in BMI or CPAP adherence. Further analyses also determined the prevalence of patients with

a significant change in BMI or CPAP adherence for those CPAP-treated patients who had a composite CVD event or an MVA in studies I and III.

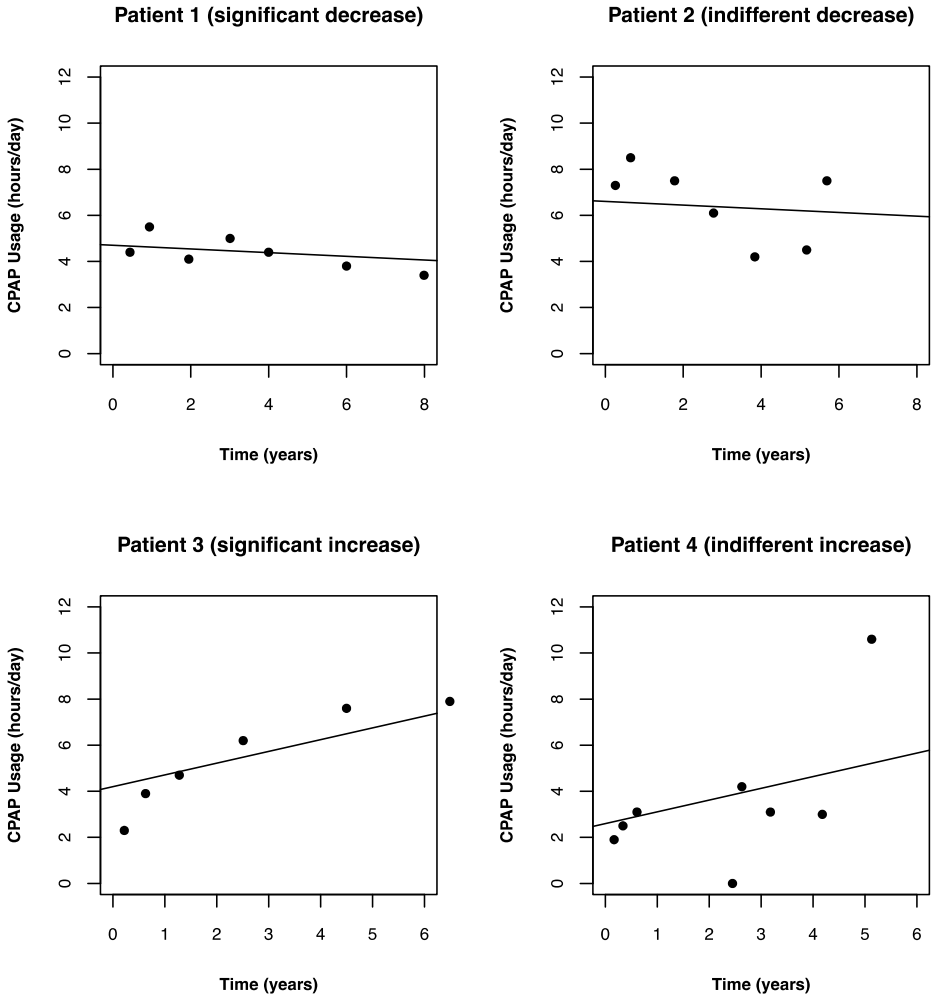


Figure 6. These examples show that two patients may have a similar slope value, but the statistical accuracy of the slope depends on the number of measurements available and the variation between sequential measurements. Only patients 1 and 3 had a significant change in CPAP usage based on the Bayesian Hierarchical model and Monte Carlo simulation at the probability level of >90 %. Reprinted with permission from original publication II.

4.3.3 Study III

The Poisson regression was used for the comparison of MVA incidences between study groups. The individual follow-up time of each patient was taken into account in the analysis. The incidence of MVAs was reported per 1000 person years and the risk for having an MVA as risk ratios (RR) and 95 % CIs. CPAP-treated patients were compared before–after treatment and to controls. The effect of the level of CPAP use (≥4 or ≥6 h/day) on the incidence of MVAs was determined separately. Among controls, the MVA incidence was also determined separately for those who had not used MAD after CPAP. Cox regression model was also used to evaluate the associations between the incidence of MVAs and potential predictors, including age, gender, BMI, smoking and AHI.

4.4 Ethical aspects

According to the national regulations, ethical committee's consideration was not required owing to the retrospective nature of the studies. The registry-based study design was approved by the Office of the Data Protection Ombudsman, Finland. Data gathering and analyses were performed with the permission of the Turku University Hospital.

5 RESULTS

5.1 Characteristics of the patients at baseline

5.1.1 Study II

Of the 1023 included CPAP-treated patients, 76 % were male, the mean age was 56 ± 10 years and the mean AHI 34 ± 23 /h. Compared to men, women differed in several aspects by being older, more obese, by having a milder OSA and a higher prevalence of psychiatric disorders **(Table 5)**. A correlation between AHI and age was not observed ($R^2 = -0.01$, p=0.7).

5.1.2 Studies I, III

CPAP-treated patients and the 1030 pairwise-matched controls did not differ in terms of gender, age or AHI, but differences in comorbidities were observed **(Table 6)**. Moderate to severe OSA was diagnosed in 76 % of the CPAP-treated patients and 77 % of controls (p=0.9; **Figure 7**), and the majority of the patients in both groups were middle-aged **(Figure 8)** and obese (BMI >30 kg/m^2, 67 vs. 60 %, respectively, p=0.001; **Figure 9**). EDS (ESS ≥11) was reported more frequently by CPAP-treated patients than controls (39 vs. 30 %, p<0.001), although the majority of the patients in both groups were non-sleepy.

Table 5. Comparison of the characteristics between the CPAP-treated male and female patients at baseline (N=1023). Modified with permission from original publication II.

	Male (N=775)	Female (N=248)	P	Total (N=1023)
Patient characteristics				
Age, years (mean, SD)	54.7 ± 9.7	58.2 ± 9.8	*<0.001*	55.6 ± 9.8
BMI, kg/m^2 (mean, SD)	33.1 ± 5.9	34.9 ± 7.6	*<0.001*	33.5 ± 6.4
OSA and questionnaires				
AHI, events/h (mean, SD)	35.7 ± 23.2	27.4 ± 21.7	*<0.001*	33.7 ± 23.1
ESS score (mean, SD)	9.5 ± 4.7	9.0 ± 4.7	0.1	9.4 ± 4.7
GHQ-12 score (mean, SD)	3.1 ± 3.6	4.0 ± 3.6	*0.002*	3.3 ± 3.6
Comorbidity and lifestyle				
IFG/ T2D (N, %)	324 (41.8)	88 (35.5)	0.08	412 (40.3)
Hypertension* (N, %)	586 (75.6)	197 (79.4)	0.2	783 (76.5)
CVD† (N, %)	48 (6.2)	7 (2.8)	*0.04*	55 (5.4)
Asthma (N, %)	68 (8.8)	32 (12.9)	0.06	100 (9.8)
COPD (N, %)	40 (5.2)	6 (2.4)	0.07	46 (4.5)
Psychiatric disorder‡ (N, %)	98 (12.6)	63 (25.4)	*<0.001*	161 (15.7)
Current smoking (N, %)	179 (23.1)	45 (18.1)	0.1	224 (21.9)

Data are presented as N (%) or mean ± standard deviation (SD). AHI, apnea-hypopnea index; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CPAP, continuous positive airway pressure; CVD, cardiovascular disease; ESS, Epworth Sleepiness Scale (data available for 977 patients); GHQ-12, General Health Questionnaire (data available for 908 patients); IFG, impaired fasting glucose; T2D, type 2 diabetes.

* Blood pressure greater than 140/90 mmHg and/ or use of antihypertensive medication.
† Coronary artery disease, myocardial infarction, angina pectoris, stroke, intracranial atherosclerosis or peripheral artery disease.
‡ Depression, anxiety or psychotic disorder.

Table 6. Comparison of the characteristics between the CPAP-treated patients and controls at baseline. Modified with permission from original publication I.

	CPAP-treated (N=1030)	Controls (N=1030)	P
Patient characteristics			
Male gender (N, %)	781 (75.8)	781 (75.8)	0.1
Age, years (mean, SD)	55.6 ± 9.8	56.4 ± 11.1	0.1
BMI, kg/m^2 (median, IQR)	32.7 (8.1)	31.5 (7.9)	*<0.001*
OSA and questionnaires			
AHI, events/h (median, IQR)	28.0 (33.0)	27.0 (28.0)	0.1
ESS score (mean, SD)	9.4 ± 4.7	8.3 ± 4.7	*<0.001*
GHQ-12 score (median, IQR)	2.0 (5.0)	2.0 (6.0)	0.1
Comorbidity and lifestyle			
IFG/ T2D (N, %)	416 (40.4)	363 (35.2)	*0.02*
Hypertension* (N, %)	788 (75.6)	724 (70.3)	*0.001*
CVD† (N, %)	56 (5.4)	130 (12.6)	*<0.001*
Asthma (N, %)	102 (9.9)	97 (9.4)	0.7
COPD (N, %)	47 (4.6)	78 (7.6)	*0.004*
Psychiatric disorder‡ (N, %)	162 (15.7)	189 (18.3)	0.1
Smoking (N, %)			*<0.001*§
Current	227 (22.0)	296 (28.7)	
Ex-smoker	668 (35.7)	355 (34.5)	

Data are presented as N (%) or mean ± standard deviation (SD) or median and interquartile range (IQR). AHI, apnea-hypopnea index; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CPAP, continuous positive airway pressure; CVD, cardiovascular disease; ESS, Epworth Sleepiness Scale (data available for 981 CPAP-treated patients and 986 controls); GHQ-12, General Health Questionnaire (data available for 912 CPAP-treated patients and 947 controls); IFG, impaired fasting glucose; T2D, type 2 diabetes.

*, †, ‡ Definitions are provided in **Table 5**.
§ P-value for the trend.

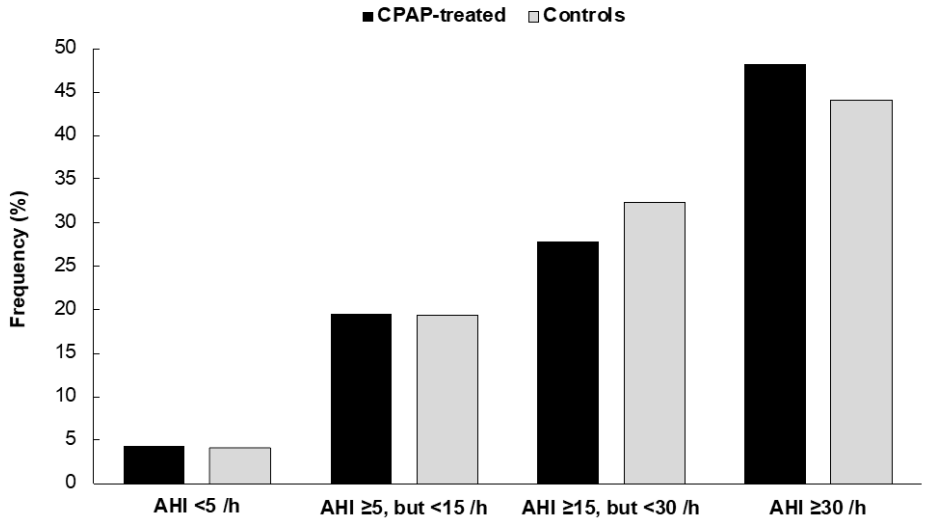


Figure 7. Comparison of the obstructive sleep apnea severity groups according to apnea-hypopnea index (AHI) between the CPAP-treated patients and controls.

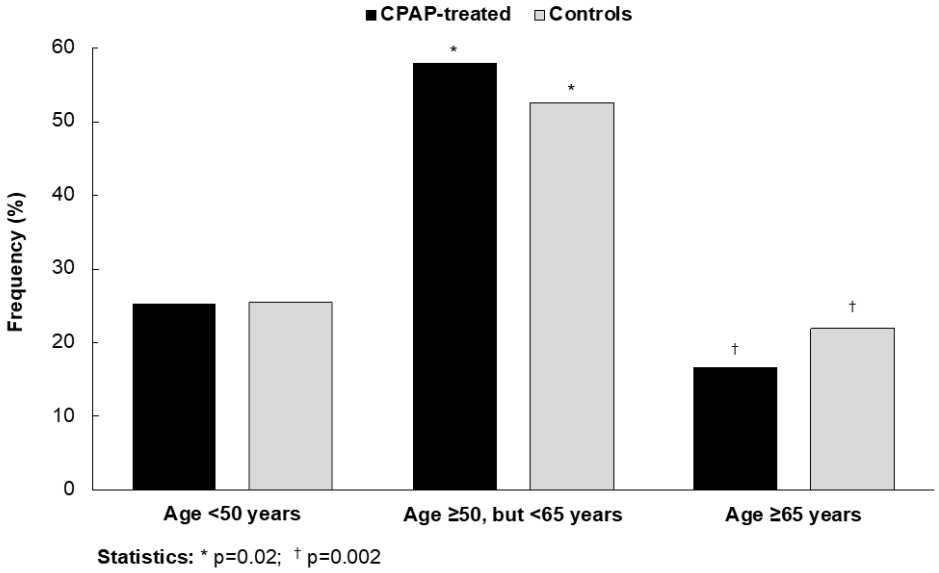


Figure 8. Comparison of the age groups between the CPAP-treated patients and controls.

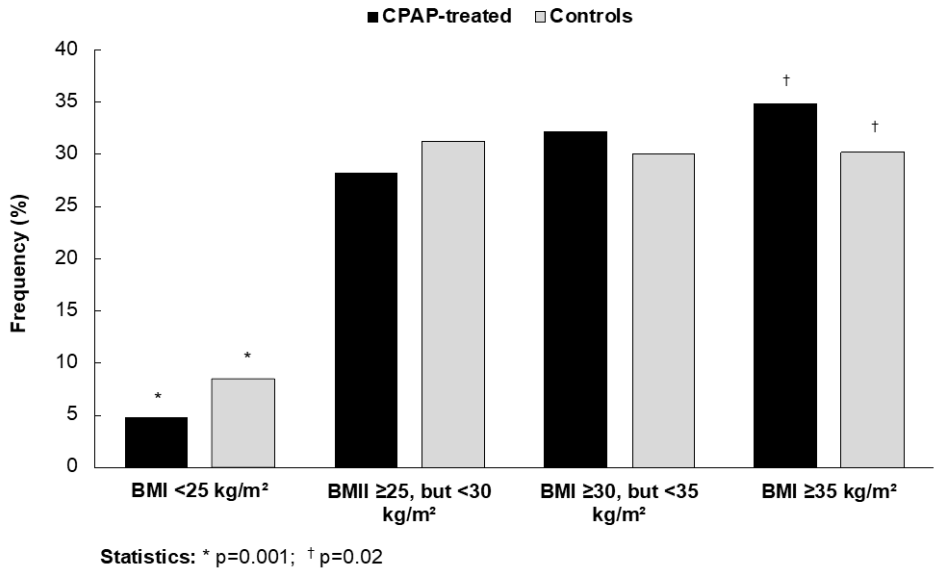


Figure 9. Comparison of the body mass index (BMI) groups between the CPAP-treated patients and controls.

5.2 OSA treatment

5.2.1 CPAP treatment and adherence (studies I–III)

In studies I and III, the median use of CPAP was 6.4 (IQR 2.3) h/day for the 1030 CPAP-treated patients over a median follow-up of 9 years. Of the patients, 598 (58 %) had used CPAP >6 h/day, 315 (31 %) 4–6 h/day, and only 117 (11 %) <4 h/day (median use of 2.9, IQR 1.3 h/day) during the follow-up. Before the initiation of the study, controls had used CPAP for a median of 0.7 (IQR 2.6) h/day during a median treatment period of 4 (IQR 16) months.

Study II evaluated CPAP adherence in more detail. CPAP usage was 5.2 ± 2.0 h/day in the short term and 6.0 ± 1.8 h/day in the long term for the 1023 CPAP-treated patients. Shor-term adherence was determined from the initiation of treatment either until the first follow-up visit or alternatively the 6-month follow-up visit. The mean change in adherence at the cohort level was 11 ± 12 min/day per year over a mean follow-up of 7 years. A weak positive correlation was found between AHI and long-term CPAP usage hours ($R^2 = 0.11$, p=0.001), and a weak negative correlation between the mean CPAP usage and ESS score slopes ($R^2 = -0.13$, $p < 0.001$). At the individual level, 76 % of the patients showed no significant change, whereas 11 %

had a significant increase (an average of 30 ± 8 min/day per year) and 13 % a significant decrease (an average of 8 ± 9 min/day per year) in CPAP adherence **(Figures 10–11)**. Gender differences were not observed in the groups with significant increase or decrease in adherence.

The multivariate logistic regression analysis showed that significant increase in CPAP adherence was associated with the presence of psychiatric disorder or a higher BMI at baseline in addition to increases in weight or the GHQ-12 score during treatment. A weak association was observed between increasing AHI and significant increase in CPAP adherence **(Table 7)**. Compared to the rest of the cohort, patients with an average CPAP use of >8 h/day (N=115) were more obese, had a more severe OSA based on AHI and a higher prevalence of psychiatric disorders and hypertension at baseline. No differences were found in terms of age, gender, other comorbidities **(Table 8)**, or the mean ESS or GHQ-12 slopes (-0.7 ± 0.7 vs. -0.6 ± 0.7, p=0.2, and -0.2 ± 0.7 vs. -0.2 ± 0.6, p=0.3 change of score/ year, respectively).

5.2.2 Bariatric surgery, lifestyle counselling and mandibular advancement device treatment (studies I–III)

Study II excluded CPAP-treated patients who had engaged in bariatric surgery before or during CPAP treatment (N=7) from the study. In studies I and III, 12 (1 %) of the CPAP-treated patients and 9 (1 %) of controls had engaged in bariatric surgery (p=0.5) and were included in the analyses. Of the control patients, 65 (6 %) had used MAD treatment after CPAP.

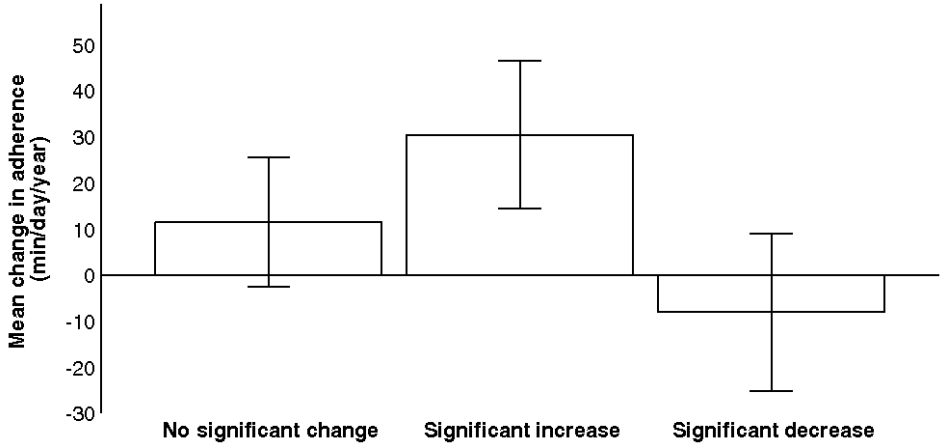


Figure 10. Mean annual change in CPAP adherence over a mean treatment period of 7 years at the individual level (N=1023). Modified with permission from original publication II.

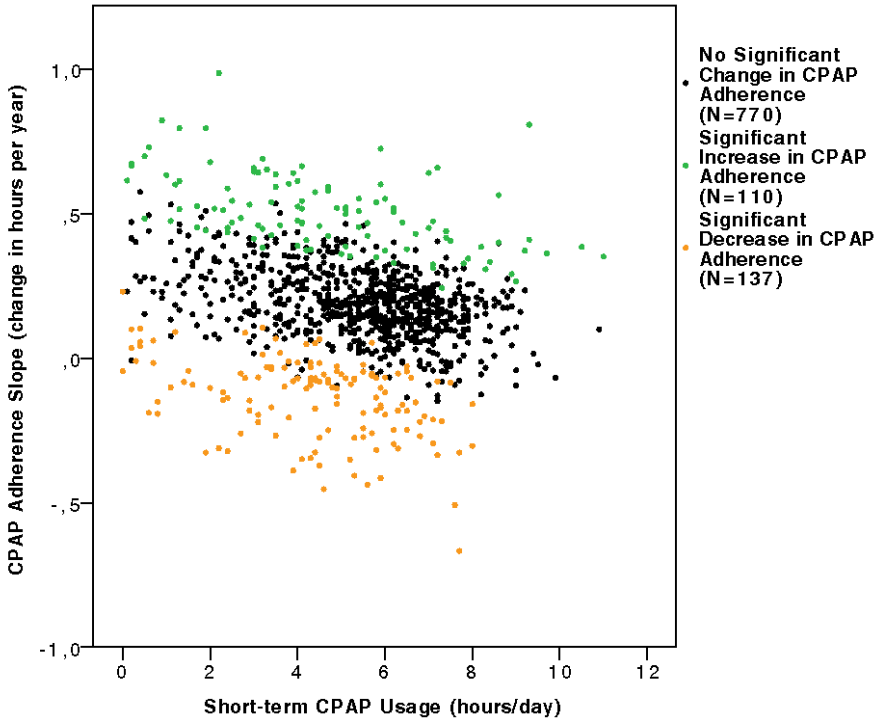


Figure 11. Individual development of CPAP adherence in relation to the usage at the beginning of treatment (N=1017). Reprinted with permission from original publication II.

Table 7. Associations between clinical characteristics and significant change in CPAP adherence determined by the multivariate logistic regression analysis. Modified with permission from original publication II.

	Significant increase in CPAP adherence*		Significant decrease in CPAP adherence*	
	OR (CI 95 %)	**P**	**OR (CI 95 %)**	**P**
Patient characteristics				
Age, years	1.02 (1.0–1.0)	0.3	0.98 (1.0–1.0)	0.2
Male gender	0.98 (0.5–1.8)	1.0	0.80 (0.5–1.4)	0.4
BMI, kg/m^2	1.07 (1.0–1.1)	*0.001*	0.94 (0.9–1.0)	*0.006*
OSA and questionnaires				
AHI, events/h	1.01 (1.0–1.0)	*0.04*	1.00 (1.0–1.0)	0.5
ESS score	0.86 (0.8–0.9)	*<0.001*	0.99 (0.9–1.1)	0.8
GHQ-12 score	1.19 (1.1–1.3)	*<0.001*	1.10 (1.0–1.2)	*0.02*
Comorbidity and lifestyle				
IFG/ T2D	1.20 (0.7–2.0)	0.5	0.93 (0.6–1.5)	0.8
Hypertension†	1.84 (0.9–3.8)	0.09	0.92 (0.5–1.6)	0.8
CVD‡	1.06 (0.4–2.9)	0.9	0.52 (0.1–2.2)	0.4
Asthma	0.83 (0.4–1.9)	0.7	0.87 (0.4–1.9)	0.7
Psychiatric disorder§	3.30 (1.8–6.0)	*<0.001*	0.70 (0.3–1.4)	0.3
Current smoking	1.41 (0.8–2.4)	0.2	0.64 (0.4–1.1)	0.1
Follow-up characteristics				
BMI slope‖	2.94 (1.7–5.2)	*<0.001*	0.26 (0.1–0.5)	*<0.001*
Short-term CPAP usage#	0.89 (0.8–1.0)	*0.04*	0.75 (0.7–0.8)	*<0.001*
ESS slope‖	0.46 (0.3–0.7)	*0.001*	1.21 (0.8–1.8)	0.4
GHQ-12 slope‖	2.47 (1.6–3.9)	*<0.001*	1.28 (0.8–2.0)	0.3

Data are presented as odds ratios (ORs) and 95 % confidence intervals (95 % CIs). Abbreviations are presented in **Table 5**.

* Patients with an ascending (significant increase) or a descending (significant decrease) trend in adherence over a mean treatment period of 7 years at the posterior probability level of >90 %.
†, ‡, § Definitions are provided in **Table 5**.
‖ Annual change in BMI, ESS (N=948) or GHQ-12 (N=948) score over a mean CPAP treatment period of 7 years.
Mean CPAP usage from the commencement of CPAP either until the first follow-up visit or alternatively until the 6-month follow-up visit (including missed days of use) (N=1017).

Table 8. Comparison of the baseline characteristics between the patients with an average CPAP use of >8 h/day and the rest of the cohort.

	CPAP use of >8 h/day (N=115)	The rest of the cohort (N=908)	P
Patient characteristics			
Age, years (mean, SD)	57.0 ± 9.4	55.4 ± 9.9	0.1
Male gender (N, %)	82 (71.3)	693 (76.3)	0.2
BMI, kg/m^2 (mean, SD)	35.8 ± 6.9	33.2 ± 6.3	*<0.001*
OSA and questionnaires			
AHI, events/h (mean, SD)	41.8 ± 26.2	32.7 ± 22.5	*<0.001*
ESS score (mean, SD)	8.9 ± 5.2	9.4 ± 4.6	0.3
GHQ-12 score (mean, SD)	4.2 ± 4.3	3.2 ± 3.5	*0.005*
Comorbidity and lifestyle			
IFG/ T2D (N, %)	53 (46.1)	359 (39.5)	0.2
Hypertension* (N, %)	99 (86.1)	684 (75.3)	*0.01*
CVD† (N, %)	6 (5.2)	49 (5.4)	0.9
Asthma (N, %)	15 (13.0)	85 (9.4)	0.2
COPD (N, %)	4 (3.5)	42 (4.6)	0.6
Psychiatric disorder‡ (N, %)	30 (26.1)	131 (14.4)	*0.001*
Current smoking (N, %)	22 (19.1)	202 (22.2)	0.4

Data are presented as N (%) or mean ± standard deviation (SD). Abbreviations are presented in **Table 5**.

*, †, ‡ Definitions are provided in **Table 5**.

5.3 The association between CPAP treatment and the risk of cardiovascular diseases (study I)

At baseline, the CPAP-treated patients and controls did not differ in terms of gender, age or AHI, but other differences in CVD risk factors were observed **(Table 6)**. CPAP-treated patients had a higher BMI and a higher prevalence of IFG/ T2D and hypertension than controls, whereas CVD, COPD and smoking were more common among controls. CAD was the most common CVD at baseline in both groups (3 % in CPAP-treated patients and 7 % in controls) **(Table 9)**. Clinically relevant differences in serum lipid concentrations were not observed **(Table 10)**.

Among all patients, those with an AHI of ≥15 /h (N=1573) had a higher median BMI (33, IQR 8 vs. 31, IQR 8 kg/m^2), a higher prevalence of hypertension (76 vs. 64 %), CVD (10 vs. 6 %) and IGT/ T2D (40 vs. 30 %) in addition to older age (57 ± 11 vs. 54 ± 0.4 years) at baseline compared to those with an AHI of <15 /h (N=487) (p <0.05). Among controls, an AHI of ≥15 /h (N=788) was associated with a 1.7-fold (95 % CI 1.0–2.7, p=0.03) increased risk of all-cause mortality over a mean follow-up of 6.2 years independent of confounding factors compared to a lower AHI. Similarly, an unadjusted 2.4-fold (95 % CI 1.6–3.7, p<0.001) increased risk of composite CVD events was observed; however, the adjusted analyses of composite CVD events (HR 1.46, 95 % CI 0.9–2.3, p=0.1) and CVD deaths (HR 2.02, 95 % CI 1.0–4.2, p=0.06) showed only a tendency towards increased risk.

The survival of the controls free from all-cause mortality is shown in adjusted Kaplan-Meier curves according to AHI **(Figure 12)**.

Table 9. Comparison of the prevalence of cardiovascular diseases between the CPAP-treated patients and controls at baseline. Modified with permission from original publication I.

	CPAP-treated (N=1030)	**Controls (N=1030)**	**P**
Cardiovascular diseases (N, %)	56 (5.4)	130 (12.6)	<0.001
Coronary artery disease	34	69	*<0.001*
Myocardial infarction	6	18	*0.01*
Angina pectoris	3	5	0.5
Stroke	10	25	*0.01*
Intracranial atherosclerosis	1	0	0.3
Peripheral artery disease	2	13	*0.004*

Data are presented as N or N (%). CPAP, continuous positive airway pressure.

Table 10. Comparison of the lipid concentrations in serum between the CPAP-treated patients and controls at baseline.

Lipid concentrations, mmol/l	CPAP-treated (N=1030)	Controls (N=1030)	P
Total cholesterol* (mean, SD)	5.1 ± 1.0	5.0 ± 1.1	*0.009*
LDL cholesterol (median, IQR)	2.9 (1.1)	2.8 (1.2)	*0.004*
HDL cholesterol (mean, SD)	1.3 ± 0.4	1.3 ± 0.4	0.4
Triglycerides† (median, IQR)	1.6 (1.1)	1.6 (1.1)	0.2

Data are presented as mean ± standard deviation (SD) or as median and interquartile range (IQR). CPAP, continuous positive airway pressure; HDL, serum high-density lipoprotein (data available for 787 CPAP-treated patients and 715 controls); LDL, serum low-density lipoprotein (data available for 773 CPAP-treated patients and 703 controls).

* Total cholesterol level in serum (data available for 845 CPAP-treated patients and 738 controls).
† Triglyceride level in serum (data available for 776 CPAP-treated patients and 708 controls).

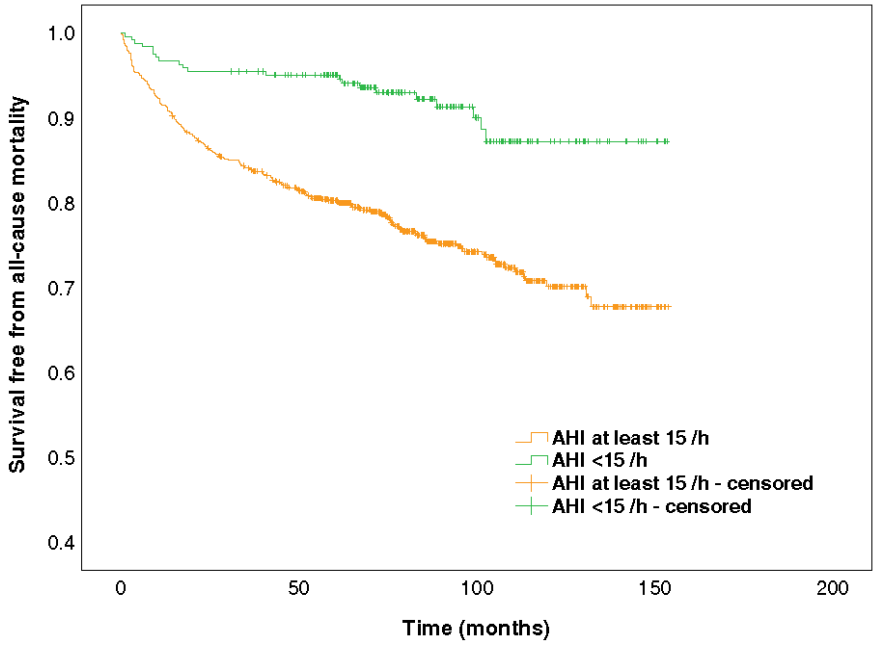


Figure 12. Survival free time from all-cause mortality among control patients with an AHI of ≥15 /h (orange, N=788) or <15 /h (green, N=242).

5.3.1 All CVD deaths

In the basic Cox regression model, CPAP treatment was associated with a decreased risk of fatal CVD events after adjustment for confounding factors when all CVD deaths of the patients, including 33 deaths in CPAP-treated patients and 106 deaths in controls, were analyzed separately (HR 0.23, CI 95 % 0.2–0.3, p <0.001). The association remained significant in the adjusted modified model (HR 0.53, 95 % CI 0.4–0.8, p=0.003). However, a subgroup analysis revealed that the beneficial impact of CPAP was shown only in those patients who had used CPAP for >6 h/day (HR 0.39, 95 % CI 0.2–0.7, p=0.001) **(Table 11)**. The most common cause of CVD death was ischemic heart disease **(Figure 13)**.

Table 11. Adjusted hazard ratios (HRs) and 95 % confidence intervals (95 % CIs) predicting the time to death from cardiovascular diseases (CVDs) (N=139) among the CPAP-treated patients and controls. Modified with permission from original publication I.

	Basic adjusted model* †			**Modified adjusted model*** †		
	HR	**CI 95%**	**P**	**HR**	**CI 95%**	**P**
Male gender	1.61	1.0–2.5	*0.04*	1.60	1.0–2.5	*0.04*
Age, years	1.08	1.1–1.1	*<0.001*	1.08	1.1–1.1	*<0.001*
BMI, kg/m^2	1.02	1.0–1.1	0.2	1.02	1.0–1.1	0.2
AHI, events/h	1.01	1.0–1.0	*0.001*	1.01	1.0–1.0	*<0.001*
CVD‡	3.33	2.2–4.9	<0.001	2.99	2.0–4.4	*<0.001*
Hypertension§	1.69	0.9–3.0	0.08	1.68	0.9–3.0	0.08
IFG/ T2D	1.42	1.0–2.0	0.05	1.42	1.0–2.0	*0.048*
COPD	1.16	0.7–1.9	0.6	1.21	0.7–2.0	0.4
CPAP treatment	0.23	0.2–0.3	*<0.001*	0.53	0.4–0.8	*0.003*
>6 h/day#	0.17	0.1–0.3	*<0.001*	0.39	0.2–0.7	*0.001*
>4, but ≤6 h/day#	0.27	0.1–0.5	*<0.001*	0.62	0.3–1.2	0.1
≤4 h/day#	0.51	0.2–1.1	0.09	1.2	0.5–2.6	0.7

AHI, apnea-hypopnea index; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CPAP, continuous positive airway pressure; IFG, impaired fasting glucose; T2D, type 2 diabetes.

* The model was adjusted for gender, age, BMI, AHI, CVD, hypertension, IFG/ T2D, COPD and CPAP treatment (CPAP vs. controls).
† In the modified model, the follow-up of all the controls was increased by 5 years from that of the basic model in order to compare the incidence of deaths between the groups more reliably.
‡ Coronary artery disease, myocardial infarction, angina pectoris, stroke, intracranial atherosclerosis or peripheral artery disease.
§ Blood pressure greater than 140/90 mmHg and/ or use of antihypertensive medication.
# Mean CPAP usage over a median treatment period of 9 years (including missed days of use).

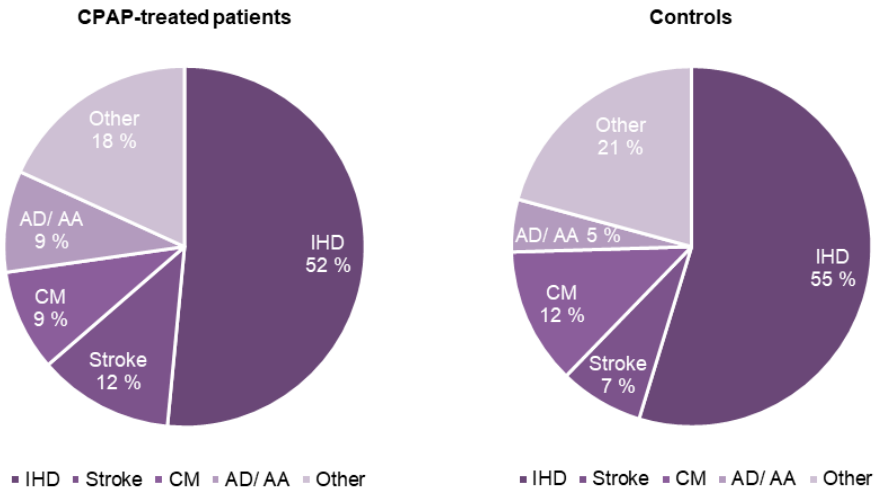


Figure 13. All cardiovascular disease deaths of the CPAP-treated patients (N=33) and controls (N=106) including death from ischemic heart disease (IHD), cardiomyopathy (CM), aortic dissection (AD), aneurysm (AA), stroke or other causes (cardiac arrhythmias, heart valve diseases, other cerebrovascular diseases than stroke, systemic atherosclerosis, complicated hypertension or thrombophlebitis of deep veins).

5.3.2 All strokes

Of the CPAP-treated patients, 47 had a nonfatal and 3 a fatal stroke. The corresponding incidences for controls were 60 and 4, respectively. CPAP-treatment was associated with a reduced risk of nonfatal and fatal strokes both in the basic (HR 0.60, 95 % CI 0.4–0.9, p=0.01) and the modified (HR 0.59, 95 % CI 0.4–0.9, p=0.008) Cox regression models. The association was independent of confounding factors in both analyses **(Table 12)**.

The association between CPAP treatment and a reduced risk of stroke remained significant both in the unadjusted (HR 0.56, 95 % CI 0.4–0.8, p=0.003) and adjusted basic Cox regression model (HR 0.60, 95 % CI 0.4–0.9, p=0.01) after fatal strokes were excluded from the analysis and nonfatal strokes (N=107) were analyzed separately **(Table 13)**. Survival rates free from nonfatal stroke are shown in unadjusted Kaplan–Meier curves **(Figure 14)**.

Subgroup analyses showed that only those patients who had used CPAP for >4 but ≤6 h/day were associated with a reduced risk of nonfatal and fatal stroke (HR 0.38, 95 % CI 0.2–0.7, p=0.005) or nonfatal stroke alone (HR 0.41, 95 % CI 0.2–0.8, p=0.01) in comparison to controls, while patients with a higher or lower CPAP usage were not **(Tables 12–13)**. However, when the model was adjusted only for AF, a significant association between patients with CPAP use of either >4 but ≤6 h/day

(HR 0.65, 95 % CI 0.4–1.0, p=0.047) or >6 h/day (HR 0.41, 95 % CI 0.2–0.8, p=0.009) and a reduced risk of stroke was observed compared to controls, but not among those with CPAP use of ≤4 h/day (HR 0.42, 95 % CI 0.2–1.2, p=0.09).

Table 12. Adjusted hazard ratios (HRs) and 95 % confidence intervals (95 % CIs) predicting the time to nonfatal and fatal stroke (N=114) among the CPAP-treated patients and controls.

	Adjusted basic model* †			**Adjusted modified model*** †		
	HR	**CI 95%**	**P**	**HR**	**CI 95%**	**P**
Male gender	1.39	0.9–2.2	0.2	1.37	0.9–2.2	0.2
Age, years	1.07	1.0–1.1	*<0.001*	1.07	1.0–1.1	*<0.001*
BMI, kg/m^2	1.00	1.0–1.0	0.8	1.00	1.0–1.0	0.9
AHI, events/h	1.00	1.0–1.0	0.6	1.00	1.0–1.0	0.6
CVD‡	3.69	2.4–5.8	*<0.001*	3.73	2.4–5.8	*<0.001*
Hypertension§	1.63	0.9–2.9	0.1	1.61	0.9–2.9	0.1
AF	1.14	0.7–1.8	0.6	1.16	0.7–1.8	0.5
IFG/ T2D	1.32	0.9–1.9	0.2	1.33	0.9–2.0	0.2
COPD	0.72	0.3–1.5	0.4	0.73	0.3–1.5	0.4
CPAP treatment	0.60	0.4–0.9	*0.01*	0.59	0.4–0.9	*0.008*
>6 h/day#	0.72	0.5–1.1	0.1	0.71	0.5–1.1	0.1
>4, but ≤6 h/day#	0.38	0.2–0.8	*0.006*	0.38	0.2–0.7	*0.005*
≤4 h/day#	0.61	0.2–1.5	0.3	0.61	0.2–1.5	0.3

AF, atrial fibrillation (all diagnoses before the end of 2014, N=314); AHI, apnea-hypopnea index; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CPAP, continuous positive airway pressure; CVD, cardiovascular disease; IFG, impaired fasting glucose; T2D, type 2 diabetes.

* In the modified model, the follow-up was increased by 5 years from that of the basic model in those controls who had fatal stroke in order to compare the incidence of fatal events between the groups more reliably.

† The model was adjusted for gender, age, BMI, AHI, CVD, hypertension, AF, IFG/ T2D, COPD and CPAP treatment (CPAP vs. controls).

‡, §, # Definitions are provided in **Table 11**.

Table 13. Unadjusted and adjusted hazard ratios (HRs) and 95 % confidence intervals (95 % CIs) predicting the time to nonfatal stroke (N=107) among the CPAP-treated patients and controls.

	Unadjusted basic model*			**Adjusted basic model†**		
	HR	**CI 95%**	**P**	**HR**	**CI 95%**	**P**
Male gender	1.19	0.7–1.9	0.5	1.32	0.8–2.1	0.3
Age, years	1.08	1.1–1.1	*<0.001*	1.06	1.0–1.1	*<0.001*
BMI, kg/m^2	0.99	1.0–1.0	0.6	1.00	1.0–1.0	0.9
AHI, events/h	1.00	1.0–1.0	0.8	1.00	1.0–1.0	0.6
CVD‡	6.98	4.6–10.6	*<0.001*	3.76	2.4–6.0	*<0.001*
Hypertension§	2.28	1.3–3.9	*0.003*	1.47	0.8–2.6	0.2
AF	2.36	1.6–3.6	*<0.001*	1.23	0.8–1.9	0.4
IFG/ T2D	1.78	1.2–2.6	*0.003*	1.45	1.0–2.2	0.07
COPD	1.43	0.7–2.9	0.3	0.77	0.4–1.6	0.5
CPAP treatment	0.56	0.4–0.8	*0.003*	0.60	0.4–0.9	*0.01*
>6 h/day#	0.66	0.4–1.0	0.06	0.73	0.5–1.1	0.2
>4, but ≤6 h/day#	0.40	0.2–0.8	*0.008*	0.41	0.2–0.8	*0.01*
≤4 h/day#	0.43	0.2–1.2	0.1	0.52	0.2–1.4	0.2

AF, atrial fibrillation (all diagnoses before the end of 2014, N=314); AHI, apnea-hypopnea index; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CPAP, continuous positive airway pressure; CVD, cardiovascular disease; IFG, impaired fasting glucose; T2D, type 2 diabetes.

* Each covariate was computed separately in the model.
† The model was adjusted for gender, age, BMI, AHI, CVD, hypertension, AF, IFG/ T2D, COPD and CPAP treatment (CPAP vs. controls).
‡, §, # Definitions are provided in **Table 11**.

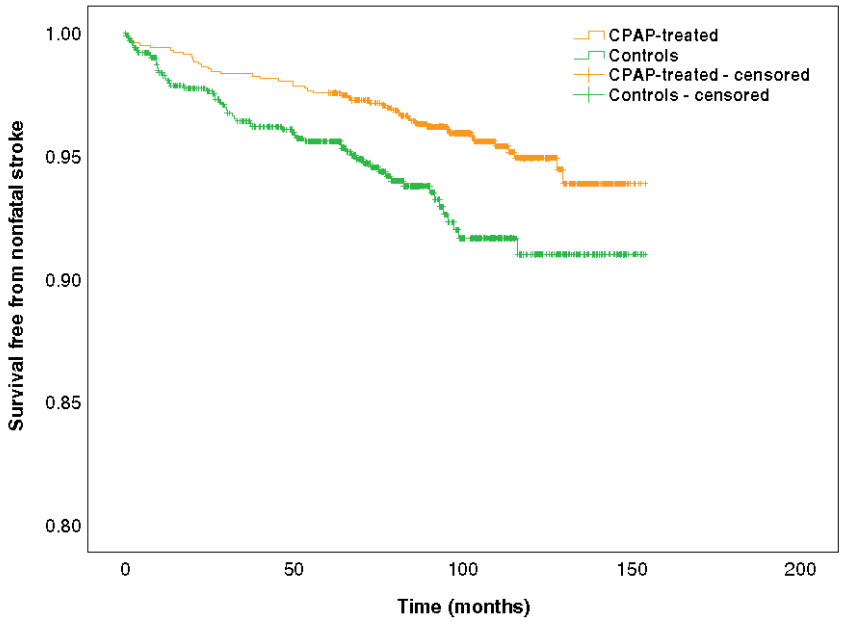


Figure 14. Survival free time from nonfatal stroke (N=107) among the CPAP-treated patients (orange, N=1030) and controls (green, N=1030).

5.3.3 All cardiac events

A nonfatal cardiac event was observed in 86 of the CPAP-treated patients and 66 of controls, while death from ischemic heart disease was found in 11 and 50 of the patients, respectively. The association between CPAP and the risk of nonfatal and fatal cardiac events was not significant in the modified Cox regression model after adjustment for confounding factors (HR 0.78, 95 % CI 0.6–1.0, p=0.1) **(Table 14)**.

A subgroup analysis found that the association became significant when patients with CPAP use of >6 h/day were compared to controls (HR 0.70, 95 % CI 0.5–1.0, p=0.04). However, when all nonfatal cardiac events (N=152) were analyzed separately, a significant association was not observed regardless of the level of CPAP use **(Table 14)**. Furthermore, no effect of CPAP was found on the primary prevention of nonfatal cardiac events, since excluding those CPAP-treated patients and controls who had an established CVD at baseline (N=186) did not change the results. Survival free time from nonfatal cardiac events is shown in unadjusted Kaplan–Meier curves **(Figure 15)**.

Table 14. Adjusted hazard ratios (HRs) and 95 % confidence intervals (95 % CIs) predicting the time to nonfatal and fatal cardiac events (N=213) or nonfatal cardiac events alone (N=152) among the CPAP-treated patients and controls.

	Nonfatal and fatal cardiac event						**Nonfatal cardiac event**		
	Adjusted basic model* †			**Adjusted modified model* †**			**Adjusted basic model* †**		
	HR	**CI 95%**	**P**	**HR**	**CI 95%**	**P**	**HR**	**CI 95%**	**P**
Male gender	1.56	1.1–2.2	*0.02*	1.57	1.1–2.3	*0.01*	1.74	1.1–2.7	*0.01*
Age, years	1.07	1.0–1.1	*<0.001*	1.07	1.0–1.1	*<0.001*	1.06	1.0–1.1	*<0.001*
BMI, kg/m^2	1.02	1.0–1.0	0.1	1.02	1.0–1.0	0.1	1.02	1.0–1.1	0.1
AHI, events/h	1.00	1.0–1.0	0.9	1.00	1.0–1.0	0.8	0.99	1.0–1.0	0.1
CVD‡	4.22	3.1–5.8	*<0.001*	4.04	2.9–5.6	*<0.001*	4.06	2.8–6.0	*<0.001*
Hypertension§	1.53	1.0–2.4	0.06	1.53	1.0–2.4	0.07	1.68	1.0–2.8	0.06
IFG/ T2D	1.83	1.4–2.4	*0.02*	1.73	1.3–2.3	*<0.001*	1.61	1.2–2.3	*0.005*
COPD	1.62	1.1–2.4	*0.02*	1.55	1.0–2.3	*0.03*	1.65	1.0–2.7	*0.04*
CPAP treatment	0.72	0.5–1.0	*0.02*	0.78	0.6–1.0	0.1	1.10	0.8–1.5	0.6
>6 h/day#	0.65	0.5–0.9	*0.01*	0.70	0.5–1.0	*0.04*	1.01	0.7–1.5	1.0
>4, but ≤6 h/day#	0.91	0.6–1.3	0.6	1.00	0.7–1.5	1.0	1.36	0.9–2.1	0.2
≤4 h/day#	0.50	0.2–1.1	0.08	0.56	0.3–1.2	0.1	0.74	0.3–1.7	0.5

Abbreviations are presented in **Table 11**.

* In the modified model, the follow-up was increased by 5 years from that of the basic model in those controls who had fatal cardiac event in order to compare the incidence of cardiac deaths between the groups more reliably.

† The model was adjusted for gender, age, BMI, AHI, CVD, hypertension, IFG/ T2D, COPD and CPAP treatment (CPAP vs. controls).

‡, §, # Definitions are provided in **Table 11**.

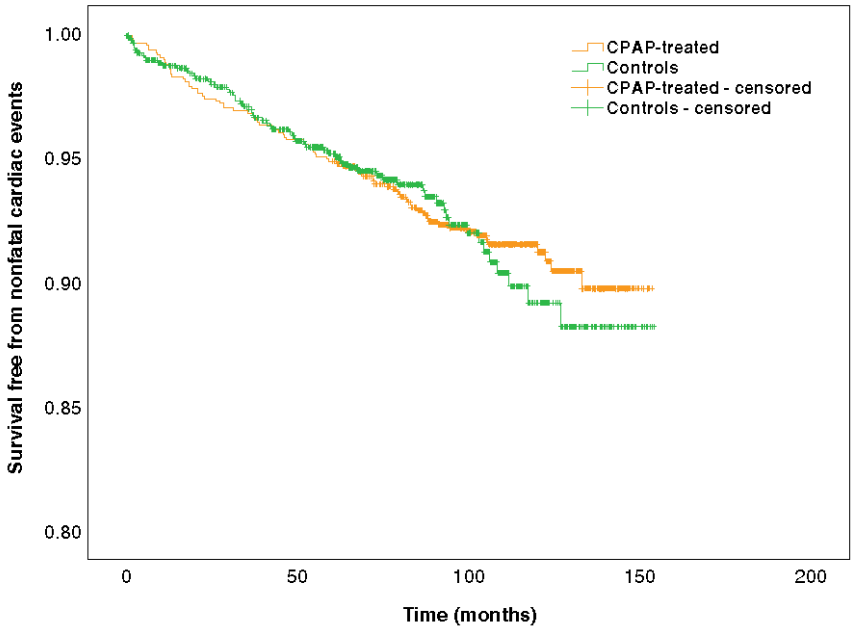


Figure 15. Survival free time from nonfatal cardiac events (N=152) among the CPAP-treated patients (orange, N=1030) and controls (green, N=1030).

5.3.4 Composite CVD events

A composite of nonfatal and fatal CVD events occurred in 14 % (N=148) of the CPAP-treated patients and in 19 % (N=194) of controls. Of these events, 22 and 79 were fatal, respectively. Stroke was the most common nonfatal CVD event in both groups **(Figure 16)**. Coronary angiography was performed for 42 of the total 81 nonfatal CAD events (52 %) among the CPAP-treated patients and for 29 of the total 60 events (48 %) among controls (p=0.7) **(Table 15)**. CPAP was independently associated with a decreased risk of a composite of nonfatal and fatal CVD events in the basic Cox regression model compared to controls (HR 0.64, CI 95 % 0.5–0.8, p <0.001). The association remained significant in the modified model (HR 0.69, 95 % CI 0.5–0.9, p=0.001). The strongest risk factor was previous CVD in both analyses and also hypertension, IFG/ T2D, male gender and older age remained independent risk factors while AHI did not **(Table 16)**.

A subgroup analysis of the modified adjusted model revealed that the association between CPAP and improved CVD outcome existed only among those who had used CPAP for >6 h/day (N=598; HR 0.64, 95 % CI 0.5–0.8, p=0.002) when compared to controls. No associations were observed among the two groups of patients with lower CPAP use **(Table 16)**, although a statistically significant difference was achieved

when those two groups were combined, and CPAP use of ≤6 h/day (N=432) was compared to controls (HR 0.75, 95 % CI 0.6–1.0, p=0.045) **(Figure 17)**. Importantly, a significant association was observed between CPAP use of >4 h/day and the primary prevention of CVDs, since CPAP use of >4, but ≤6 h/day (HR 0.68, 95 % CI 0.5–1.0, p=0.04) or >6 h/day (HR 0.50, 95 % CI 0.4–0.7, p<0.001) were both associated with a reduced risk of a composite CVD event (N=241 CVD events) after those with established CVD at baseline (N=186) were excluded from the modified model. The model was adjusted for gender, age, BMI, AHI, the prevalence of hypertension, IFG/ T2D and COPD at baseline. CPAP did not have an effect on the secondary prevention of CVDs, but however, the analysis likely lacked statistical power, since only 186 patients had CVD at baseline, and the model failed to show any significant associations between the studied covariates and the CVD outcome.

The unadjusted risk of a composite CVD event did not differ between the CPAP-treated patients with CPAP use of >6 or ≤6 h/day (HR 0.82, CI 95 % 0.6–1.1, p=0.2). Additional analyses were also conducted to evaluate the effect of smoking on the CVD risk in more detail. CPAP was associated with a decreased risk of a composite CVD event compared to controls in the adjusted modified Cox regression model (HR 0.68, 95 % CI 0.5–0.9, p=0.001), even though the data on active/ former smoking and/ or the prevalence of COPD were included as a covariate in the analysis in addition to gender, age, BMI, AHI, the prevalence of CVD, hypertension and IFG/ T2D at baseline. Furthermore, excluding active/ former smokers and/ or those with COPD (N=1252) did not change the results (HR 0.57, 95 % CI 0.4–0.8, p=0.006).

Of the 1023 CPAP-treated patients in study II, 146 patients had a composite CVD event. Of these events, 74 % occurred in patients with no significant change, 12 % in patients with a significant increase and 14 % in those with a significant decrease in CPAP adherence over a mean follow-up of 7 years. Similarly, 82 % of those who had a composite CVD event had no significant change in BMI, while 10 % had a significant increase and 8 % a significant decrease in BMI.

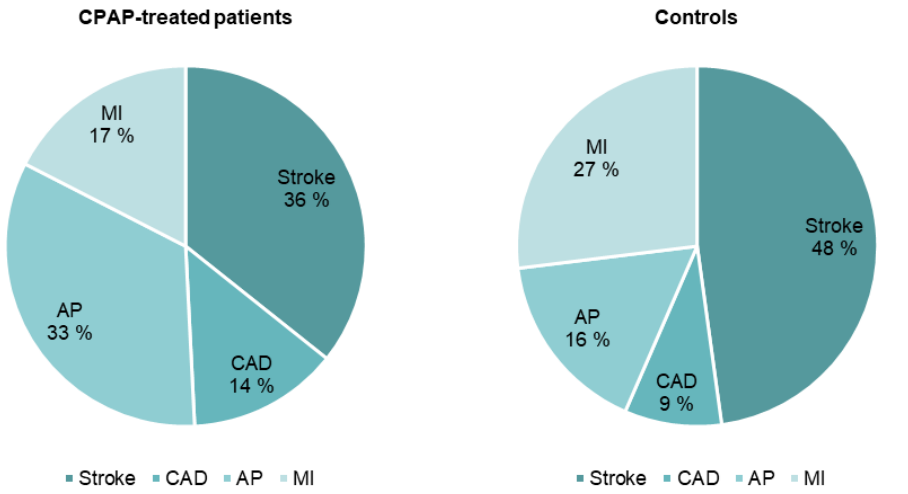


Figure 16. First occurred nonfatal cardiovascular disease events in the CPAP-treated patients (N=126) and controls (N=115) including stroke, coronary artery disease (CAD), angina pectoris (AP) and myocardial infarction (MI). Modified with permission from original publication I.

Table 15. Coronary angiography data on incident nonfatal coronary artery disease (CAD) events of the patients. Reprinted with permission from original publication I.

Coronary angiography data	CPAP-treated (N=42/1030)	Controls (N=29/1030)	Total (N=71/2060)
Findings in angiography			
CAD diagnosed and invasively treated	17	10	27
Unstable angina pectoris	8	4	12
Nonfatal myocardial infarction	17	15	32
Number of occluded coronary arteries			
Three arteries or the left main	11	7	18
Two arteries	13	8	21
One artery	18	14	32
Treatment			
Percutaneous coronary intervention	26	22	48
Coronary artery bypass grafting	11	4	15
Heart valve procedure	3	0	3
Conservative treatment	2	3	5

Data are presented as N. CPAP, continuous positive airway pressure.

Table 16. Hazard ratios (HRs) and 95 % confidence intervals (95 % CIs) predicting the time to the first nonfatal or fatal cardiovascular disease event (N=342) among the CPAP-treated patients and controls. Modified with permission from original publication I.

	Basic model*			**Modified model***					
	Adjusted HR†			**Unadjusted HR‡**			**Adjusted HR†**		
	HR	**CI 95%**	**P**	**HR**	**CI 95%**	**P**	**HR**	**CI 95%**	**P**
Male gender	1.42	1.1–1.9	*0.01*	1.25	1.0–1.6	0.09	1.39	1.1–1.8	*0.02*
Age, years	1.06	1.0–1.1	*<0.001*	1.08	1.1–1.1	*<0.001*	1.06	1.0–1.1	*<0.001*
BMI, kg/m^2	1.01	1.0–1.0	0.3	1.01	1.0–1.0	0.2	1.01	1.0–1.0	0.2
AHI, events/h	1.00	1.0–1.0	0.7	1.01	1.0–1.0	*0.04*	1.00	1.0–1.0	0.9
CVD§	4.09	3.1–5.3	*<0.001*	7.60	6.0–9.8	*<0.001*	3.69	2.8–4.8	*<0.001*
Hypertension‖	1.58	1.1–2.2	*0.008*	2.63	1.9–3.6	*<0.001*	1.57	1.1–2.2	*0.009*
IFG/ T2D	1.47	1.2–1.8	*0.001*	1.92	1.5–2.4	*<0.001*	1.39	1.1–1.7	*0.005*
COPD	1.36	1.0–1.9	0.07	2.56	1.9–3.5	*<0.001*	1.26	0.9–1.8	0.2
CPAP treatment	0.64	0.5–0.8	*<0.001*	0.55	0.4–0.7	*<0.001*	0.69	0.5–0.9	*0.001*
>6 h/day#	0.61	0.5–0.8	*<0.001*	0.51	0.4–0.7	*<0.001*	0.64	0.5–0.8	*0.002*
>4, but ≤6 h/day#	0.71	0.5–1.0	*0.03*	0.66	0.5–0.9	*0.008*	0.77	0.6–1.1	0.1
≤4 h/day#	0.62	0.4–1.0	0.07	0.51	0.3–0.9	*0.01*	0.67	0.4–1.1	0.1
Current smokerα	–	–	–	0.98	0.8–1.3	0.9	–	–	–
Cholesterolα	–	–	–	0.72	0.6–0.8	*<0.001*	–	–	–
ESS scoreα	–	–	–	0.98	1.0–1.0	0.2	–	–	–

AHI, apnea-hypopnea index; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CPAP, continuous positive airway pressure; CVD, cardiovascular disease; ESS, Epworth Sleepiness Scale (data available for 981 CPAP-treated patients and 986 controls); IFG, impaired fasting glucose; T2D, type 2 diabetes.

* In the modified model, the follow-up was increased by 5 years from that of the basic model in those controls who had CVD death in order to compare the incidence of deaths between the groups more reliably.

† The model was adjusted for gender, age, BMI, AHI, CVD, hypertension, IFG/ T2D, COPD and CPAP treatment (CPAP vs. controls).

‡ Each covariate was computed separately in the model.

§ Coronary artery disease, myocardial infarction, angina pectoris, stroke, intracranial atherosclerosis or peripheral artery disease.

‖ Blood pressure greater than 140/90 mmHg and/ or use of antihypertensive medication.

Mean CPAP usage over a median treatment period of 9 years (including missed days of use).

α History of COPD instead of smoking was used in the final adjusted model in order to better elucidate the amount of exposure. Data on serum cholesterol concentrations (mmol/l; data available for 845 CPAP-treated patients and 738 controls) and ESS score did not affect the HR of the CPAP-treated patients and were thus omitted from the final adjusted model.

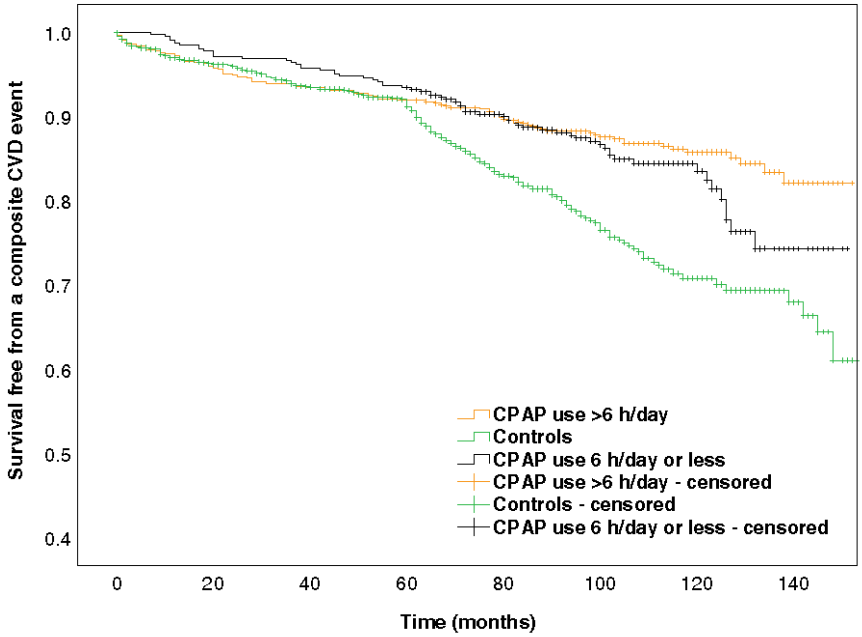


Figure 17. Survival free time from a composite of nonfatal and fatal cardiovascular disease (CVD) events (N=342) among the CPAP-treated patients with CPAP use of >6 (orange, N=598) or ≤6 h/day (black, N=432) and controls (green, N=1030). The follow-up duration was increased by 5 years in those controls who had fatal CVD event. Modified with permission from original publication I.

5.4 The association between CPAP treatment, all-cause and cancer mortality (study I)

During follow-up, 77 of the CPAP-treated patients and 215 of controls had died from any cause. The most common underlying causes of death were CVD and cancer **(Table 17)**. CPAP treatment was associated with a reduced risk of all-cause mortality independent of confounding factors both in the basic (HR 0.26, 95 % CI 0.2–0.3) and the modified Cox regression model (HR 0.60, 95 % CI 0.5–0.8) (both: p <0.001).

A subgroup analysis of the adjusted modified Cox regression model showed that the association was, however, significant only among those who had used CPAP for >6 h/day (HR 0.49, 95 % CI 0.3–0.7, p <0.001) in comparison to controls. The most significant associations were found between all-cause mortality and male gender, established CVD and psychiatric disorder. Every 1 /h-unit elevation in AHI increased the risk by 1 %. **(Table 18)**. A higher ESS score was associated with a lower risk of death in unadjusted analyses (HR 0.9–1.0, p <0.05), but the association did not remain significant after adjustment for confounding factors.

Table 17. Underlying cause of death of the CPAP-treated patients (N=77) and controls (N=215) during the study follow-up. All deaths of the patients were included.

Underlying cause of death	CPAP treated (N, %)	Controls (N, %)
Cardiovascular disease	33 (42.9)	106 (49.3)
Cancer	20 (26.0)	50 (23.3)
Pulmonary or neurological disease	7 (9.1)	17 (7.9)
Accident/ suicide/ chronic alcohol misuse	10 (13.0)	31 (14.4)
Unclear cause	3 (3.9)	4 (1.9)
Other cause	4 (5.2)	7 (3.3)

Table 18. Adjusted hazard ratios (HRs) and 95 % confidence intervals (95 % CIs) predicting the time to death from all-causes among the CPAP-treated patients and controls.

	Basic adjusted model* †			Modified adjusted model* †		
	HR	CI 95%	P	HR	CI 95%	P
Male gender	2.29	1.6–3.3	<0.001	1.95	1.4–2.7	*<0.001*
Age, years	1.09	1.1–1.1	*<0.001*	1.09	1.1–1.1	*<0.001*
BMI, kg/m^2	1.03	1.0–1.0	*0.02*	1.03	1.0–1.0	*0.01*
AHI, events/h	1.01	1.0–1.0	<0.001	1.01	1.0–1.0	*<0.001*
CVD‡	2.27	1.7–3.1	*<0.001*	2.04	1.5–2.7	<0.001
Hypertension§	1.07	0.8–1.5	0.7	1.15	0.8–1.6	0.4
IFG/ T2D	1.36	1.1–1.7	*0.02*	1.33	1.0–1.7	*0.02*
COPD	1.53	1.1–2.1	*0.02*	1.65	1.2–2.3	*0.002*
Psychiatric disorder‖	2.02	1.5–2.8	*<0.001*	2.07	1.5–2.8	<0.001
CPAP treatment	0.26	0.2–0.3	*<0.001*	0.60	0.5–0.8	*<0.001*
>6 h/day#	0.20	0.1–0.3	*<0.001*	0.49	0.3–0.7	*<0.001*
>4, but ≤6 h/day#	0.28	0.2–0.4	*<0.001*	0.68	0.4–1.0	0.07
≤4 h/day#	0.43	0.2–0.8	0.004	1.1	0.6–1.9	0.8

Abbreviations are presented in **Table 16**.

* The model was adjusted for gender, age, BMI, AHI, CVD, hypertension, IFG/ T2D, COPD, psychiatric disorder and CPAP treatment (CPAP vs. controls).
† In the modified model, the follow-up of all controls was increased by 5 years from that of the basic model in order to compare the incidence of deaths between the groups more reliably.
‡, §, # Definitions are provided in **Table 16**.
‖ Depression, anxiety or psychotic disorder.

Death from cancer occurred in 20 of the CPAP-treated patients and 50 of controls. The most common cancers leading to death included gastroenterological cancers (N=30, 43 %), urological/ gynecological cancers (N=16, 23 %), hematological cancers/ lymphoma (N=8, 11 %) and lung cancers (N=8, 11 %). A significant association between CPAP treatment and a reduced risk of death from cancer was not observed in the modified Cox regression model after adjustment for confounding factors (HR 0.76, 95 % CI 0.4–1.3, p=0.3). The association remained insignificant regardless of the level of CPAP use. The strongest predictors of cancer mortality were COPD, male gender and older age **(Table 19)**.

Table 19. Adjusted hazard ratios (HRs) and 95 % confidence intervals (95 % CIs) predicting the time to death from cancer among the CPAP-treated patients and controls.

	Basic adjusted model* †			**Modified adjusted model*** †		
	HR	**CI 95%**	**P**	**HR**	**CI 95%**	**P**
Male gender	1.98	1.0–3.8	*0.04*	1.95	1.0–3.8	*0.045*
Age, years	1.11	1.1–1.1	*<0.001*	1.11	1.1–1.1	*<0.001*
BMI, kg/m^2	1.05	1.0–1.1	*0.03*	1.04	1.0–1.1	*0.04*
AHI, events/h	1.01	1.0–1.0	0.2	1.01	1.0–1.0	0.2
CVD‡	1.63	0.9–3.0	0.1	1.45	0.8–2.7	0.2
Hypertension§	0.77	0.4–1.5	0.4	0.77	0.4–1.4	0.4
IFG/ T2D	1.14	0.7–1.9	0.6	1.17	0.7–1.9	0.5
COPD	2.65	1.5–4.7	*0.001*	2.70	1.5–4.8	*0.001*
CPAP treatment	0.27	0.2–0.5	*<0.001*	0.76	0.4–1.3	0.3
>6 h/day#	0.25	0.1–0.5	*<0.001*	0.70	0.3–1.4	0.3
>4, but ≤6 h/day#	0.30	0.1–0.7	*0.003*	0.85	0.4–1.9	0.7
≤4 h/day#	0.32	0.1–1.3	0.1	0.92	0.2–3.9	0.9

Abbreviations are presented in **Table 16**.

* The model was adjusted for gender, age, BMI, AHI, CVD, hypertension, IFG/ T2D, COPD and CPAP treatment (CPAP vs. controls).
† In the modified model, the follow-up of all controls was increased by 5 years from that of the basic model in order to compare the incidence of deaths between the groups more reliably.
‡, §, # Definitions are provided in **Table 16**.

5.5 The association between CPAP treatment and body mass index (study II)

At baseline, the mean BMI was 34 ± 6 kg/m^2, and 67 % of the 1023 CPAP-treated patients were obese (BMI >30 kg/m^2). Those aged ≤40 years (N=59) had a significantly higher BMI than older patients (37 ± 9 vs. 33 ± 6 kg/m^2, p <0.001). A positive correlation between AHI and BMI was also shown (R^2 = 0.24, p <0.001).

The mean change in BMI during CPAP treatment was 0.06 ± 0.4 kg/m^2 per year over a mean follow-up of 7 years at the cohort level. At the individual level, 84 % of the patients showed no significant change, whereas 10 % had a significant increase (an average of 0.6 ± 0.4 kg/m^2 per year) and 6 % a significant decrease (an average of 0.5 ± 0.4 kg/m^2 per year) in BMI during treatment **(Figures 18–19)**. Differences were observed between the patients with a significant increase in BMI and the rest of the cohort **(Table 20)**.

In the multivariate logistic regression analysis, male gender, current smoking, a higher BMI, younger age and a higher GHQ-12 score at baseline in addition to an ascending GHQ-12 slope were associated with a significant increase in BMI during CPAP treatment. The odds of having a significant decrease in BMI was decreased by an ascending CPAP adherence slope, while no other associations were observed **(Table 21)**.

5.6 The association between CPAP treatment and daytime sleepiness and psychological distress (study II)

The majority of the 1023 CPAP-treated patients were non-sleepy, since EDS (ESS ≥11) was reported only by 37 % of the patients. The mean ESS and GHQ-12 scores were 9 ± 5 and 3 ± 4, respectively. Women had a higher GHQ-12 score compared to men, but no gender difference was observed in ESS score at baseline (**Table 5)**. Correlation between AHI and ESS (R^2 = 0.05, p=0.1) or GHQ-12 (R^2 = −0.04, p=0.3) score was not observed, whereas BMI correlated weakly with ESS (R^2 = 0.11, p=0.001) and GHQ-12 (R^2 = 0.09, p=0.007) scores.

After a mean follow-up of 7 years, the mean ESS and GHQ-12 slopes of the cohort were both slightly descending (ESS slope −0.6 ± 0.7 and GHQ-12 slope −0.2 ± 0.6 change of score/year), suggesting that daytime sleepiness and psychological distress tended to reduce during CPAP treatment for the majority of the patients.

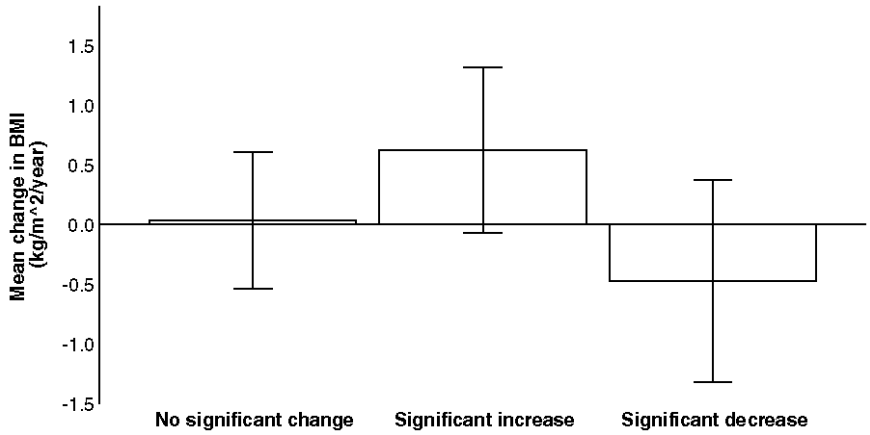


Figure 18. Mean annual change in body mass index (BMI) over a mean CPAP treatment period of 7 years at the individual level (N=1023). Modified with permission from original publication II.

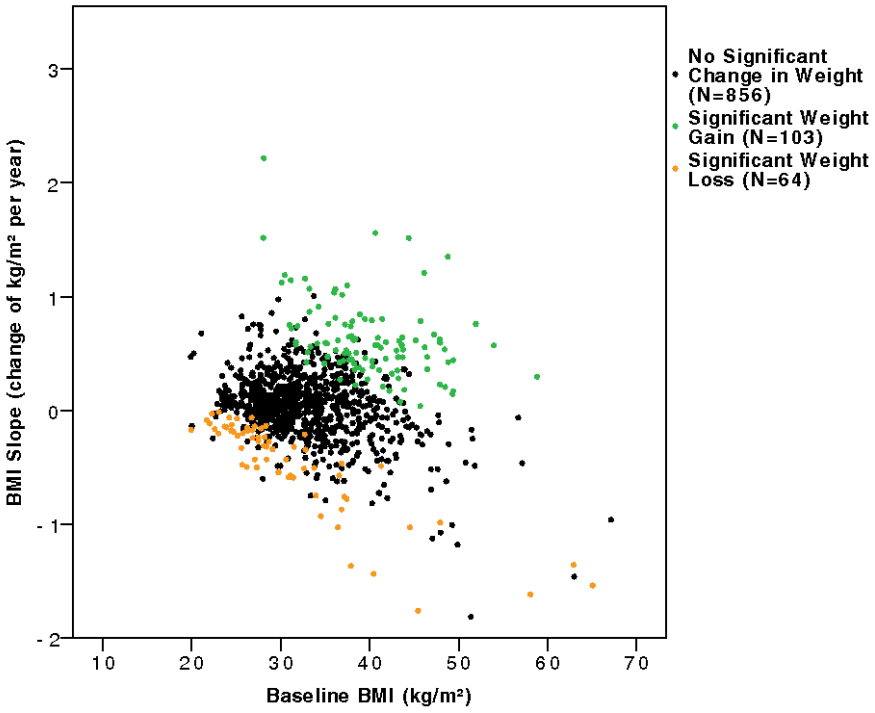


Figure 19. Individual body mass index (BMI) development during CPAP treatment in relation to the BMI at the beginning of treatment. Reprinted with permission from original publication II.

Table 20. Comparison of the baseline characteristics between the patients with a significant increase in body mass index (BMI) and the rest of the cohort.

	Significant increase in BMI* (N=103)	The rest of the cohort (N=920)	P
Patient characteristics			
Age, years (mean, SD)	50.9 ± 9.5	56.1 ± 9.7	*<0.001*
Male gender (N, %)	89 (86.4)	686 (74.6)	*0.008*
BMI, kg/m^2 (mean, SD)	40.0 ± 5.9	32.8 ± 6.0	*<0.001*
OSA and questionnaires			
AHI, events/h (mean, SD)	38.8 ± 26.3	33.1 ± 22.7	*0.02*
ESS score (mean, SD)	10.0 ± 4.3	9.3 ± 4.7	0.2
GHQ-12 score (mean, SD)	4.1 ± 4.0	3.2 ± 3.5	*0.04*
Comorbidity and lifestyle			
IFG/ T2D (N, %)	57 (55.3)	355 (38.6)	*0.001*
Hypertension† (N, %)	89 (86.4)	694 (75.4)	*0.01*
CVD‡ (N, %)	9 (8.7)	46 (5.0)	0.1
Asthma (N, %)	7 (6.8)	93 (10.1)	0.3
COPD (N, %)	3 (2.9)	43 (4.7)	0.4
Psychiatric disorder§ (N, %)	21 (20.4)	140 (15.2)	0.2
Current smoking (N, %)	35 (34.0)	189 (20.5)	*0.002*

Data are presented as N (%) or mean ± standard deviation (SD). AHI, apnea-hypopnea index; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CPAP, continuous positive airway pressure; CVD, cardiovascular disease; ESS, Epworth Sleepiness Scale (N=977); GHQ-12, General Health Questionnaire (N=908); IFG, impaired fasting glucose; T2D, type 2 diabetes.

* Patients with an ascending trend in BMI over a mean CPAP treatment period of 7 years at the posterior probability level of >90%.
† Blood pressure greater than 140/90 mmHg and/ or use of antihypertensive medication.
‡ Coronary artery disease, myocardial infarction, angina pectoris, stroke, intracranial atherosclerosis or peripheral artery disease.
§ Depression, anxiety or psychotic disorder.

Table 21. Associations between the clinical characteristics and significant change in BMI during CPAP treatment determined by the multivariate logistic regression analysis. Modified with permission from original publication II.

	Significant increase in BMI*		**Significant decrease in BMI***	
	OR (CI 95 %)	**P**	**OR (CI 95 %)**	**P**
Patient characteristics				
Age, years	0.96 (0.9–1.0)	*0.01*	1.03 (1.0–1.1)	0.1
Male gender	5.13 (2.2–11.8)	*<0.001*	2.12 (0.9–5.0)	0.09
BMI, kg/m^2	1.18 (1.1–1.2)	*<0.001*	0.97 (0.9–1.0)	0.3
OSA and questionnaires				
AHI, events/h	1.00 (1.0–1.0)	0.5	1.01 (1.0–1.0)	0.4
ESS score	1.02 (1.0–1.1)	0.6	0.91 (0.8–1.0)	0.05
GHQ-12 score	1.10 (1.0–1.2)	*0.03*	1.11 (1.0–1.2)	0.09
Comorbidity and lifestyle				
IFG/ T2D	0.98 (0.6–1.7)	0.9	0.69 (0.3–1.4)	0.3
Hypertension†	1.48 (0.7–3.0)	0.3	0.71 (0.3–1.4)	0.3
CVD‡	1.98 (0.8–5.1)	0.2	2.14 (0.7–6.9)	0.2
Psychiatric disorder§	0.85 (0.4–1.7)	0.7	0.36 (0.1–1.3)	0.1
Current smoking	1.80 (1.0–3.1)	*0.04*	1.62 (0.8–3.4)	0.2
Follow-up characteristics				
CPAP adherence slope‖	2.12 (0.5–8.3)	0.3	0.03 (0.0–0.1)	*<0.001*
ESS slope‖	1.47 (0.9–2.3)	0.1	0.69 (0.4–1.2)	0.2
GHQ-12 slope‖	1.76 (1.1–2.8)	*0.02*	1.12 (0.6–2.2)	0.8

Data are presented as odds ratios (ORs) and 95 % confidence intervals (95 % CIs). Abbreviations are presented in **Table 20**.

* Patients with an ascending (significant increase) or a descending (significant decrease) trend in BMI over a mean CPAP treatment period of 7 years at the posterior probability level of >90 %.
†, ‡, § Definitions are provided in **Table 20**.
‖ Annual change in CPAP adherence, ESS (N=948) or GHQ-12 score (N=948) over a mean CPAP treatment period of 7 years.

5.7 The association between CPAP treatment and MVAs (study III)

5.7.1 CPAP-treated patients before and after the initiation of CPAP treatment

Of the 1030 CPAP-treated patients, MVAs were registered in 30 patients before and 39 patients after CPAP. The observation period in both was 9 years on average. Of the latter, 3 MVAs occurred after a several months' break from CPAP and were thus excluded from the analyses. Two patients had multiple accidents. The incidence of MVAs per 1000 person years was 3.2 (95 % CI 2.3–4.6) before and 3.9 (95 % CI 2.8–5.3) after CPAP **(Figure 20)**. Risk for having an MVA did not differ between the after and before treatment groups (RR 1.2, 95 % CI 0.7–1.9, p=0.5).

CPAP usage did not differ between those who had or did not have an MVA (median 6.4, IQR 2.2 vs. 6.4, IQR 2.3 h/day, p=0.8). Furthermore, the MVA incidence did not differ when patients with CPAP use of ≥4 h/day were compared before-after **(Figure 20)** or to those with lower usage. Patients with CPAP use of ≥6 h/day similarly did not differ from those who had used it for <6 h/day **(Figure 21)**.

Of the 36 CPAP-treated patients with MVA after CPAP in study III, 14 % had a significant increase, 11 % a significant decrease, while 75 % had no significant change in adherence over a mean follow-up of 7 years in study II. A significant increase and decrease in BMI were similarly observed in 28 % and <9 % of the patients, respectively, while the majority had no significant change. The ESS (-0.5 ± 0.5 vs. -0.6 ± 0.7 score/ year, p=0.5) or the GHQ-12 (-0.1 ± 0.5 vs. -0.2 ± 0.6, p=0.5) slopes over a mean follow-up of 7 years in study II did not differ between those who had or did not have an MVA. Overall, a mean increase of 1.2 ± 3.7 kg/m^2-units in BMI and a mean decrease of 3.7 ± 3.6 scores in ESS were found in the CPAP-treated patients with MVA during the median treatment period of 9 years in study III.

5.7.2 CPAP-treated patients after the initiation of CPAP and control patients

MVAs were registered in 17 of the 1030 controls, and the MVA incidence per 1000 person years was 2.6 (95 % CI 1.6–4.1). None of them had multiple accidents. The risk for having an MVA did not differ from CPAP-treated patients when all CPAP-treated patients (RR 1.5, 95 % CI 0.9–2.7, p=0.2) or only those with CPAP use of ≥4 h/day were compared to controls **(Figure 20)**. The results did not change when all CPAP-treated patients (RR 1.8, 95 % CI 1.0–3.5, p=0.06) or those with CPAP use of ≥4 h/day (RR 1.8, 95 % CI 1.0–3.5, p=0.07) were compared to controls who had not used MAD after CPAP (N=965, incidence of MVAs 2.1, 95 % CI 1.2–3.6).

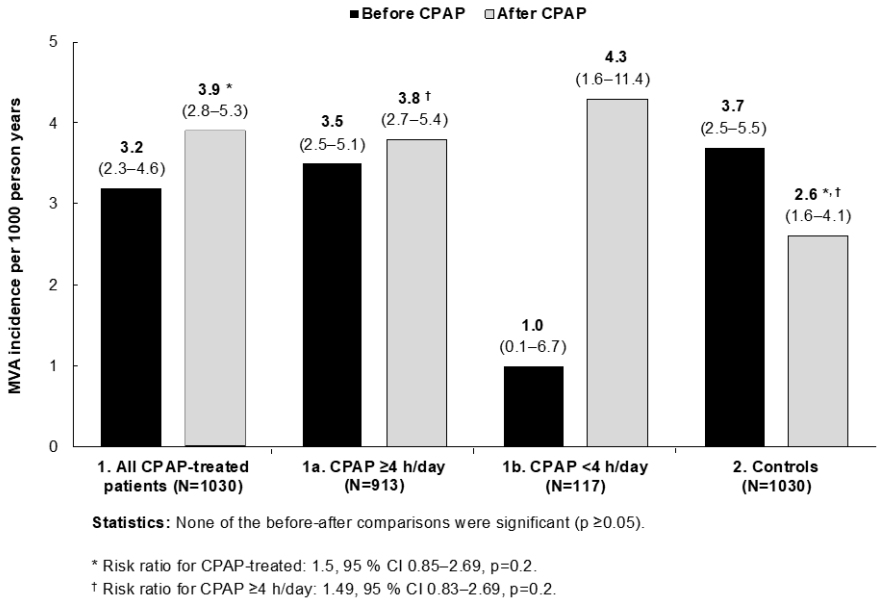


Figure 20. Incidence of motor vehicle accidents (MVAs) per 1000 person years 9 years before and after CPAP in 1) all CPAP-treated patients, in those with 1a) CPAP use of ≥4 h/day or 1b) <4 h/day, and in 2) controls 6.5 years before and after the discontinuation of CPAP. Modified with permission from original publication III.

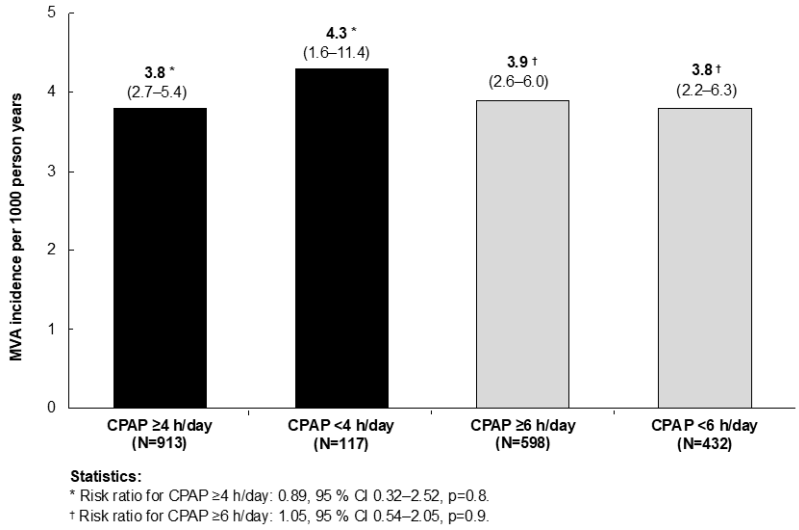


Figure 21. Incidence of motor vehicle accidents (MVAs) per 1000 person years 9 years after CPAP treatment according to the level of CPAP use. Modified with permission from original publication III.

Compared to the rest of the cohort, the CPAP-treated patients and controls with MVA (N=53) were more frequently men, younger and had a higher prevalence of smokers. No differences were observed in terms of baseline ESS or GHQ-12 score or other comorbidities **(Table 22)**. Male gender was associated with a 5.5-fold (95 % CI 1.7–17.6, p=0.004) and current smoking with a 2.4-fold (1.4–4.1, p=0.002) increased risk for MVAs in an unadjusted Cox regression model, whereas a 1-year elevation in age reduced the risk by 4 % (HR 0.96, 95 % CI 0.9–1.0, p=0.001).

An AHI of ≥15 /h was not associated with an increased risk of MVAs compared to <15 /h when all patients (HR 1.4, 95 % CI 0.7–2.8, p=0.3) or only controls (HR 2.5, 95 % CI 0.6–11.0, p=0.2) were analyzed. However, HR tended to increase with increasing AHI among controls, since HRs were 3.0 (95 % CI 0.6–14.2) and 2.1 (95 % CI 0.4–10.2) for those with an AHI of ≥30 /h or ≥15 but <30 /h, respectively, when compared to a lower AHI of <15 /h (p ≥0.05).

Among patients with MVA, the only baseline difference was higher BMI in CPAP-treated patients than controls (median 34 vs. 31 kg/m^2, p=0.03). Interestingly, a BMI of ≥30 kg/m^2 was associated with an increased risk for MVAs only among the CPAP-treated patients (HR 2.45, 95 % CI 1.0–5.9, p=0.045) but not among controls. The association remained significant after the Cox regression model was adjusted for age, gender, smoking and an AHI of ≥15 /h (HR 2.43, 95 % CI 1.0–5.9, p=0.049). The prevalence of CVD and the number of professional drivers were low and did not differ between the groups. No differences were observed in sleep study data **(Table 22)** or accident conditions, including the hour of the accident **(Table 23)**.

Time to the first MVA was almost three times longer among CPAP-treated patients than among controls (median 43 vs. 15 months, p=0.02). A further analysis revealed that the MVA incidence did not, however, significantly differ between the groups when the length of observation was reduced in both groups to 2 (MVAs N=11 vs. N=12, p=0.8, respectively), 3.5 (MVAs N=21 vs. N=12, p=0.1, respectively), or 5 (MVAs N=26 vs. N=14, p=0.06, respectively) years.

Table 22. Comparison of the baseline characteristics between the CPAP-treated patients and controls with a motor vehicle accident (MVA), and between the patients with and without an MVA. Modified with permission from original publication III.

	CPAP vs. Controls			MVA vs. without MVA		
	MVA CPAP (N=36)	**MVA Controls (N=17)**	**P**	**MVA Total (N=53)**	**Without MVA (N=2007)**	**P**
Patient characteristics						
Male gender, %	91.7	100.0	0.2	94.3	75.3	*<0.001*
Age, years (mean, SD)	51.5 ± 10.1	49.6 ± 12.3	0.6	50.9 ± 10.8	56.1 ± 10.4	*<0.001*
BMI, kg/m^2 (median, IQR)	34.2 (6.7) ‡	31.3 (7.5)	*0.03*	33.2 (7.6)	32.0 (8.1) ‡	0.3
OSA & questionnaires						
AHI, events/h (median, IQR)	28.0 (28.5)	25.0 (38.0)	0.9	27.0 (28.5)	28.0 (30.0)	0.4
ODI4/5, /h (median, IQR)	14.6 (25.4)	21.1 (26.8)	0.8	15.1 (24.1)	–	–
SpO_2, % (median, IQR)						
Mean	93.5 (2.8)	93.3 (3.1)	0.7	93.4 (3.0)	–	–
Minimum	82.0 (10.3)	78.0 (11.0)	0.4	81.3 (11.0)	–	–
T90	5.5 (15.2)	8.5 (31.4)	0.6	6.2 (24.4)	–	–
ESS						
Mean score (SD)	8.8 ± 3.9	6.4 ± 4.8	0.06	8.1 ± 4.3	8.8 ± 4.7	0.2
≥16 scores, %	5.6	6.3	0.9	5.8	10.1	0.3
GHQ-12 (median, IQR)	1.0 (6.0)	1.0 (4.0)	0.4	1.0 (6.0)	2.0 (6.0)	0.2
Comorbidity & lifestyle						
IFG/ T2D, %	41.7	29.4	0.4	37.7	37.8	1.0
Hypertension/CVD*, %	61.1	70.6	0.5	64.2	73.6	0.1
Psychiatric disorder†, %	22.2	17.6	0.7	20.8	16.9	0.5
Current smoking, %	41.7	47.1	0.7	43.4	24.9	*0.002*

Data are presented as % or mean ± standard deviation (SD) or median and interquartile range (IQR). AHI, apnea-hypopnea index; BMI, body mass index; CPAP, continuous positive airway pressure; ESS, Epworth Sleepiness Scale (N=1967); GHQ-12, General Health Questionnaire (N=1859); IFG, impaired fasting glucose; ODI4/5, oxygen desaturation index of ≥4 or ≥5 % (N=50); OSA, obstructive sleep apnea; SpO_2, level of blood oxygen saturation [mean (N=49), minimum (N=49), T90 (N=38)]; T2D, type 2 diabetes; T90, percentage of time spent under SpO_2 of 90 %.

* Blood pressure greater than 140/90 mmHg and/ or use of antihypertensive medication or coronary artery disease, myocardial infarction, angina pectoris, stroke, intracranial atherosclerosis or peripheral artery disease.

† Depression, anxiety or psychotic disorder.

‡ BMI of the CPAP-treated patients with MVA compared to that among those without MVA, p=0.04.

Table 23. Comparison of the characteristics of motor vehicle accidents between the CPAP-treated patients and controls. Reprinted with permission from original publication III.

	MVA CPAP (N=36)	MVA controls (N=17)	P
Time to the accident, months* (median, IQR)	42.5 (48.5)	15.0 (41.5)	*0.02*
Time of day, hour, %			
8:00 p.m.–7:59 a.m.	22.2	29.4	0.6§
8:00 a.m.–7:59 p.m.	77.8	70.6	
Autumn/ winter, %	50.0	47.1	0.8
Weather/ road surface condition worsen†, %	44.4	29.4	0.3
Speed limit ≥60 km/h, %	41.7	47.1	0.7
Outside urban area, %	44.4	41.2	0.8
Junction or traffic lights, %	41.7	58.8	0.2
Alcohol/ drug/ medicine use, %	11.1	17.6	0.5
DL CDE, %	62.9	66.7	0.8
Vehicle type‡, %			
Car, moped or motorcycle	83.3	82.4	0.9§
Heavy vehicle	16.7	17.6	
Injured, %	38.9	41.2	0.9

Data are presented as % or median and interquartile range (IQR). CPAP, continuous positive airway pressure; DL, driver's license (data missing for 1 CPAP-treated and 5 control patients); MVA, motor vehicle accident.

* Time from study baseline to the occurrence of motor vehicle accident.
† The presence of fog, rain or snow or road surface bare and wet, snowy or icy.
‡ Car including passenger car, van, truck ≤3500 kg; heavy vehicle including truck >3500 kg, bus.
§ P value for the trend.

5.8 Patients with a normal apnea-hypopnea index treated with CPAP (studies I–III)

Of the 1023 CPAP-treated patients in study II, 47 patients with an AHI of <5 /h fulfilled the study's inclusion criteria, and were thus, included in the statistical analyses. Later during the data collection of the studies I and III, among 3 of these patients the previously observed normal AHI was discovered to be measured during CPAP treatment. Thus, the corrected number of patients with an AHI of <5 /h was 44 out of the 1023 patients (4 %). On this account, the difference in IFG/ T2D prevalence became significant when patients with an AHI of <5 /h and the rest of the cohort were compared.

Like the rest of the cohort, patients with an AHI of <5 /h were highly adherent to CPAP, since they did not differ in terms of short- or long-term use of CPAP or the mean CPAP usage slope. Differences in the mean BMI, ESS or GHQ-12 slopes were also not observed between the groups. However, they were more often women and had a higher prevalence of psychiatric disorders, while the prevalence of IFG/ T2D and hypertension were lower compared to the rest of the cohort. The prevalence of CVDs was low and did not differ **(Table 24)**.

Of all the CPAP-treated patients and controls with an AHI of <5 /h (N=86), a composite CVD event was observed in 11 of the patients (12.8 %). Of these patients, 7 had been treated with CPAP and 4 were controls. In the adjusted Cox regression model, the risk of a composite CVD event (HR 0.97, 95 % CI 0.4–2.7, p=1.0), CVD death (HR 0.60, 95 % CI 0.08–4.4, p=0.6) or all-cause mortality (HR 0.68, 95 % CI 0.2–2.2, p=0.5) did not differ between the controls with an AHI of <5 /h (N=42) and the rest of the controls with a higher AHI. The incidence of MVAs among all the patients with an AHI of <5 /h was low (≤3.5 % of the patients).

Table 24. Comparison of the characteristics between the CPAP-treated patients with an apnea-hypopnea index (AHI) of <5 /h and the rest of the cohort.

	AHI <5 /h (N=44)	The rest of the cohort (N=979)	P
Patient characteristics (N, % or mean, SD)			
Female gender	18 (40.9)	230 (23.5)	*0.008*
Age, years	53.5 ± 9.1	55.7 ± 9.8	0.1
BMI, kg/m^2	31.9 ± 5.3	33.6 ± 6.4	0.09
Questionnaires (mean, SD)			
ESS score	9.5 ± 5.1	9.4 ± 4.7	0.9
GHQ-12 score	3.1 ± 3.1	3.3 ± 3.6	0.7
Comorbidity and lifestyle (N, %)			
Impaired fasting glucose/ type 2 diabetes	10 (22.7)	402 (41.1)	*0.02*
Hypertension*	27 (61.4)	756 (77.2)	*0.02*
Asthma	7 (15.9)	93 (9.5)	0.2
Chronic obstructive pulmonary disease	3 (6.8)	43 (4.4)	0.4
Psychiatric disorder†	16 (36.4)	145 (14.8)	*<0.001*
Current smoking	8 (18.2)	216 (22.1)	0.5
Follow-up characteristics (mean, SD)			
Short-term use, h/day‡	5.3 ± 1.8	5.2 ± 2.80	0.8
Long-term use, h/day §	6.2 ± 1.8	6.0 ± 1.8	0.5
Usage slope, (h/day)/year‖	0.2 ± 0.2	0.2 ± 0.2	0.8
BMI slope, (kg/m^2)/year‖	0.1 ± 0.3	0.1 ± 0.4	0.2
ESS slope, score/year‖	-0.5 ± 0.7	-0.6 ± 0.7	0.3
GHQ-12 slope, score/year‖	0.0 ± 0.6	-0.2 ± 0.6	0.1

Data are presented as N (%) or mean ± standard deviation (SD). BMI, body mass index; CPAP, continuous positive airway pressure; ESS, Epworth Sleepiness Scale (data available for 977 patients); GHQ-12, General Health Questionnaire (data available for 908 patients).

* Blood pressure greater than 140/90 mmHg and/ or use of antihypertensive medication.
† Depression, anxiety or psychotic disorder.
‡ Mean CPAP usage from the commencement of CPAP either until the first follow-up visit or alternatively until the 6-month follow-up visit (including missed days of use) (N=1017).
§ Mean CPAP usage over a mean treatment period of 7 years (including missed days of use).
‖ Annual change in CPAP adherence, BMI, ESS (N=948) or GHQ-12 score (N=948) over a mean treatment period of 7 years.

6 DISCUSSION

The main finding of this thesis was that CPAP adherence had a major impact on CVD outcome, since only those who had used CPAP for >6 h/day had a reduced risk of CVD death, a composite of cardiac events and all-cause mortality compared to controls independent of confounding factors. No association was found between AHI and the risk of CVD events or MVAs, implying that different OSA phenotypes may be related to different outcomes, and the effectiveness of CPAP may also differ between these phenotypes. Thus, the question may not only be whether CPAP is beneficial in reducing CVD risk, other comorbidities or MVAs in OSAS, but also which populations are likely to benefit the most from CPAP and at what level of compliance this may be achieved. Furthermore, patients with an AHI of <15 /h were shown to adhere to CPAP similar to those who had a higher AHI, suggesting that the evaluation of the need for treatment should not be merely based on AHI. Finally, this thesis further emphasized the importance of lifestyle interventions, since 10 % of the patients gained significantly weight during CPAP treatment.

This thesis is based on real-world, retrospective observational studies, since all patients who had sufficient data on the assessment of OSAS and follow-up were included without further selection. Its results may be extrapolated to the clinic-based population but with caution to the general population. The methods used and the statistical aspects, in addition to the results obtained, are discussed in detail next.

6.1 Methodology

6.1.1 Subject selection and characteristics of the included patients

All the CPAP-treated subjects included in the study had initiated CPAP treatment for OSAS at the Department of Pulmonary Diseases at the Turku University Hospital during 2002–2006. The only inclusion criteria were long-term use of CPAP (≥5 years) in addition to adequate data on sleep studies and follow-up (≥4 follow-up visits). Study II further excluded from the analyses those who had engaged in bariatric surgery during treatment to more reliably investigate the associations

between CPAP and weight changes. Studies I and III selected controls from the same group as the CPAP-treated patients in order to minimize the selection bias. All included controls had adequate data on sleep studies, and they had discontinued CPAP treatment within 5 years (median 4 months) despite their doctor's advice.

CPAP-treated patients and their controls were matched according to age, gender and AHI, but however, the CPAP-treated patients did have a higher BMI in addition to a higher prevalence of IFG/ T2D and hypertension at baseline, while CVD, COPD and smoking were more common among controls.

6.1.2 Diagnosis of OSAS

All the 2060 included patients had OSA-related symptoms (e.g. daytime sleepiness, witnessed apnea) and were referred to an ambulatory or an in-hospital cardiorespiratory polygraphy to verify their OSAS. CPAP treatment was generally recommended for patients who had an AHI of ≥15 /h. Among those with a lower AHI, the need for treatment was assessed individually based on the patients' symptoms and clinical findings strongly suggestive for OSAS. The initiation of CPAP in the region was centralized in the Department of Pulmonary Diseases, which likely reduced the selection bias of the patients.

6.1.3 Study design, data collection and statistical aspects

Careful manual examination of the electronic medical records enabled gathering of data on basic patient characteristics, sleep studies, self-administered questionnaires, comorbidities and other CVD risk factors both at baseline and follow-up visits. The data on adherence and treatment pressure were accurate and objective, since they were measured by an inbuilt-counter clock of the CPAP device. Mean long-term adherence to CPAP reported the mean CPAP usage over the entire treatment period (including missed days of use). Finland's national registries on all-cause death and the incidence of police-reported MVAs enabled the gathering of objective data on these outcomes.

The prevalence of patients engaging in bariatric surgery during study follow-up did not differ between the CPAP-treated patients and controls. Only a minority of controls had been treated with MAD after CPAP, and there were no reassurances regarding whether they had been compliant or continued the treatment. The exclusion of these controls did not change the results on the associations between CPAP and CVD or MVA incidence in the Cox regression or Poisson regression models, and thus, they were included in the final analyses. Furthermore, the follow-up durations of controls were modified in those Cox regression models, which included death as an endpoint or as a composite of an endpoint, since none of the

CPAP-treated patients could have died during the first 5 years due to the inclusion criteria of long-term CPAP treatment for the study. Time to death was used in the analyses of CPAP-treated patients with death as an endpoint. It was assumed that they had continued CPAP until death, since a follow-up visit cannot occur afterwards. Among those CPAP-treated patients who did not have death as an endpoint, follow-up ended with the last CPAP follow-up visit.

Individual slope values of both BMI and CPAP adherence were determined for each CPAP-treated patient based on the linear mixed model. The Bayesian Hierarchical model and the Monte Carlo simulation were used to account for model uncertainty and to minimize the effect of within-patient variation. Patients with a significant constant change were identified at the posterior probability level of >90 %. A multivariate logistic regression was further used to identify clinical variables that could potentially explicate differences between the patients.

6.2 Beyond the apnea-hypopnea index

CPAP treatment has been generally recommended for patients with an AHI of ≥15 /h and for milder OSA in the presence of OSA-related symptoms or comorbidities (Chowdhuri et al. 2016, Gay et al. 2006, Loube et al. 1999). This thesis found that approximately one quarter of the CPAP-treated patients had an AHI of <15 /h. Patients with an AHI of <5 /h were also highly adherent to CPAP similar to those who had a higher AHI. They were more frequently women and had a higher prevalence of psychiatric disorders, while IFG/ T2D and hypertension were more common among the rest of the cohort. The ESS scores decreased similarly in both groups during treatment. Furthermore, no differences were observed in the risk of a composite CVD event when untreated patients with an AHI of <15 /h, or <5 /h were compared to those with a higher AHI, although among the latter the statistical power may not have been sufficient to detect a significant difference due to a small sample size. Those with an AHI of ≥15 /h did have an independent higher risk of all-cause mortality, while the risk for MVAs did not differ.

The results of this thesis imply that the use of AHI alone is not a good predictor in the assessment of adherence to CPAP or the risk for CVD events, weight changes or MVAs. However, it should be acknowledged that AHI was determined by cardiorespiratory polygraphy, which has been shown to underestimate the AHI by approximately 20 to 30 % compared to PSG since an EEG is not included (Escourrou et al. 2015, Hedner et al. 2011). All studied patients were examined with the same approach, which should minimize the bias related to the AHI assessment. Night-to-night variability may also lead to false negative results in a sleep study (Skiba et al. 2015), and especially females with an AHI of <5 /h may have had prolonged episodes of partial upper airway obstruction, which could partly explain the good CPAP

adherence in this patient group (Anttalainen et al. 2016b). Furthermore, an OSAS diagnosis was not usually repeated during follow-up; thus, an OSAS resolution or progression in some patients over time cannot be excluded.

More recent studies have focused on identifying different OSA phenotypes based on the complex pathophysiology, diverse symptoms, OSA-related comorbidities and polysomnographic findings instead of classifying patients merely according to AHI (Zinchuk & Yaggi 2020). Hypothesis-driven (traditional regression analyses) and hypothesis-generating (cluster analyses, such as K-means analyses) methods have been used to identify different OSA phenotypes (Zinchuk & Yaggi 2020). The PALM scale was developed to assess at which extent anatomical (defined as P_{crit}) and non-anatomical (including arousal threshold, loop gain and muscle responsiveness) factors affect OSA development. PALM scale 1 consists of patients with severe (P_{crit} > +2 cmH_2O), PALM scale 2 of those with moderate (P_{crit} between -2 and +2 cmH_2O) and PALM scale 3 of those with minor (P_{crit} < -2 cmH_2O) anatomical impairment. Patients in PALM scale 2 are further categorized into two subgroups based on whether they have impairments in non-anatomical factors (PALM scale 2b), or not (PALM scale 2a). Approximately 70 % of OSA patients are likely to have an impairment in ≥1 of the non-anatomical factors (Eckert et al. 2013).

The Icelandic Sleep Apnoea Cohort study of 822 patients with an AHI of ≥15 /h identified three symptom-based OSA clusters, of which EDS (primarily sleepiness, mean ESS 16) was the most common (42 %), followed by disturbed sleep (primarily insomnia symptoms, mean ESS 10; 33 %) and minimally symptomatic patients (less sleepiness or disturbed sleep, mean ESS 8; 25 %). The highest prevalence of hypertension and CVD was found among minimally symptomatic patients and the lowest among those with EDS, which could be partly explained by a delayed OSA diagnosis in the former group (Ye et al. 2014). Another study of 757 patients with an AHI of ≥15 /h suggested that these three symptom-based clusters may be accompanied by two additional clusters: EDS (mean ESS 12–16) with (22 %) or without (20 %) upper airway symptoms, disturbed sleep (mean ESS 8; 19 %), minimal symptoms (mean ESS 5; 20 %) and upper airway symptoms dominant OSA (mean ESS 8; 19 %). The highest prevalence of hypertension and CVD was observed among disturbed sleep (Keenan et al. 2018), possibly partly due to insomnia-related short sleep duration (Anttalainen et al. 2019). Those with upper airway symptoms dominant OSA were more likely younger, less obese and males. AHI and ODI were >40 /h in all groups. Thus, patients with the same AHI may have different symptoms, emphasizing the need for other tools to recognize heterogeneity (Keenan et al. 2018).

The European Sleep Apnea Database study of patients with an AHI of ≥5 /h also showed that patients with insomnia-like symptoms (mean ESS 6) had the highest CVD prevalence, which was independently associated with a lower nadir SpO_2. Those with EDS (mean ESS 15) had the lowest CVD prevalence, even though they

had a higher AHI (Anttalainen et al. 2019, Saaresranta et al. 2016). Conversely, the Sleep Heart Health Study of 1207 patients with an AHI of ≥15 /h identified four clusters, of which only the EDS group (mean ESS 14) had an adjusted 2-fold increased risk of incident CVD compared to subjects without OSA, while those with disturbed sleep (mean ESS 7) had a reduced risk of stroke compared to other clusters (Mazzotti et al. 2019). This thesis did not find an association between the baseline ESS score and the CVD risk, but the mean ESS was <10. However, ESS alone may be insufficient to identify the EDS phenotype (Mazzotti et al. 2019).

Four polysomnographic-based, partly overlapping phenotypes were identified in a study of 1184 patients with an AHI of 5– 30 /h. These included rapid eye movement (REM) predominant OSA (45 %), non-rapid eye movement (NREM) predominant OSA (19 %), supine predominant OSA (62 %) and intermittent OSA, which was characterized by scattered respiratory events throughout the night (12 %) (Joosten et al. 2012). Particularly REM-predominant OSA has been associated with an increased CVD risk due to more frequent obstructive events, longer apneas and greater desaturations compared to NREM sleep. Sympathetic tone increases during REM sleep, while both respiratory drive and muscle tone decrease, which predispose the upper airway to collapse (Findley et al. 1985, Varga & Mokhlesi 2019). REM-predominant OSA has usually been defined as a ratio of REM AHI/ NREM AHI of >2 with a REM sleep duration of ≥30 minutes. The definition's reliability may be improved by additional criteria, including a total AHI of ≥5 /h and a NREM AHI of ≤15 /h. Based on these criteria, its prevalence has been 10–20 %, being more common among women than men (Varga & Mokhlesi 2019).

The Wisconsin Sleep Cohort Study reported that REM-predominant OSA was independently associated with prevalent and incident hypertension (Mokhlesi et al. 2014), and a smaller study of 837 males similarly showed that the risk was over 2-fold higher among those with an AHI of ≥30 /h of REM sleep (Appleton et al. 2016). Neither of the studies observed significant associations between hypertension and non-REM AHI (Appleton et al. 2016, Mokhlesi et al. 2014). However, a study of 1247 veterans identified seven polysomnographic-based clusters, of which the cluster of REM and hypoxia was not associated with the risk of incident CVD events or hypertension. Interestingly, the clusters of PLMS, hypopnea and hypoxia (primarily hypopneas with desaturations) and combined severe (combined apneas, hypopneas and desaturations) all had approximately a 2-fold increased risk of CVD events when compared to a cluster of mild polysomnographic findings. AHI was in the range of 10–84 /h in these three groups. Conventionally measured, an AHI of <15 /h did not differ in terms of CVD risk from a higher AHI (Zinchuk et al. 2018).

Based on the clinical and polysomnographic patient characteristics published in previous studies, a recent review identified six potential OSA phenotypes, which **Table 25** summarizes (Zinchuk & Yaggi 2020). Overall, it has been suggested that

OSA's severity should be based on several components instead of AHI alone. One grading system suggested that patients with an AHI of ≥15 /h may be categorized according to the level of symptoms (ESS ≥9 or less, dozing episodes, hypersomnia, insomnia, vigilance test) and the presence of comorbidities. Those with severe symptoms in addition to recurrent or poorly controlled comorbidities are defined as having the most severe form of OSA (Randerath et al. 2018).

Furthermore, this thesis showed that male gender, younger age and current smoking were associated with an increased risk of MVAs, consistent with previous studies (Karimi et al. 2015, Sacks et al. 1994, Tregear et al. 2009). Smoking has been suggested to increase the MVA risk due to smoking-related diseases, distractibility, and smokers' susceptibility to risky behavior (Sacks et al. 1994). Among patients with MVA, the only baseline characteristic that differed between the CPAP-treated patients and controls was baseline BMI, which was higher among the former. Interestingly, a BMI of ≥30 kg/m^2 increased the likelihood of an MVA only among CPAP-treated patients. Most of the CPAP-treated patients with MVA tended to gain more weight during treatment. Previous studies have also found an association between a higher BMI and an increased MVA risk (Tregear et al. 2009). Adipocytes have been shown to secrete cytokines, which may increase daytime sleepiness and predispose to MVAs (Vgontzas et al. 2006). However, no association was found between the baseline ESS of ≥16 scores and the MVA incidence, although it has been previously identified as a risk factor for MVAs (Tregear et al. 2009). ESS also tended to decrease after CPAP in most patients regardless of having an MVA or not. Overall, a recent review of OSA phenotypes suggested that those who are younger, obese and male with symptoms of sleepiness, fatigue and involuntary sleep may be at the highest risk for drowsy driving and MVAs (Zinchuk & Yaggi 2020).

Table 25. Potential phenotypes of obstructive sleep apnea (OSA) based on cluster analyses of clinical and polysomnographic patient characteristics. Modified from the American College of Chest Physicians (Zinchuk & Yaggi 2020) with permission from Elsevier.

	Potential phenotypes of OSA					
	A "Classic"	**B** "Oldest, comorbid"	**C** "Female, insomnia"	**D** "Youngest, upper airway symptoms"	**E** "Severe, hypoxemic"	**F** "Severe, non-hypoxemic"
Age	Younger	Oldest	Middle-aged	Youngest	Younger	Older
Gender	Male	Male	Female	Male	Male	Male
BMI	Obese	Obese	Overweight/ obese	Not obese	Severely obese	Obese
Symptoms	Sleepy, fatigue, involuntary sleep	Need for naps, snoring	Difficulty to fall asleep, early awakening, sleep not refreshing	Snoring, sudden awakening, less sleepy (low ESS), +/- insomnia	Sleepy	Less sleepy
Comorbidities	Low	Highest	Medium	Lowest	–	–
Sleep studies						
AHI	High	High	Medium	High	High	High
T90 %	Medium	High	Medium	Low	High	Low
Apnea length	–	–	–	–	Medium	Low
SpO_2 nadir	–	–	–	–	Low	High
Consequences	Drowsy driving, ↑ CVD risk?	Inadequate adherence to CPAP, no incident CVD risk (but high prevalent risk)	Inadequate adherence to CPAP, ↓ incident stroke risk?	Inadequate adherence to CPAP, CVD risk unknown	↑ incident CVD risk	Inadequate adherence to CPAP, cognitive dysfunction?
Effectiveness of CPAP	Highest	Least	Medium	Medium	–	–

AHI, apnea-hypopnea index; BMI, body mass index; CPAP, continuous positive airway pressure; CVD, cardiovascular disease; SpO_2, blood oxygen saturation level; T90, percentage of time spent under SpO_2 of 90 %.

6.3 The significance of the level of CPAP adherence

This thesis found that approximately one half of the patients commencing CPAP continued the treatment for ≥5 years, and furthermore, long-term commitment to CPAP could be predicted shortly after the initiation of treatment, since the mean short-term usage was already on the recommended level. These findings are in agreement with previous studies (Sawyer et al. 2011, Weaver et al. 1997, Weaver & Grunstein 2008). Long-term adherence to CPAP was increased by a mean of 11 min/day per year over a mean follow-up of 7 years at the cohort level, which is similar to a previous, smaller study that reported a mean increase of 8 min/day per year in adherence over a follow-up of ≥5 years (Sucena et al. 2006). This thesis further showed that approximately a quarter of the patients had either a significant increase or decrease in adherence, while the majority showed no significant change.

No single factor has been consistently associated with CPAP adherence (Weaver & Grunstein 2008). This thesis found that psychiatric disorders, a higher baseline BMI and increases in weight or the GHQ-12 score during treatment were associated with a significant increase in adherence. A weak association was observed between AHI and adherence, consistent with previous studies (Sawyer et al. 2011). Those with a higher baseline ESS score were less likely to achieve a significant increase in adherence, potentially since they may have committed to CPAP in a steady manner. Even though only a minority reported EDS, ESS was reduced in most of the patients, and a weak negative correlation was found between the mean slopes of CPAP usage and ESS. The GHQ-12 slope was also slightly descending, suggesting that psychological distress tended to reduce during treatment. Symptoms of psychiatric disorders may interact with OSA-related symptoms, and this patient group should not be overlooked when considering CPAP treatment. Overall, clinically significant improvements in sleepiness and other symptoms may be achieved by CPAP despite having a low baseline ESS score. The assessment of need for CPAP or response to the treatment should not be merely based on the ESS (Patil et al. 2019).

Inadequate adherence has been a notable problem in RCTs and could explain the modest results on the associations between CPAP and the risk of CVDs. The exclusion of patients with EDS or the most severe OSA may also affect the results (McEvoy et al. 2016, Sánchez-de-la-Torre et al. 2020), since the effect of CPAP on BP has been reported to be greater in these patients than in those who are non-sleepy or have a milder OSA (Javaheri et al. 2017, Peker & Balcan 2018). A randomization of these patients to no treatment is ethically unacceptable, and it may only be hypothesized whether CPAP could have improved the CVD outcome in these OSA subgroups (Peker & Balcan 2018). CPAP may also be less effective in secondary than in primary prevention of CVDs potentially due to altered vascular structures related to established CVDs (Javaheri et al. 2017, Randerath et al. 2018). This thesis

demonstrated that CPAP use of >6 h/day was associated with a reduced risk of a composite CVD event in patients with or without established CVDs, while CPAP use of >4 h/day but ≤6 h/day was linked to a reduced risk only in the primary prevention of CVDs. Post-hoc analyses and meta-analyses of RCTs have suggested that CPAP use of ≥4 h/day may improve CVD outcome, particularly stroke and other cerebrovascular events (Javaheri et al. 2020b, McEvoy et al. 2016, Peker et al. 2016).

This thesis further emphasized the importance of the level of CPAP adherence in CVD outcome, since only those who had used CPAP for >6 h/day had an independent reduced risk of CVD death, a composite of cardiac events and all-cause mortality compared to controls. A reduction in the risk of stroke was observed only among those who had used CPAP for >4 but ≤6 h/day. CPAP use of >4 h/day was, however, associated with a reduced stroke risk when the model was adjusted only for AF, while those with lower CPAP usage were not. Overall, the results of this thesis imply that CPAP use of >4–6 h/day is likely needed to achieve a potential improvement in CVD risk, although the impact may vary between specific outcomes. No association was observed between CPAP and the risk of cancer mortality regardless of the level of CPAP use.

OSA phenotypes may also affect the effectiveness of CPAP (Randerath et al. 2018, Zinchuk & Yaggi 2020). Poor CPAP adherence may result in the use of the device only during the early hours of the night, thus predisposing to unbeneficial effects of REM-related OSA on CVD outcomes. CPAP use of 3 to 4 h/day from the beginning of the sleep period has been estimated to leave 60–75 % of REM-related obstructive events untreated, since REM sleep is mainly concentrated in the early hours of the morning (Varga & Mokhlesi 2019). CPAP should preferably be used for the entire night to treat REM OSA, which is unlikely to be achieved in a notable proportion of patients, implying the need for alternative treatment strategies (Varga & Mokhlesi 2019). This thesis observed the beneficial effect of CPAP on most CVD outcomes only among those with CPAP use of >6 h/day, possibly at least partly since this level of compliance was sufficient to cover also REM sleep.

Furthermore, some studies have shown an increased CVD risk particularly in patients with insomnia symptoms (Keenan et al. 2018, Saaresranta et al. 2016), while others have suggested that those with EDS could be at the greatest risk (Mazzotti et al. 2019). Insomnia symptoms have generally been associated with lower, and those with EDS with higher, CPAP adherence (Pien et al. 2018, Saaresranta et al. 2016). Long-term compliance with CPAP has also been reported to be challenging for CAD patients with non-sleepy OSA (Luyster et al. 2017). CPAP has been shown to help maintain sleep, but not the difficulties in falling asleep, suggesting a need for additional treatment options for those with insomnia symptoms (Pien et al. 2018). Moreover, a study of 706 patients from the Icelandic Sleep Apnea Cohort showed a reduction in diastolic BP in minimally symptomatic

and sleepy patients after a 2-year treatment with CPAP but not in those with disturbed sleep. The CVD incidence did not differ after adjustment for confounding factors (Pien et al. 2018). A study of veterans further reported that CPAP use of >4 h/day was associated with a reduced CVD risk among the clusters of hypopnea and hypoxia and PLMS, an interesting finding, since the latter has not been traditionally included in the consideration of CPAP treatment in an AHI of <15 /h. Only 29 % of the patients in the cluster of arousal and poor sleep had used CPAP >4 h/day, and they also tended to benefit the least from CPAP in terms of CVD outcomes. Thus, the CVD risk may remain increased regardless of treatment for some patient groups (Zinchuk et al. 2018).

Studies have also shown a risk reduction by CPAP in terms of MVAs, although the effect of the level of adherence on the MVA risk has not been thoroughly established (Karimi et al. 2015, Tregear et al. 2010). No RCTs have been particularly designed to examine the impact of CPAP on MVAs due to ethical reasons (Tregear et al. 2010). The results of this thesis on the risk of MVAs differed from most previous studies, since no association between CPAP and the MVA incidence was observed regardless of the level of CPAP adherence. The MVA incidence before CPAP was, however, already at a lower level in comparison to a similar study from Sweden (Karimi et al. 2015). It has also been suggested that cognitive impairment and daytime sleepiness may not be fully normalized by CPAP despite good adherence (Antic et al. 2011). However, current data on the association between long-term CPAP treatment and cognitive changes are scarce, and the possible effect of the residual cognitive impairment on the results of the present study remains as a speculation. Overall, the risk of MVAs is likely to be multifactorial.

Conversely, adherence to CPAP has also been linked to a modest increase or no significant changes in weight (Drager et al. 2015). Baseline BMI has been shown to predict the BMI outcome, while no other predictors have been consistently identified (Drager et al. 2015). This thesis showed that the mean change in BMI was 0.06 kg/m^2 per year for the entire cohort over a 7-year follow-up, which was similar to that observed among a middle-aged Finnish population (mean change in BMI 0.06–0.11 kg/m^2 per year) (Silventoinen et al. 2013). However, the baseline BMI was clinically significantly higher among the former than the latter (men: 33 vs. 26, women: 35 vs. 25 kg/m^2, respectively). Heterogeneity was observed at the individual level, since 10 % of the patients significantly gained weight with a mean rate of 0.6 kg/m^2 per year. Male gender, younger age, current smoking, a higher BMI or GHQ-12 score at baseline and an increasing GHQ-12 score during treatment, were associated with a significant increase in BMI. The results of this thesis further emphasize that lifestyle interventions should be offered for all OSAS patients, and particularly for those who are younger and severely obese already at the initiation of CPAP.

6.4 Strengths and limitations

The retrospective study design is the most significant limitation of this thesis. There may be underlying patient characteristics, such as different OSA phenotypes and personal types, causing bias in the results, since patients compliant with CPAP may differ from those who discontinue the treatment. The latter may adhere poorly to other medical therapies, while the former may have a healthier overall lifestyle, a phenomenon known as the "healthy adherer" effect. These potential, underlying biases are extremely difficult to control in retrospective studies except by matching cases and controls, which was conducted in this thesis by matching the CPAP-treated patients and controls for age, gender and AHI. The patients were recruited from the same clinic based on the same principles to minimize the selection bias.

The search for controls was extended by several years to find the best matching case-control pairs. The treatment protocol did not essentially change during these years. However, the AASM hypopnea criteria did change in 2007, and thus, the same AHI value of those controls diagnosed with OSAS in 2007 or later is likely to differ from that of the CPAP-treated patients, since their diagnosis was based on the Chicago criteria (Iber et al. 2007, The Report of an American Academy of Sleep Medicine Task Force 1999). This may have reduced the accuracy of pairwise matching of the patients according to AHI, since the 2007 hypopnea criteria were generally stricter than the Chicago criteria (Ruehland et al. 2009). Sleep recordings were also scored by pulmonologists or clinical neurophysiologists, which may have affected the AHI of the patients, although the scoring principles were the same. Furthermore, data on nocturnal SpO_2 levels were not available for all studied patients, and variably reported ODI values (ODI of ≥4, ≥5 or ≥10 %) complicated comparisons between patients. Thus, data on SpO_2 and ODI were utilized only for those who had an MVA and were not used in the analyses of CVDs. Follow-ups were not modified in terms of non-fatal outcomes, since both cases and controls could have had an event from the beginning of observation period. Other well-known risk factors were included in adjusted analyses on the associations between CPAP and the risk of CVDs or mortality. Data on alcohol consumption, medications, physical activity and family history of CVD were unavailable due to the retrospective nature of the studies.

As a further limitation, data on patients' waist circumference or the amount of adipose tissue were unavailable, and thus, it is not clear how much of the gained weight was fat and how much fluid in those with a significant increase in BMI during CPAP treatment. Long-term weight changes of the CPAP-treated patients could not be compared to a control group, since no data on weight changes were available for controls after they had discontinued CPAP. Instead, the development of BMI during CPAP treatment was compared to that among middle-aged Finns from the general

population (Silventoinen et al. 2013). No data on changes in BMI or ESS score were available for controls in studies II–III for the same reason.

The statistical power or sample size estimation were not conducted prior to the study. This could at least partly explain why a significant difference in the MVA incidence was not observed after CPAP, since MVAs are likely to occur rarely, especially in a sparsely populated country such as Finland. The MVA incidence of the patients was already low 9 years before CPAP. Furthermore, data on actual annual driving exposure in the cohort was unavailable, although differences in driving habits were likely reduced by matching the cases and controls for age and gender. Potential differences should not affect before and after comparisons.

Overall, the sample size of the studies, even though unpowered, was large and the proportion of females significant. Those with concomitant diseases or an AHI of <5 /h with clinical presentation strongly suggestive for OSAS were included in the study to better represent real-world patients. Most of the treated patients showed good adherence to CPAP in both the short and long term. However, despite good compliance, the sleep duration of the patients may have been insufficient. The data on both CVD events and MVAs were objective. The latter was based on a national registry in which small, near-miss accidents or close shaves on the road are not reported. Only MVAs involving the study subject as the actual driver were included. Data on accident conditions, a possible confounding factor for MVAs, were provided, which previous studies have not assessed.

CPAP-treated patients had multiple follow-up visits during treatment with objectively measured data on CPAP usage and weight, which enabled the evaluation of individual trends of BMI and adherence over time. This differs from the traditional statistical methods, in which the outcome measures are compared between before and after treatment or determined for the whole cohort at one cross-sectional time point. These methods do not acknowledge the model uncertainty, while the approach of individual development enables the classification of patients into high- or low-risk at a specific probability level. The number of patients in this thesis with a significant increase in adherence was likely restricted due to a ceiling effect, since most of the patients had already adhered adequately to CPAP from the initiation of treatment. The evaluation of individual trends of patient characteristics provides a step towards a more personalized medicine.

7 SUMMARY/CONCLUSIONS

OSA has a range of adverse consequences to patients' health and is a heavy burden on health care systems. Its prevalence is increasing, particularly due to a growing rate of obesity and to an aging population. CPAP has been the primary treatment for OSA, particularly in patients with moderate to severe disease, for forty years. Identifying those who benefit the most from CPAP in addition to those who are likely to require additional support to achieve adequate treatment response remains a challenge. However, advances in the knowledge of OSA pathogenesis provide an opportunity towards more personalized medicine, since new targeted therapies could be developed. The main purpose of this thesis was to investigate long-term adherence to CPAP treatment, the risk of CVD events and MVAs and the associations between CPAP and weight maintenance. Another aim was to further evaluate whether the level of CPAP adherence would affect the results.

The main conclusions are the following:

1) Approximately one half of the patients with OSAS commencing CPAP had continued the treatment for ≥5 years. Among these patients, CPAP adherence was extremely good both in the short and long term. Adherence increased slightly at the cohort level by a mean of 11 min/day per year of follow-up. Most of the patients had no significant change in adherence at the individual level, implying that long-term CPAP adherence can be predicted shortly after initiation, which is in agreement with previous studies.
2) A significant increase in adherence was associated with the presence of psychiatric disorders, a higher baseline BMI and increases in weight or the GHQ-12 score during treatment. A weak association was found between AHI and CPAP adherence. Mean long-term adherence to CPAP was 6 h/day in the cohort, even though only 37 % of the patients had reported EDS (ESS ≥11). These findings emphasize that the assessment of treatment response should not be merely based on the ESS score and that symptoms of psychiatric disorders may interact with OSA-related symptoms, and this patient group should not be overlooked when considering CPAP treatment.

3) In comparison to controls matched for age, gender and AHI, CPAP treatment was associated with an independent, reduced risk of CVD events and all-cause mortality over a median follow-up of 9 years. However, this was only observed among those with CPAP use of >4–6 h/day depending on the specific outcome. As an exception, no association was found between CPAP and the risk of nonfatal cardiac events regardless of the level of CPAP adherence. The results further imply that CPAP use of >4–6 h/day is likely needed to achieve potential improvements in CVD risk. This finding is consistent with several recent meta-analyses and post-hoc analyses of RCTs.

4) The CPAP-treated patients at the cohort level slightly gained weight at a comparable rate to that observed in the general middle-aged Finnish population, although their baseline BMI was clinically significantly higher. Heterogeneity was observed at the individual level, since 10 % of the patients significantly gained weight. The most concerning observation was that these patients were already more severely obese despite being younger than the rest of the cohort. The results underline the urge for lifestyle interventions for all OSAS patients and particularly for the younger and severely obese who appear to be at the highest risk for weight gain.

5) The incidence of police-reported MVAs did not change after CPAP when compared between 9 years before and after treatment or between the CPAP-treated patients and controls. The level of CPAP adherence did not affect the results. Among patients who had an MVA, no differences were observed in sleep study data or accident conditions. Baseline BMI was the only characteristic that differed between the CPAP-treated patients and controls who had an MVA and tended to further increase during CPAP treatment. Male gender, younger age and smoking were associated with an increased risk for MVAs, which is consistent with previous studies. A BMI of ≥30 kg/m^2 increased the likelihood of an MVA only among CPAP-treated patients. No association was found between the baseline ESS score and the risk for MVAs. The MVA risk is likely to be multifactorial, and even longer observation periods may be needed to detect a significant difference.

6) No association could be verified between AHI and the risk of weight changes, CVD events or MVAs. This emphasizes that OSAS is a heterogeneous disease, and the use of AHI alone is not sufficient in the assessment of OSAS severity or in the identification of high-risk patients for adverse outcomes. New tools for these purposes are needed.

7) Daytime sleepiness and psychological distress tended to reduce during CPAP treatment in the majority of the CPAP-treated patients, which is consistent with earlier studies.

8 FUTURE ASPECTS

Mounting evidence has shown that symptoms related to OSA are heterogeneous and do not associate with AHI, and furthermore, all symptom-based phenotypes are not presented with increased ESS score (Zinchuk & Yaggi 2020). The identification of OSA phenotypes that are most likely to benefit from CPAP would be useful, particularly for those asymptomatic or minimally symptomatic patients who are unwilling to initiate or continue CPAP unless other benefits of treatment can be predicted (Randerath et al. 2018). New pathophysiological mechanisms, genetic risk factors and potential treatment alternatives for OSA could also be revealed, and lead to a more personalized OSA treatment (Zinchuk & Yaggi 2020).

Patients with moderate to severe anatomical impairment are likely to differ from those who have only minor impairment in anatomical factors in terms of treatment alternatives (Eckert et al. 2013). The former probably benefit the most from interventions that aim to protect the patency of the upper airway, such as CPAP, MAD, surgical approaches, positional therapy and weight loss. As the role of non-anatomical factors, particularly a high loop gain or a low respiratory arousal threshold, becomes dominant, patients may be less likely to respond to anatomical interventions. These patients are more likely to benefit from interventions targeted towards one or more non-anatomical factors or a combination of these approaches.

Accordingly, patients with impaired nocturnal dilator muscle function may benefit from interventions that aim to improve the muscle function such as upper airway muscle training, hypoglossal nerve stimulation or a medication that increases the muscle activity of genioglossus during sleep (e.g. desipramine). Patients with a low respiratory arousal threshold may benefit from the use of hypnotics that increase the arousal threshold but do not predispose to muscle relaxation, while those with a high loop gain may benefit from supplemental oxygen, stabilization of CO_2, and the use of acetazolamide, which has been shown to reduce loop gain approximately by 40 %. Patients who have both moderate anatomical and non-anatomical impairments (PALM scale 2b) may particularly benefit from a targeted combination therapy such as MAD treatment in addition to supplemental oxygen (Eckert et al. 2013). At present, these potential treatment options are, however, only suggestive, and further studies are needed to verify their effectiveness in different OSA-related outcomes.

Optimal treatment and the effect of CPAP in patients with different clinical and polysomnographic phenotypes may also vary. For example, patients with insomnia-like symptoms may benefit from a combination of cognitive behavioral therapy and CPAP in order to improve symptoms and CPAP adherence (Anttalainen et al. 2019). The timing of CPAP use in relation to sleep onset and adequate adherence to CPAP may be particularly important for patients with REM-predominant OSA in order to cover REM sleep. Preliminary data has suggested that MAD may not be as effective in the treatment of OSA during REM sleep when compared to NREM sleep or CPAP. Furthermore, patients with REM predominant OSA may also benefit from interventions that aim to improve the upper airway muscle function, since REM sleep is characterized by muscle atonia (Varga & Mokhlesi 2019). The potential role of medications that suppress REM sleep such as serotonin/ norepinephrine reuptake inhibitors and tricyclic antidepressants have yet not been explored in the treatment of REM OSA in human subjects (Varga & Mokhlesi 2019).

Most of the studies investigating OSA phenotypes have mainly included middle-aged or older male subjects with moderate to severe OSA. Thus, studies on patients of different ages, including more women, are needed both from clinic- and population-based cohorts, since those who have visited clinics may differ particularly in terms of symptoms from subjects of the general population. Even though specific phenotypes have already been identified, it is not clear whether the same phenotypes are present in mild OSA, or how clinical phenotypes interact with pathophysiological-, polysomnographic-, biomarker- (e.g. inflammatory markers, markers of sympathetic activation) or genetic-based phenotypes. Multidomain analyses are needed to combine different patient characteristics, although these are likely to provide a broad spectrum of data that may be difficult to interpret (Zinchuk & Yaggi 2020).

Overall, the identification of OSA phenotypes is likely to expand our perception of OSA, its consequences on health, and treatment options towards a more personalized medicine. Future OSA treatment is likely to be based on the assessment of phenotypes similar to the current treatment of asthma and COPD. A better understanding of phenotypes could also enable exact identification of those patients who are at the highest risk for a CVD, MVA or other unbeneficial OSA-related outcomes. CPAP has been constantly shown to be efficacious in OSA's treatment. However, inadequate adherence to CPAP has been a notable problem, and the effectiveness of second-line treatments in these patients has varied. Thus, in addition to studies investigating the effectiveness of adequate CPAP use and methods to achieve it, there is also a need for new treatments for OSA (Eckert et al. 2013, Keenan et al. 2018, Randerath et al. 2018, Zinchuk & Yaggi 2020).

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Minna Myllylä

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APPENDICES

Appendix 1. Epworth Sleepiness Scale (Johns 1991)

Sitting and reading
- Would never doze or sleep (0 points)
- Slight chance of dozing or sleeping (1 point)
- Moderate chance of dozing or sleeping (2 points)
- High chance of dozing or sleeping (3 points)

Watching television
- Would never doze or sleep (0 points)
- Slight chance of dozing or sleeping (1 point)
- Moderate chance of dozing or sleeping (2 points)
- High chance of dozing or sleeping (3 points)

Sitting inactive in a public place
- Would never doze or sleep (0 points)
- Slight chance of dozing or sleeping (1 point)
- Moderate chance of dozing or sleeping (2 points)
- High chance of dozing or sleeping (3 points)

Being a passenger in a car for an hour
- Would never doze or sleep (0 points)
- Slight chance of dozing or sleeping (1 point)
- Moderate chance of dozing or sleeping (2 points)
- High chance of dozing or sleeping (3 points)

Lying down in the afternoon
- Would never doze or sleep (0 points)
- Slight chance of dozing or sleeping (1 point)

Moderate chance of dozing or sleeping (2 points)
High chance of dozing or sleeping (3 points)

Sitting and talking to someone
Would never doze or sleep (0 points)
Slight chance of dozing or sleeping (1 point)
Moderate chance of dozing or sleeping (2 points)
High chance of dozing or sleeping (3 points)

Sitting quietly after lunch (no alcohol)
Would never doze or sleep (0 points)
Slight chance of dozing or sleeping (1 point)
Moderate chance of dozing or sleeping (2 points)
High chance of dozing or sleeping (3 points)

Stopping for a few minutes in traffic while driving
Would never doze or sleep (0 points)
Slight chance of dozing or sleeping (1 point)
Moderate chance of dozing or sleeping (2 points)
High chance of dozing or sleeping (3 points)

Appendix 2. General Health Questionnaire (Goldberg et al. 1997)

How have you been feeling, in general, over the past few weeks?

Have you been able to concentrate on what you were doing?
More than usual (0 points)
Same as usual (0 points)
Less than usual (1 point)
Much less than usual (1 point)

Have you lost much sleep over worry?
Not at all (0 points)
No more than usual (0 points)
Rather more than usual (1 point)
Much more than usual (1 point)

Have you felt that you were playing a useful part in things?
- More than usual (0 points)
- Same as usual (0 points)
- Less than usual (1 point)
- Much less than usual (1 point)

Have you felt capable of making decisions about things?
- More than usual (0 points)
- Same as usual (0 points)
- Less than usual (1 point)
- Much less than usual (1 point)

Have you felt constantly under strain?
- Not at all (0 points)
- No more than usual (0 points)
- Rather more than usual (1 point)
- Much more than usual (1 point)

Have you felt you could not overcome your difficulties?
- Not at all (0 points)
- No more than usual (0 points)
- Rather more than usual (1 point)
- Much more than usual (1 point)

Have you been able to enjoy your normal day-to-day activities?
- More than usual (0 points)
- Same as usual (0 points)
- Less than usual (1 point)
- Much less than usual (1 point)

Have you been able to face up to your problems?
- More than usual (0 points)
- Same as usual (0 points)
- Less than usual (1 point)
- Much less than usual (1 point)

Have you been feeling unhappy and depressed?
- Not at all (0 points)
- No more than usual (0 points)

Rather more than usual (1 point)
Much more than usual (1 point)

Have you been losing confidence in yourself?
Not at all (0 points)
No more than usual (0 points)
Rather more than usual (1 point)
Much more than usual (1 point)

Have you been thinking of yourself as a worthless person?
Not at all (0 points)
No more than usual (0 points)
Rather more than usual (1 point)
Much more than usual (1 point)

Have you been reasonably happy, all things considered?
More than usual (0 points)
Same as usual (0 points)
Less than usual (1 point)
Much less than usual (1 point)

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