OSAS: The Magnitude of the Problem

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Introduction

Obstructive sleep apnea syndrome (OSAS) is very common [1, 2] and represents an increasing part of clinical (respiratory) practice in developed countries. OSAS is currently recognised to be one of the most common chronic respiratory disorders, with only asthma and possibly COPD having a similar prevalence [3–5]. Questions regarding risks, diagnosis and therapeutical options are of importance to both clinicians and healthcare policymakers. As the medical community and the general public have become more aware of the relationships among snoring, excessive daytime sleepiness, cardiovascular disease and OSAS, doctors are seeing an increasing number of patients with such problems. Excessive daytime sleepiness is one of the cardinal symptoms [6]. Untreated OSAS has substantial health consequences [7]. Moderate to severe OSAS is associated with an increased risk of death from any cause in middle-aged adults, especially men. They are closely related to increases in body weight and, as a result, the tendency to develop upper airway collapse during sleep. It is obvious that OSAS has different phenotypes and that there are relevant gender differences and important aging effects [8–10]. Moreover, the condition carries significant morbidity and is associated with an increased risk of stroke, myocardial infarction, arrhythmias, hypertension and metabolic and neurobehavioural consequences [11].

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N. de Vries et al. (eds.), *Positional Therapy in Obstructive Sleep Apnea*,
DOI 10.1007/978-3-319-09626-1_2

Definitions

Obstructive sleep apnea syndrome is part of a spectrum of respiratory disturbances that occur during sleep, described with a widely used term as sleep-disordered breathing (SDB) [12]. The International Classification of Sleep Disorders (ICSD-3) has defined four major categories of SDB: obstructive sleep apnea disorders (including obstructive sleep apnea hypopnea syndrome or OSAS), central sleep apnea syndrome (CSA), sleep-related hypoventilation disorders and sleep -related hypoxemia disorders [13]. The fundamental difference between the first two major categories is the pathophysiological mechanism which causes the respiratory disturbance [14]. In OSAS, the upper airway occlusion is most often caused by abnormal anatomy and/or abnormal control of the muscles that maintain the patency of the upper airway. In CSA, dysfunctional ventilatory control in the central neurons is involved, finally resulting in loss of ventilatory effort. Central and obstructive apneas are rarely seen in isolation in a single patient, which suggests that the mechanisms responsible for the different types of apnea must overlap. It was more preferable to discuss each of these separately, although they could be placed under the common denominator of "sleep-disordered breathing syndrome" [14]. An obstructive apnea-hypopnea can be defined as an event that lasts for at least 10 s and is characterised by a transient reduction in (hypopnea) or complete cessation (apnea) of breathing [12]. Based on the AASM criteria from 1999, a hypopnea can be defined as a decrease from baseline in the amplitude of a valid measure of breathing during sleep that either reaches >50 % with an oxygen desaturation of 3 % or an arousal or alternatively a 30 % reduction with 4 % oxygen desaturation [12]. Recently, the AASM adopted a simplified hypopnea definition which considers a hypopnea if the peak signal excursions drop by ≥3 % of pre-event baseline using nasal cannula, with a duration of ≥10 s, and ≥3 % oxygen desaturation from pre-event baseline or the event is associated with an arousal [15].

Central sleep apnea refers to the cessation of ventilation lasting for at least 10 s (in adults) due to transient loss of neural output to the respiratory muscles [12]. The degree of severity is defined on the basis of the number of apneas and hypopneas occurring during 1 h of sleep (apnea-hypopnea index or AHI) and the severity of daytime symptoms. According to ICSD-3, the presence of criteria A and B, or C satisfies the diagnosis of a clinically significant obstructive sleep apnea-hypopnea syndrome (see Table 1) [12]. The severity of OSAS can be defined as mild for an AHI ≥ 5 and <15, moderate for an AHI ≥ 15 and ≤30 and severe for an AHI > 30 [16]. Based on these criteria, sleep apnea occurs in 4 % of men and 2 % of women who are 30–60 years old [1]. The definition of OSAS, using two components, breathing pattern disturbances during sleep and daytime symptoms, indicates that there are also subjects who present with sleep apnea without symptoms. These cases are referred to as OSAS and have an even higher prevalence, recently estimated to be 20 % for OSAS in a Spanish population [10]. OSAS can be subdivided into adult type and paediatric type, since the diagnostic criteria and clinical presentation for abnormal breathing during sleep are different for adult cases and paediatric ones [15]. Obstructive breathing events may include apneas, hypopneas and respiratory

Table 1 ICSD-3 Criteria for the diagnosis of a clinically significant obstructive sleep apnea-hypopnea syndrome

A → The presence of one or more of the following applies:
i. The patient complains of sleepiness, nonrestorative sleep, fatigue, or insomnia symptoms.
ii. The patient wakes with breath holding, gasping, or choking
iii. The bed partner or other observer reports loud snoring, breathing interruptions, or both during the patient's sleep
iv. The patient has been diagnosed with hypertension, a mood disorder, cognitive dysfunction, coronary artery disease, stroke, congestive heart failure, atrial fibrillation, or type 2 diabetes mellitus
B → Polysomnographic (PSG) of ambulatory polygraphic (PG) recording shows the following:
i. Five or more scoreable predominantly obstructive respiratory events (obstructive and mixed apneas, hypopneas, or RERA's) per hour of sleep during a PSG or per hour of monitoring (PG)
OR
C. Polysomnographic recording shows the following:
i. Fifteen or more predominantly obstructive respiratory events (apneas, hypopneas, or RERAs) per hour of sleep during a PSG or per hour of monitoring (PG)

effort-related arousals (RERAs) [17]. A RERA can be defined as a sequence of breaths characterised by increasing respiratory effort leading to arousal from sleep, but not fulfilling the criteria for apnea or hypopnea [15, 17]. Moreover, these events present with a pattern of progressively more negative esophageal pressures, terminated by an abrupt change in pressure to a less negative level and an arousal. Esophageal pressure is still recommended as the method of choice [15, 18], but the flattening of the flow curve obtained by nasal pressure is explicitly mentioned, together with induction plethysmography, as feasible alternatives [15]. In daily practice, nasal pressure is the method of choice for most sleep laboratories. These events also last 10 s or more. If a definition for hypopnea is used which requires an associated desaturation OR arousal, then there are relatively few events scored as RERAs. Upper airway resistance syndrome (UARS) is characterised by increased upper airway resistance, followed by repetitive arousals, finally resulting in daytime sleepiness [19, 20]. The essential polysomnographic features are the absence of obstructive sleep apneas, an AHI < 5 and a lack of significant oxygen desaturation, which differ from the laboratory findings of OSAS [15]. Currently, the term UARS is no longer used as an independent disease, but is subsumed under the diagnosis of OSAS because the pathophysiology does not significantly differ from that of OSAS.

The diagnosis of CSA is made by criteria recommended by the ICSD-3 manual as well [13]. Patients with primary central sleep apnea present with (1) sleepiness or difficulty initiatiing or maintaining sleep, frequent awakenings, or non restorative sleep or awakening, short of breath or snoring or witnessed apneas. PSG demonstrates five or more central apneas and/or hypopneas per hour of sleep (PSG). The number of central apneas and/or central hypopneas is > 50 % of the total number of apneas and hypopneas, with absence of Cheyne-Stokes breathing. There is no evidence of daytime or nocturnal hypoventilation. All these criteria

must be met (2) repetitive nocturnal arousals and awakenings during sleep or insomnia complaints or (3) awakening short of breath, combined with five or more central apneas per hour of sleep. The disorder is not better explained by another current sleep disorder, medication use (e.g. opioids) or substance use disorder. Very often, many patients with CSA have mild hypocapnia or normocapnia, but rarely hypercapnia and hypoventilation are also observed. A periodic pattern of waxing and waning of ventilation with periods of hyperventilation alternating with central apnea-hypopnea is defined as central sleep apnea with Cheyne-Stokes breathing (CSB). According to ICSD-3 manual, CSB can be considered if (A) presence of one or more of the following: (1) sleepiness, (2) difficulty initiating or maintaining sleep, frequent awakenings, or nonrestorative sleep, (3) awakening short of breath, (4) snoring, or (5) witnessed apneas. (B) The presence of atrial fibrillation/flutter, congestive heart failure, or a neurological disorder. (C) PSG (during diagnostic or positive airway pressure titration) shows all of the following: (1) Five or more central apneas and/or central hypopneas per hour of sleep. (2) The total number of central apneas and/or hypopneas is > 50 % of the total number of apneas and hypopneas. (3) The pattern of ventilation meets criteria for Cheyne-Stokes breathing. (D) The disorder is not better explained by another current sleep disorder, medication use (e.g. opioids), or substance use disorder.

Although symptoms are not mandatory to make the final diagnosis, patients often report excessive daytime sleepiness, repetitive arousals and awakenings during sleep, insomnia complaints or awakening short of breath [13].

A third patient group in the spectrum of SDB is termed sleep-related hypoventilation/hypoxemic syndrome. Sleep-induced hypoventilation is characterised by arterial carbon dioxide tension ($PaCO_2$) >45 mmHg or disproportionately increased levels while asleep relative to levels during wakefulness [12]. This group encompasses obesity hypoventilation syndrome, congenital central alveolar hypoventilation syndrome, late onset central hypoventilation with hypothalamic dysfunction, idiopathic central alveolar hypoventilation, sleep related hypoventilation due to a medication or substance and sleep related hypoventilation due to a medical disorder [13]. Obesity hypoventilation syndrome (OHS) is probably the most prevalent clinical presentation of this syndrome. OHS is defined as the association of obesity (BMI > 30 kg/m^2) and hypercapnia ($PaCO_2$ > 45 mmHg) that is not primarily due to lung parenchymal or airway disease, pulmonary vascular pathology, chest wall disorder (other than mass loading from obesity), medication use, neurologic disorder, muscle weakness, or a known congenital or idiopathic central alveolar hypoventilation syndrome [21–24]. There is however not a commonly accepted definition for OHS. A last patient group is defined as sleep related hypoxemia disorder and is characterised by significant hypoxemia during sleep, and believed to be secondary to a medical or neurological disorder. PSG, PG or nocturnal oximetry shows the arterial oxygen saturation during sleep of <= 88 % in adults for >= 5 min. Sleep hypoventilation has not been documented.

Different definitions have been proposed by the AASM for the different entities of sleep-disordered breathing (ICSD-3 versus scoring manual), which may complicate the understanding of the problem [13–18].

Epidemiology of Obstructive Sleep Apnea

Epidemiological studies investigating the prevalence of SDB are all biased by the lack of a uniform definition [1, 10]. The prevalence of an AHI>5 in the general population has previously been estimated to be 24 % in males, without symptoms of sleepiness taken into account [1]. When symptoms of sleepiness were also included, the prevalence decreased to 4 % in males and 2 % in females. Using a more restrictive definition including only symptomatic subjects with a fair amount of respiratory events that warrant CPAP therapy, the prevalence is about 0.5 % for middle-aged men with a normal BMI and 1.5 % for the same group with an increased BMI [25, 26]. The growing prevalence of SDB is in parallel with the growing prevalence of obesity. Most of the cases are however unsuspected, since the two most important complaints of loud snoring and a tendency to fall asleep during daytime are often considered normal variants, and patients frequently do not seek medical attention [27]. Unfortunately, many patients who do seek medical attention are dismissed as having no significant disturbance, without formal assessment, and it is very common for patients who have been suffering for many years to present to sleep clinics. Snoring is the hallmark of relevant OSAS, with a prevalence based on epidemiological studies of 9–50 % in men and 4–17 % in women. In a multicentre study performed in Iceland, Belgium and Sweden, asking for snoring at least 3 nights a week, very similar results were found [28]. Several population-based studies have reported an increase in snoring with age, followed by a decrease after the age of 50–60 years in both males and females [26, 28–32]. Some cross-sectional epidemiological surveys have found significant associations between cigarette smoking and snoring, linked to airway inflammation and nocturnal nicotine withdrawal [33].

Common risk factors for OSAS are obesity, gender, aging, race, smoking and alcohol use, besides co-morbidities as enlarged tonsils, adenoids and craniofacial abnormalities.

Obesity

About 80 % of OSAS patients are obese and obesity is an established risk factor for OSAS. A very tight relationship has been observed between body weight change and AHI: a 10 % weight gain has been shown to predict an approximate 32 % increase in the AHI, a 10 % weight loss predicts a 26 % decrease in the AHI, and a 10 % weight gain predicts a sixfold increase in the odds of developing moderate to severe OSAS [34]. Obesity causes upper airway narrowing as a result of excess fat in the (peri- and para)pharyngeal tissues [35]. Despite the strong relationship with obesity, it is important to remember that not all subjects who are obese or have a large neck circumference suffer from relevant sleep apnea and that one-third of OSAS patients are not obese [36, 37].

Age

Several papers have shown a higher prevalence of OSAS in the elderly. In the Sleep Heart Health Study, it was shown that 25 % of males and 11 % of females in the age group 40–98 years had an AHI of higher than 15 events per hour [38]. However, daytime symptoms may be less common with advancing age [39]. The influence of male gender and BMI on OSAS tends to wane with age, and the overall prevalence of symptomatic OSAS seems to stabilise after age 65 years, while the age distribution of OSAS seems to increase regardless of age [9]. On the other hand, the age distribution of patients first diagnosed with OSAS generally peaks at the age of 50. Anyway, the high prevalence of sleep apnea in the elderly has led to a debate regarding its causes and consequences in older people [40, 41]. It could be suggested that older OSAS patients may be habituated to the added disease-related sleep disruption of OSAS and, therefore, do not suffer symptoms of daytime sleepiness in the same way as younger patients.

Gender

Epidemiological studies have reported that OSAS is much more prevalent in males. Possible explanations include the effects of hormonal influences affecting upper airway musculature and its ability to collapse, differences in body fat distribution and sex differences in pharyngeal structure and function [36].

A referral bias and gender differences in clinical presentation may have resulted in more males than females being diagnosed [42]. Males with OSAS are more likely to have symptoms of loud snoring, witnessed apneas or sleepiness.

Symptoms expressed by female OSAS patients are less typical and encompass insomnia, fatigue, morning headache and depression, while male bed partners are less likely to report snoring and apneas to their family physician as compared to their female counterpart. Therefore, female OSAS patients are less likely to be diagnosed and treated as compared to their male counterpart. Currently, there is increasing recognition that the disease is also prevalent in females, particularly after the menopause, and that the clinical manifestations may differ from those in males [43, 44].

Smoking and Alcohol Use

The role of smoking as an established risk factor for OSAS remains controversial. Wetter et al. found a dose-response relationship between smoking and AHI, while smokers in the Sleep Heart Health Study displayed less sleep apnea than nonsmokers [45, 46]. These discrepancies remain unexplained, and there is a need to unravel the link between tobacco consumption and OSAS. Solid epidemiological studies related to chronic alcohol intake and sleep apnea are missing, due to a lack of

reliable instruments for estimating alcohol use. Some population-based cross-sectional studies have reported a significant association between chronic alcohol intake and OSAS, whereas other cross-sectional or longitudinal studies did not [30, 47].

Race

Although data are scarce, African-Americans and Asians appear to be at higher risk of developing OSAS than Caucasians [48]. This finding could at least partly be explained by differences in craniofacial structure [49].

Symptoms and Signs

Symptoms of OSAS can be divided in symptoms experienced by the patient himself and symptoms recognised by the bed partner [50, 51].

Snoring

Obstructive sleep apnea is mainly characterised clinically by loud snoring. It is often more cumbersome for the bed partner than for the patient himself and is often existing for a long time. Four or five loud snores followed by a silence (apnea) and another series of loud snores is a very suggestive description of a subject with obstructive apnea. The resumption of ventilation can be associated with loud stridorous breathing ("gasping"). Typically, these symptoms are more prominent in the supine position or after alcohol consumption. Occasionally, however, snoring may not be so obvious even in the presence of severe sleep apnea [52]. There is also a growing body of evidence that snoring might cause daytime sleepiness in the absence of OSAS [1]. This might be explained by the upper airway resistance syndrome that is characterised by episodes of increased respiratory effort followed by arousals and daytime sleepiness or by upper airway inflammation due to snoring-induced vibrations within the pharynx [53, 54].

Sleepiness

Pathological daytime sleepiness is the second key symptom in the diagnosis of sleep apnea [51, 55, 56]. It is caused by loss of deep sleep, which presents 20 % of total sleep time in young subjects. The obstruction of the upper airways leads to the activation of the central nervous system, the so-called arousal, with sleep fragmentation

as a consequence. A more fragmented sleep will result in a more sleepy patient during daytime. In general, patient and environment will not take much attention towards this daytime sleepiness, as far as it does not lead to repetitive car accidents or occupational accidents. Extreme sleepiness is characterised by falling asleep inadvertently during motor activity (talking, eating). Unequivocal sleepiness means falling asleep at rest, or while driving. The extension of normal diurnal sleepiness is considered as mild sleepiness. Tests have been developed to measure sleepiness more objectively [57]. The multiple sleep latency test (MSLT), maintenance of wakefulness test (MWT) and vigilance tests are used for this purpose. The use of the self-administered questionnaire, the Epworth Sleepiness Scale (ESS), which was validated with MSLT, enhances the accessibility of the quantification of EDS. There is however some controversy, since the ESS does not correlate well with the MSLT and other vigilance tests. Also the AHI only weakly correlates with quantified measures of sleepiness, which indicates that some individuals cope better with sleep fragmentation than others, or could be related to brain susceptibility and subjective perception of the consequences of hypoxemia [58]. Using a cut-off value of 18 events per hour including all apneas, hypopneas and flow limitation events, a sensitivity of 71 % and a specificity of 60 % for identifying subjects with excessive daytime sleepiness were obtained. When flow limitations are not taken into account, the sensitivity/specificity is even far worse [59]. Hence, for clinical purposes, it must be clear that the respiratory disturbance index is a more reliable parameter, but even then, its correlation with daytime symptoms also remains suboptimal.

In the Sleep Heart Health Study, also a weak correlation between the AHI and sleepiness was reported: the ESS only rose from 7.2 to 9.3 when the AHI changed from less than 5 to more than 30 [6]. It is however important to decide whether CPAP therapy should be instituted to treat daytime sleepiness. In case of sleep apnea, MSLT and vigilance testing are most often restricted to patients with persistent hypersomnolence despite adequate continuous positive airway pressure (CPAP) therapy or surgical or oral device therapy. On the other hand, routine use of these tests could be recommended for medicolegal reasons [60]. While tasks arising at regular intervals can even be performed at decreased levels of vigilance, fulfilling the criteria of light sleep, this is not the case for unexpected tasks and events. Therefore, up to 9 % of all traffic accidents are ascribed to sleepiness. In those car accidents in which sleepiness was the obvious cause, the rate of deaths was three times as high as in other accidents. Falling asleep while driving seems to be the cause of 3 % of the accidents causing material damage, 20 % of the accidents causing injuries and 50 % of the accidents causing death [61]. Not rarely, a recent accident can give occasion to consult a physician. A polysomnographic study revealed that socially disturbing loud snoring is associated with OSAS (AHI > 10) in 20 % of the patients referred to exclude sleep apnea. The combination of loud snoring with excessive daytime sleepiness reveals OSAS in 35 % of the referred patients [62]. The difficulty particularly in moderately severe OSAS is to identify EDS resulting from causes other than sleep apnea. Depression and mood disturbance are among the most important confounding factors [63–65]. Obesity alone may also interfere

through adipokines and chemokines being activated even in the absence of OSAS. In OSAS, stress activation involving both the HPA axis and the sympathetic system may also play some role.

Other Symptoms at Night

Abnormal motor activity, problems with maintaining sleep and awakening too early in the morning, nightmares, nocturnal dyspnea, nocturnal suffocation and nycturia are often reported. OSAS patients often sleep restless and turn and toss. Apneas are often associated with movements, which can sometimes be limited to mild movements, but abrupt more pronounced arm and leg movements with involuntary kicking and beating of the bed partner can occur [66]. Due to this nocturnal motor activity, OSAS patients often suffer from severe nocturnal transpiration. Nevertheless, the patient is often convinced that he/she is sleeping well at night and is unconscious of the breathing disturbances.

Other Daytime Symptoms

Detailed history taking of patient and bed partner can unravel the association between main symptoms and the sleep apnea syndrome: matinal headache (due to nocturnal CO_2 retention), being not refreshed in the morning, behaviour changes, decreased intellectual performance, depression, anxiety, automatic behaviour, social problems, marital problems, impotence (men), decreased libido, unexplained muscle discomfort and—last but not least—decreased quality of life. The absence of symptoms does not exclude OSAS. On the other hand, it is remarkable that, despite these typical symptoms, the interval between the first symptoms and the final diagnosis can often take some years.

Gender and Age Bias

It should be kept in mind that most studies have been performed in middle-aged subjects (range 50–60 years), clearly overweight male subjects with moderate to severe OSAS. Hence, the symptoms and neurobehavioural as well as cardiovascular and metabolic sequelae in OSAS mainly apply to this cohort. Nevertheless, OSAS can also have a large impact on daytime sleepiness and quality of life in the elderly (>70 years old). Surprisingly, history and daytime symptoms can be less specific in this age category [67]. A gender bias also takes place in the OSAS population, as discussed earlier.

Morbidity and Mortality

Cardiovascular Morbidity

OSAS is a serious health hazard being recognised as an independent risk factor for arterial hypertension, stroke, cardiac arrhythmias and coronary artery disease [7, 68, 69].

Arterial Hypertension

Elevated blood pressure can be present during sleep as a consequence of OSAS [70]. Moreover, hypertension during wakefulness may be related to OSAS. 45 % of patients with OSAS have hypertension. In OSAS, hypoxia increases sympathetic tone via chemo- and baroreflex activation, thus increasing blood pressure [70, 71]. Increased negative intrathoracic pressure (causing increased venous return) and arousal from sleep, both in association with apnoeic events, also contribute to the rise in blood pressure seen in OSAS [72–74]. The absence in OSAS patients of the normal decrease in BP during sleep, termed as "non-dipping", may be the earliest sign of OSAS-related hypertension and an independent risk factor for developing coronary artery disease [75, 76], as well as heart failure, especially heart failure with preserved ejection fraction and a strong risk factor for stroke. The Wisconsin Sleep Cohort Study, a large population-based study ($n = 1{,}060$), reported a dose-response relationship between OSAS and hypertension. After correction for known risk factors of hypertension, this relationship was still present [77]. Also the Sleep Heart Health Study ($n = 6{,}424$) identified OSAS as an independent risk factor for hypertension [78]. In the 4-year follow-up period, the odds ratio of developing hypertension increased linearly with increasing AHI [79].

Stroke

Evidence from a variety of studies has suggested a link between stroke and OSAS. OSAS patients have an increased risk of stroke [80–82], with the 10-year predicted occurrence of stroke being 14 % [83]. Vice versa, a high prevalence of OSAS was also demonstrated in patients with stroke [84–87].

Central apneas and Cheyne-Stokes respiration have been shown to occur quite commonly in the acute phase of stroke but spontaneously resolve with time and seldom need treatment.

Intermittent hypoxia is probably the most critical factor in the cerebrovascular abnormalities predisposing OSAS patients to stroke. Moreover, impaired cerebrovascular response to hypoxia has been reported in OSAS patients, which is consistent with underlying abnormal endothelial function. Overall, fluctuations in

blood pressure, reduction in cerebral blood flow, altered cerebral autoregulation, endothelial dysfunction, accelerated atherogenesis and pro-thrombotic and pro-inflammatory states are mechanisms implicated in the increased risk for stroke in OSAS [88]. Studies have found a direct relationship between nocturnal oxygen desaturations, intima-media thickness and atherosclerotic plaques in the carotid artery, independent of the presence of hypertension, and thereby support a causal relation between OSAS, atherosclerosis and subsequent stroke [89, 90]. Another correlation was found between increased severity of OSAS and incidence of stroke and death in a cohort of OSAS patients after a median follow-up of 3.4 years [80]. Consequently, increased mortality was reported in patients with severe OSAS (AHI > 30) after stroke [85, 91], and cross-sectional data from the Sleep Heart Health Study have shown greater odds for stroke in the highest quartile (AHI > 11) (1.58 [95 % CI 1.02–2.46]) than in the lower quartile (AHI 4.4–11) (1.42 [75 % CI 0.91–2.21]) [82]. Another group showed an odds ratio of 4.33 (95 % CI 1.32–14.24) for prevalent stroke in moderate to severe OSAS (AHI ≥ 20), independent of other risk factors, compared to patients without OSAS. After 4 years of follow-up, an AHI ≥ 20 at baseline was associated with an increased risk of incident stroke after adjustment for age and sex, but not for body mass index (OR 4.48 [95 % CI 1.31–5.33]). However, after adjustment for age, sex and BMI, the OR was still elevated but no longer statistically significant (OR 3.08 [95 % CI 0.74–12.81]) [81].

Cardiac Arrhythmias

Different types of cardiac arrhythmias have been observed and associated with OSAS. The most common arrhythmias during sleep include non-sustained tachycardia, sinus arrest, second-degree atrioventricular conduction block and premature ventricular contractions. Their prevalence and complexity increase with the severity of the OSAS and the associated hypoxemia [92–94]. The Sleep Heart Health Study suggested that patients with OSAS had increased likelihood of atrial fibrillation (OR 4.02 [95 % CI 1.03–15.74]), non-sustained tachycardia (OR 3.40 [95 % CI 1.03–11.20]) and complex ventricular ectopy (OR 1.75 [95 % CI 1.11–2.74]) [95]. The mechanisms by which OSAS induces ventricular arrhythmias are uncertain, but hypoxia, bradyarrhythmias and sympathetic activation induced by apneic events may play an important role. It has been shown that ventricular premature beats decreased by 58 % after 1 month of CPAP treatment in OSAS patients with congestive heart failure (CHF) [96]. The Sleep Heart Health Study assessed a fourfold increase in the prevalence of atrial fibrillation in subjects with an AHI ≥ 30 [95]. Hypoxemia, sympathetic activation, blood pressure changes, transmural pressure surges and systemic inflammation may be mechanisms that predispose to the development of atrial fibrillation. The relationship between OSAS and atrial fibrillation may also contribute to the increased risk of stroke observed in patients with OSAS.

Coronary Artery Disease

Some studies suggest an independent association between OSAS and coronary artery disease (CAD) in middle-aged males and females [97]. One study assessed not only the association between coronary artery calcification (CAC) and OSAS but also highlighted the association between CAC and increasing OSAS severity. The odds ratio for CAC increased with OSAS severity: mild (OR 2.1 [50 % CI 0.8–5.4]), moderate (OR 2.4 [75 % CI 1.0–6.4]) and severe OSAS (OR 3.3 [95 % CI 1.2–9.4]) [98]. The frequency of nocturnal oxygen desaturation correlated with the extent of coronary lesions and explained 13.4 % of their variance, suggesting a pathogenetic role of OSAS in coronary atherosclerosis [99]. The chronic effects of OSAS, such as systemic inflammation, oxidative stress, vascular smooth cell activation, lymphocyte activation, increased lipid levels, lowering in macrophages, lipid peroxidation, high-density lipoprotein dysfunction and endothelial dysfunction, potentially trigger the formation of atherosclerotic plaques. Plaque rupture can be provoked by the acute effects of OSAS, such as intermittent hypoxemia, acidosis, increased BP and systemic vasoconstriction, in conjunction with simultaneous changes in intrathoracic and transmural pressure [88]. Hence, the increased oxygen demand and reduced oxygen supply at night in OSAS patients may trigger an attack of myocardial ischemia and nocturnal angina. Nocturnal angina and ST depression have been described in OSAS patients, which may be diminished after CPAP treatment [100, 101]. However, another study did not find evidence of nocturnal myocardial injury detectable by measurements of cardiac troponin T in patients with established CAD and moderate/severe OSAS [102]. In addition, observations of the occurrence of myocardial infarction (MI) in OSAS patients assessed an altered time interval of nocturnal sudden death compared to the general population. In general, the likelihood of onset of MI is between 06:00 and 11.00 h. In contrast, almost half of OSAS patients have their onset of MI during the sleep hours, between 22:00 and 06:00 h. This may implicate that OSAS may precipitate nocturnal MI [103, 104].

Subclinical Cardiocirculatory Impairment

One of the recent major clinical findings in the past years is the occurrence of atherosclerosis in OSAS patients free of any cardiovascular morbidity and of other cardiovascular risk factors [89, 105]. This is part of the subclinical cardiocirculatory impairment described in OSAS, together with masked hypertension [106], increase in arterial stiffness [107], diastolic dysfunction [108, 109] and left but also right ventricle hypertrophy [110]. Some of these early cardiovascular changes have been correlated with systemic inflammation [111], related to intermittent hypoxemia [112]. About half of the cases presenting with the clinical syndrome of heart failure have a normal left ventricular ejection fraction (so-called heart failure with preserved ejection fraction), and left ventricular diastolic dysfunction is considered to be a common underlying pathology [113]. Studies have shown that the impairment of left ventricular diastolic function is common in OSAS patients, suggesting

subclinical myocardial disease that may account for the risk of heart failure [114–116] and also suggesting a role of OSAS in pulmonary hypertension. OSAS appears to be associated with cardiac remodelling and altered diastolic function and to exert an additive effect to that of increased blood pressure in patients with both hypertension and OSAS [108]. Cross-sectional data from the Sleep Heart Health Study have shown a strong association of SDB in moderate and severe OSAS with heart failure (OR 2.38 [95 % CI 1.22–4.62]) and a less strong association for mild OSAS (OR 1.95 [75 % CI 0.99–3.83]) [117].

Cardiovascular Mortality

Observational cohort studies indicate that untreated patients with OSAS have an increased risk of fatal and nonfatal cardiovascular events, an increased risk of sudden cardiac death during the sleeping hours and a higher risk of stroke or death from any cause [7, 68]. According to He et al., the probability of cumulative 8-year survival was 0.96 for patients with an apnea index <20 and 0.63 for those with an apnea index >20. Difference in mortality related to apnea index was particularly true in the patients less than 50 years of age, in whom mortality from other causes is uncommon [118]. In the study of Marin et al., multivariate analysis, adjusted for potential confounders, showed that untreated severe OSAS significantly increased the risk of fatal (OR 2.87 [95 % CI 1.17–7.51]) cardiovascular events compared with healthy participants [7]. Treatment with tracheostomy or CPAP attenuated this risk [7, 118].

Since the group treated with CPAP received more intensive follow-up during the first year after diagnosis (two additional visits), outcome could be improved in this group independently of the CPAP treatment. Moreover, these results were only applicable to men. In patients with coronary artery disease but also in stroke, the occurrence of OSAS was a significant predictor of (early) death [119, 120]. These studies have the inherent limitation of lacking a randomised controlled design, which clearly limits the evidence level. In one prospective study, it was found that the apnea index was a predictor of excess mortality in the fourth and fifth decade, but not in the elderly [121]. In some population-based cohorts, a decrease in survival was reported with increasing OSAS severity, with an OR of 3.0 (95 % CI 1.4–6.3) (Wisconsin) and 1.46 (1.14–1.86) (Sleep Heart Health Study) in subjects with an AHI ≥ 30 compared with those with an AHI < 5 [122, 123]. However, after stratification by age and gender in the Sleep Heart Health Study, the OR remained only significant in males aged <70 years. Lavie et al. proposed a survival advantage in moderate OSAS, suggesting, as a potential mechanism, that chronic intermittent hypoxia during sleep may activate adaptive pathways in the elderly [124]. For example, older subjects have a reduced acute cardiovascular response to arousal from sleep, compared with younger people [125]. Hence, the poorer cardiovascular reactivity of older adults may, paradoxically, reduce the impact of arousals from sleep and protect against cardiovascular morbidity and mortality. However, it has to be reminded that the cardiovascular consequences of sleep apnea in older people may

also be influenced by survival bias, as middle-aged, hypertensive OSAS patients may not survive into old age. Discrepancies among studies could potentially be explained by the heterogeneity of the patients included in the elderly populations.

Metabolic Consequences

A number of OSAS metabolic consequences have been identified. Some studies found increased insulin resistance and impaired glucose tolerance in OSAS patients, independent of body weight [126–128], and a worsening of insulin resistance with increasing AHI [129]. However, other investigations failed to demonstrate an independent effect of AHI owing to the major impact of obesity [130]. In cohort of the general population, both the Wisconsin Cohort Study and the Sleep Heart Health Study have identified OSAS as an independent risk factor for insulin resistance, after adjustment for potential confounding variables, such as age, sex and BMI [131, 132]. However, subjects with an AHI $\geq$ 15 did not differ significantly from those with an AHI < 5 when it came to the risk of developing diabetes over a 4-year period (OR 1.62 [95 % CI 0.7–3.6]), after adjustment for age, sex and BMI [132]. Intermittent hypoxia and sleep fragmentation are thought to play a key role in the development of metabolic disturbances through the activation of the sympathetic nervous system and pro-inflammatory pathways. It was shown that even lower-grade desaturations are strongly linked with glycaemic status abnormalities [133]. Furthermore, the increase in risk for developing diabetes overtime is increased in OSAS independent of the decrease in arterial oxygen saturation [134]. Sleep fragmentation due to cortical and automatic arousals accounts for alterations in sympathetic/parasympathetic activity, and the simultaneous presence of metabolic syndrome and OSAS further increases sympathetic activity and worsens glycaemic control, even after adjustment for body mass index [135]. Alteration in glucose metabolism and sympathovagal balance has been observed previously in normal subjects following two nights of experimental sleep fragmentation [136].

Cognitive Deficits

It comes as no surprise that OSAS with the consecutive sleep disturbance has detrimental effects on cerebral function. Memory, attention and learning ability have been reported to be abnormal in some OSAS patients [137–140]. Both "lower-level" processes (arousal and alertness) and "higher-level" cognitive processes (e.g. executive attention) have been disturbed, including the ability to inhibit inappropriate behaviours and thoughts, regulate attention and plan and organise for the future [50, 141, 142]. Specific cognitive impairments (like thinking, perception, memory, communication or the ability to learn new information) are present in 76 % of OSAS patients [143]. Studies using functional MRI or PET indicate sleep

loss as the primary cause of neurocognitive deficits, mainly a basal slowing in information processing, more so than hypoxemia [142]. Whether there are not only functional but also anatomical sequels of OSAS is more difficult to evaluate, since the profound effects of decreased alertness on higher cognitive functioning mimic cerebral damage due to hypoxia. OSAS can promote axonal dysfunction or loss, as well as myelin metabolism impairment in the frontal periventricular white matter, which causes cognitive executive dysfunction [144]. A therapeutic challenge with CPAP can learn that not all cognitive function alterations reverse, and they may represent neuronal damage. Moreover, when cognitive function is preserved in OSAS patients, functional brain imaging has revealed that brain activation is increased, compared with the activation that occurs in healthy controls performing the same task. The association between preserved cognitive function and greater activation in OSAS patients suggests that increased cerebral recruitment (overrecruitment) is required to maintain cognitive performance [145, 146]. Currently, it is also well established that cognitive and attentional deficits may occur in OSAS in the absence of perceived subjective EDS [147]. It questions the sensitivity of the tools used for evaluating EDS. Moreover, attentional deficits may occur without objective EDS [147]. Reaction time and sustained and divided attention tasks may be altered in the absence of sleepiness. It should further be studied whether these attentional deficits may impair driving ability and other social and professional abilities. If confirmed, it raises the question of who should be treated, since the absence of perceived sleepiness would then not be required for treating OSAS.

Associations

Epidemiological studies provide strong evidence that OSAS is highly prevalent in patients with obesity [34, 148], diabetes mellitus [36, 51, 149], arterial hypertension [88, 150], metabolic syndrome [151], cardiovascular disease [152–155] and endocrinopathies [51, 156]. Often, patients with OSAS suffer from sleepiness during daytime, but other symptoms can be present as well, while others remain asymptomatic. In the presence of other disorders, symptoms in OSAS may not conform to the typical history and physical findings. Moreover, sleepiness is a frequently reported symptom in the absence of OSAS and is thereby not a useful clinical symptom to suggest the diagnosis of OSAS in these patients. On the other hand, patients with medical disorders often express fatigue, tiredness or lack of energy rather than sleepiness itself, which can be related to the medical disturbance but can also be the cardinal symptom of an underlying OSAS [12, 157–159] or any other sleep disorder. Their negative effects are more frequent, rapid and intensive if patients suffering from medical disorders also suffer from OSAS. Due to this coincidence of OSAS and disorders of other systems, their consequences are mutually increased [160].

Comorbid OSAS in Obesity

Obesity is linked with OSAS. According to various data, the simultaneous occurrence of obesity and OSAS is approximately 35 %, and their mutual relationship is reciprocal. Deposition of fat even in the neck area, especially in men with central type of obesity, contributes to upper airway obstruction and to easier development of apneas during sleep.

Controversy remains as to whether specific anthropometric indices of body habitus, such as neck or waist circumference, are better predictors of OSAS as compared with BMI alone [36, 149].

However, despite the strong relationship with obesity, it is important to remember that not all subjects who are obese or have a large neck circumference suffer from sleep apnea and that some one-third of OSAS patients are not obese [36].

Comorbid OSAS in Arterial Hypertension

Several large population-based cross-sectional studies have reported an independent link between arterial hypertension and OSAS, when controlling for multiple potential confounding variables. OSAS and systemic hypertension commonly coexist: OSAS is present in at least 30 % of hypertensive patients, while about half of OSAS patients suffer from systemic hypertension [88]. In patients with refractory hypertension, up to 85 % has OSAS. Currently, OSAS is also considered a risk factor in the hypertension management guidelines [150, 161].

Comorbid OSAS in Congestive Heart Failure

Studies have suggested an increased prevalence of OSAS as well as CSA in patients with CHF, even in patients with asymptomatic left ventricular dysfunction, between 20 and 50 % [152]. A failing heart with reduced left ventricular ejection fraction, diastolic dysfunction and increased filling pressures is more vulnerable to stressors such as increased blood pressure (afterload) or sympathetic activation as compared with a healthy heart. It explains why OSAS is particularly detrimental in patients with established heart failure. These data imply that strategies to recognise sleep apnea are highly warranted in CHF patients. Predictive factors for the presence of CSA were male gender, the presence of atrial fibrillation, daytime hypocapnia or age >60 years. The predictive factors for OSAS include an increased BMI (BMI > 35 kg/m^2) in men and age >60 in women [162]. Surprisingly, the majority of patients with CHF and comorbid OSAS do not complain of excessive daytime sleepiness, possibly owing to chronically elevated sympathetic activity [163].

Comorbid OSAS in Atrial Fibrillation

In a study comparing patients with atrial fibrillation (AF) ($n=151$) to patients with no history of AF in a general cardiology practice ($n=312$), Gami et al. demonstrated that the proportion of patients with OSAS was significantly higher in the patients with AF than in the patients without AF (49 % vs. 32 %, $p=0.0004$) [154]. The adjusted OR for AF was 2.19 in OSAS subjects ($p=0.0006$). In a multivariate analysis, BMI, neck circumference, hypertension, diabetes mellitus and AF remained significantly associated with OSAS, and the OR was largest for AF. A higher recurrence of atrial fibrillation after cardioversion has also been reported in those with untreated OSAS compared to those without OSAS [164]. Therefore, patients referred for the evaluation of significant tachyarrhythmia or bradyarrhythmia should be questioned about symptoms of sleep apnea.

Comorbid OSAS in Coronary Artery Disease

There is a high prevalence of OSAS among patients with angiographically proven coronary artery disease and an increased incidence of coronary artery disease in patients free of coronary symptoms at the time of OSAS diagnosis [155]. Data suggest that patients with coronary artery disease should be particularly questioned for symptoms and signs of sleep apnea. If there is even the slightest suspicion of sleep apnea, the patients should undergo a polysomnography [162].

Comorbid OSAS in Endocrine and Metabolic Disorders

OSAS is common in many endocrine and metabolic conditions, like insulin resistance, type 2 diabetes and the metabolic syndrome [51, 156, 165]. Given the high prevalence of OSAS among these patient categories, specialists treating metabolic disorders and abnormalities should consider investigation for OSAS in their patients.

Hypothyroidism

OSAS has been reported to occur frequently in patients with untreated hypothyroidism (50–100 %), especially when myxoedema (dry skin and hair, loss of mental and physical vigour) is present [166]. However, there are no conclusive studies since an association could largely be explained by coexisting obesity and male sex. No large prospective studies investigating the prevalence of OSAS in patients with hypothyroidism are available. However, patients with hypothyroidism, especially when clinical signs are present, should be screened for the presence of OSAS. Symptoms

of OSAS in patients with comorbid hypothyroidism do not substantially differ from those with normal thyroid function [51, 165].

Pathogenesis appears to involve both myopathy and upper airway edema [167]. Both maximal and median apnea duration and maximum oxyhaemoglobin saturation are significantly correlated with thyroxin levels and improve with substitution therapy. Hormone therapy also significantly improves apnea index and arousal index. Some studies report persisting apneas despite adequate replacement therapy, which supports the view of a chance rather than causal association. In these circumstances, such patients continue to require regular nasal CPAP.

Acromegaly

OSAS is common in acromegaly, a condition resulting from excessive growth hormone, with prevalence rates ranging from 12 % to 75 % in unselected patients with acromegaly [168]. Sleep apnea is more likely to occur with increased severity of acromegaly, higher age, greater neck circumference, greater initial tongue volume, presence of alterations in craniofacial dimensions (predominantly of the mandible) and upper airway narrowing due to changes in pharyngeal soft tissues [169]. Other factors involved are facial bone deformity, mucosal edema, hypertrophy of the pharyngeal and laryngeal cartilages and the presence of nasal polyps. Increases in BMI in acromegaly may be due to increased muscle mass rather than the increased body fat typically seen in obesity, and BMI is often normal [170]. There appears to be no relationship between OSAS and biochemical parameters of disease activity such as growth hormone and IGF-1 levels. OSAS may still persist despite normalisation of growth hormone levels during therapy. CSA is also common and is associated with higher random growth hormone and IGF-1 levels than in OSAS. Possible mechanisms for the development of central apneas in patients with acromegaly include reflex inhibition of the respiratory centre as a result of the narrowing of the upper airways or due to an increase in the ventilatory response of the respiratory centre to CO_2. At present, it is not known what proportion of patients with both sleep apnea and acromegaly will have complete resolution of their sleep apnea after cure of acromegaly. Nevertheless, it is clear that sleep apnea does occur in cured acromegaly, due to coincidence, slow resolution of the effects of acromegaly, or maybe permanent effects on upper airway function or sleep-related regulation [156, 165].

Cushing's Syndrome

Patients with Cushing's syndrome (CS) have an excess of adrenocorticosteroid hormones. Sleep complaints are common, including an increased incidence of OSAS of approximately 18–32 % in patients with CS (in those with pituitary disease) [171]. In one study all CS patients had an AHI of at least 5. Fat accumulation in the parapharyngeal area may be important in the pathogenesis of OSAS [172]. Patients with CS can also present with steroid-induced changes in sleep architecture

including more fragmented sleep, poorer sleep continuity, shortened REM latency, a decrease in delta sleep and an increased REM density, which may explain the insomnia and fatigue and possibly some of the psychiatric symptoms. These features can be aggravated by concomitant OSAS [12, 51, 156, 173].

OSAS and Diabetes Mellitus

Both type 2 diabetes mellitus and OSAS have a prevalence of 3–5 % of the general population and occur with increased frequency in the obese [174]. Therefore, it is not surprising that a significant number of patients suffer from both conditions. Recent reports have indicated that many patients with type 2 diabetes have OSAS, but the relationship between OSAS and metabolic disturbance is most likely bidirectional and at least partially independent of adiposity [175]. In type 2 diabetic patients with OSAS, several studies have assessed the impact of CPAP treatment on glycaemic control [176]. Recent observational studies using continuous glucose monitoring techniques have reported positive effects of CPAP on glycaemic control, already present during the first night of treatment, as variability of glycaemic values decreased compared with baseline conditions [177]. The reduction in HbA1c level was significantly correlated with CPAP use. Hence, screening for OSAS in diabetes may help to improve glycaemic control, especially in insufficiently controlled type 2 diabetic patients. In diabetic patients with autonomic neuropathy, OSAS is also more prevalent (26 %) than in those without, and diabetic neuropathy appears to be directly linked to OSAS [178].

OSAS and Metabolic Syndrome

According to clinical and epidemiological studies, the cluster of risk factors known as the metabolic syndrome is associated with increased risk of diabetes, cardiovascular events and mortality in the general population [179]. Insulin resistance is considered as the major metabolic abnormality and is usually associated with an increased amount of visceral fat [180, 181]. A very high prevalence of severe OSAS (82 %) was reported in metabolic syndrome patients [151]. Prevalence of the metabolic syndrome is also higher in patients with OSAS than in the European general population (15–20 %) or in obese subjects without OSAS [182]. This indicates a bidirectional association between OSAS and metabolic syndrome. Indeed, visceral obesity and the cluster of the metabolic risk factors may lead to OSAS, which in turn may accelerate these metabolic abnormalities, possibly through the induction of inflammation and oxidative stress [151]. Co-occurrence of these two conditions increases remarkably the risk of cardiovascular events and mortality, with higher blood pressure and sympathetic activity, compared with patients with metabolic syndrome without OSAS. The need for screening of metabolic syndrome patients for OSAS is furthermore highlighted by several studies demonstrating improvements in insulin sensitivity in patients with metabolic syndrome after successful treatment of comorbid OSAS by CPAP [183].

OSAS in COPD

Patients with COPD sleep poorly compared to healthy subjects [184]. By coincidence they have a high prevalence of OSAS. The incidence of sleep complaints is related to the rates of respiratory symptoms in COPD patients [184, 185]. However, compared with patients who only have COPD, those suffering also from OSAS have higher ESS scores, lower total sleep time, lower sleep efficiency and higher arousal index [186]. The coexistence of COPD and OSAS favors the presence of daytime hypoxemia and can lead to earlier development of hypercapnia relative to the COPD severity class. Arousals may or may not be related to hypoxemia [165, 187].

OSAS in Chronic Renal Failure and End-Stage Renal Disease

OSAS is ten times more prevalent in patients with end-stage renal disease than in the normal population and is improved by haemodialysis [188]. The pathophysiology of OSAS in this population is mainly related to metabolic disturbances including uraemia, fluid overload, dialysis treatments (with accompanying changes in serum electrolytes, osmolarity and acid-base balance) and the production of somnogenic substances such as IL-1 and TNF-α during dialysis. Patients with end-stage renal disease do not often conform to the stereotypical presentation of OSAS and are generally not obese [189, 190]. Patients with end-stage renal disease often have multiple sleep disturbances, which may complicate the interpretation of signs and symptoms of OSAS and may result in underdiagnosis of OSAS in this population [51, 189].

OSAS and Polycythaemia

Hypoxemic states are frequently associated with increased haematocrit levels [191]. In OSAS, it is thought that this hypoxic stress might lead to secondary polycythaemia. The evidence is largely anecdotal, and there have been few studies that systematically examined this phenomenon [192, 193]. However, after controlling for possible confounding variables, haematocrit is only modestly increased (just 2–3 %) in patients with severe OSAS, compared to controls, and still within the clinically accepted normal range. Hence, OSAS does not lead to clinically significant polycythaemia. On the other hand, the search for the origin of unexplained polycythaemia anecdotally reveals the presence of OSAS.

Moreover, the observation that successful treatment of OSAS with nasal CPAP decreases haematocrit after 1 night indicates a causal relationship between polycythaemia and OSAS [194]. An association with OSAS will more often be found in the presence of other comorbid respiratory conditions, with hypoventilation and chronic nocturnal hypoxemia, as present in obesity hypoventilation [21].

Economical Burden of Untreated OSAS

OSAS gives rise to several complications like motor vehicle accidents (MVAs) and occupational accidents secondary to hypersomnolence, cardiovascular complications and metabolic disturbances like insulin resistance and lipid disturbances. Patients with OSAS have not only more accidents but very often also repeated accidents [195]. It may therefore also represent a health hazard for unaffected individuals who happen to cross the road in front of these patients. There is no doubt that medical consumption in OSAS is also significantly increased: there are more hospitalisations, more ambulatory contacts and a higher consumption of drugs [196]. In 2000, the costs related to car accidents in the USA due to OSAS were estimated at more than 15 billion dollars [197]. A very effective method to document the additional cost of OSAS is the comparison of the costs before and after treatment. In a retrospective study, the hospitalisation duration was evaluated 2 years before and 2 years after the start of CPAP therapy [198]. 88 patients were studied and the number of hospitalisation days decreased (from 413 in the 2 years before the therapy to 54 in the 2 years following the start of the therapy), which is a very convincing effect. Several studies have also demonstrated the effect of CPAP therapy on the costs related to accidents due to OSAS. In a study in 547 OSAS patients looking at the incidence of accidents before and after the start of CPAP therapy, it was shown that the number of effective accidents decreased from 1.6 to 1.1 per patient and the number of near-miss accidents from 4.5 to 1.8 per patient [199]. The number of hospitalisation days related to accidents decreased from 885 days to 84 days. It has to be remarked that not only MVAs were taken into account but also occupational and domestic accidents. Sassani et al. calculated that this could reduce the cost of 15 billion dollars to almost 3 billion dollars [197]. Although these data originate from the USA, there is no reason to believe that this data would be different in Europe. The cost per QALY related to MVAs amounts for only 3,354 dollars [200, 201]. These values compare very favourably with other publicly funded therapies and are lower than the cost per QALY for coronary reperfusion in ischaemic heart disease (18,000 dollars), the use of inhalation corticoids in COPD (19,000 dollars) [202] or the use of cholesterol-lowering therapy (54,000 dollars to 1.4 million dollars) [203]. Moreover, the overall medical consumption seems to decrease after the start of an efficient therapy [204], while medical consumption is increasing gradually in patients with untreated OSAS. After the diagnostic assessment and start of therapy, there was a decrease of 1.95 visits per year versus an increase of 0.48 visits in the control group. Of course, the correct and efficient performance of tasks in an occupational setting has also a great economic impact, although it is hard to measure this directly. In an older study excessive daytime sleepiness at work was evaluated in workers with and without complaints of snoring. Those with snoring had four times more sleepiness than those without. Also the ability to concentrate on new tasks and to learn and execute them was significantly worse [205]. Therefore, it is not surprising that economic models have clearly demonstrated the cost-effectiveness of interventions for OSAS [200, 206, 207].

Meanwhile, it has also become clear that this cost-effectivity is not only related to the effects in males [208]. Also in women a decrease in medical consumption could be achieved after the start of CPAP therapy. Again, also in women a gradual increase in medical consumption in the 2 years before diagnosis and a significant decrease in the 2 following years took place [209]. Altogether, there is enough evidence that demonstrates that SDB, particularly OSAS, is associated with a strong increase in medical consumption. On the one hand, this is the consequence of the co-morbidities but on the other hand also due to excessive daytime sleepiness-related accidents on the road or at work. Several studies have also indicated that an efficient treatment, predominantly CPAP, can significantly decrease this increased medical consumption. Economic models show a very favourable cost per QALY for CPAP therapy. Therefore, screening and treatment of OSAS is one of the better cost-effective interventions.

Conclusions

OSAS is a highly prevalent disorder and characterised by considerable cardiovascular, metabolic and neurocognitive morbidity. Untreated patients with OSAS also have an increased risk of fatal cardiovascular events and death from any cause. Loud snoring is the most prominent symptom. There is still no final agreement on the definitions to be used to describe patients with OSAS. OSAS is also very often associated in common medical disorders.

Patients with OSAS have increased utilisation of health resources, related to the severity of the disease and the associated co-morbidities. These costs increase over time until diagnosis and decrease after the administration of an effective treatment. Moreover, OSAS represents a serious hazard on the road. Therefore, early identification of abnormalities is warranted and may reduce end-organ damage and economic burden.

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