

Epidemiological aspects of obstructive sleep apnea

John F. Garvey¹, Martino F. Pengo², Panagis Drakatos², Brian D. Kent²

¹Department of Respiratory Medicine, Galway University Hospitals, Galway, Ireland; ²Sleep Disorders Centre, Guy's & St. Thomas' Hospitals, London, UK
Correspondence to: Brian D. Kent. Sleep Disorders Centre, Guy's & St. Thomas' Hospitals, London, UK. Email: Brian.kent@gstt.nhs.uk.

Abstract: Obstructive sleep apnea (OSA) is probably the most common respiratory disorder, with recent data from the United States and Europe suggesting that between 14% and 49% of middle-aged men have clinically significant OSA. The intimate relationship between OSA and obesity means that its prevalence will only increase as the global obesity epidemic evolves. At an individual level, OSA leads to a significant decrease in quality of life (QOL) and functional capacity, alongside a markedly increased risk of cardiovascular disease and death. Emerging data also suggest that the presence and severity of OSA and associated nocturnal hypoxemia are associated with an increased risk of diabetes and cancer. At a societal level, OSA not only leads to reduced economic productivity, but also constitutes a major treatable risk factor for hypertension, coronary artery disease (CAD) and stroke. This article addresses OSA from an epidemiological perspective, from prevalence studies to economic aspects to co-morbidity.

Keywords: Sleep apnea; cardiovascular; economic; obesity

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Introduction

Obstructive sleep apnea (OSA) is a highly prevalent disorder, characterised by recurrent episodes of upper airway obstruction occurring during sleep, and associated with recurrent cycles of desaturation and re-oxygenation, sympathetic over-activity and intra-thoracic pressure changes, leading to fragmentation of sleep and consequent daytime fatigue and sleepiness (1). OSA is associated with decreased quality of life (QOL), significant functional impairment, and increased risk of road traffic accidents. However, the relationship of OSA with medical co-morbidity, and in particular cardiovascular co-morbidity, is perhaps the area of most interest from a medical perspective (2). This review will discuss several epidemiological aspects of OSA, namely its prevalence, its close relationship with obesity, and its economic impact, alongside a discussion of population-level, epidemiological data evaluating the impact of OSA on cardiovascular and metabolic disease, and its emerging association with cancer.

Prevalence of OSA

When defined as repetitive upper airway obstruction during

sleep, OSA is a very common disorder. Sleep apnea severity is usually assessed by the apnea-hypopnoea index (AHI) which is the number of complete (apneas) or incomplete (hypopneas) obstructive events per hour of sleep. Defining OSA as an AHI ≥ 5 events/hour in the Wisconsin Sleep Cohort, the prevalence of OSA was 24% in men and 9% in women aged 30-60 years of age (3). The prevalence of OSA with associated excessive daytime somnolence is approximately 3% to 7% in adult men and 2% to 5% in adult women (4). Prevalence estimates don't vary significantly worldwide suggesting that OSA is as common in the developing world as in western society (5).

As will be discussed in greater detail below, OSA has a particularly intimate association with obesity (4). Therefore, as the global obesity epidemic unfolds, it may be expected that the incidence and prevalence of sleep disordered breathing will increase in parallel with this. When data from the Wisconsin sleep cohort study were re-examined with adjustment for current levels of overweight and obesity, a marked increase in the prevalence of OSA was observed (6). Based on these data, 34% of men and 17.4% of women between the ages of 30-70 would be expected to have an AHI ≥ 5 , which would be associated with excessive daytime

sleepiness in 14% of men and 5% of women. Emerging data from Europe suggest that the societal prevalence of the disorder may be even greater when modern diagnostic techniques are used: a community-based Swiss study of over 2,000 subjects diagnosed moderate-severe OSA (i.e., an AHI ≥ 15) in 23.4% and 49% of female and male subjects, respectively (7), potentially alarming findings which need to be confirmed in other studies and other population groups.

OSA and obesity

Obesity, especially central adiposity, is consistently recognised as one of the strongest risk factors for OSA. Given the worsening modern pandemic of obesity in western society, the prevalence of OSA is likely to increase further (4). In the Wisconsin Sleep Cohort study, weight gain over a 4-year period was an important predictor of OSA progression; a 10% increase in body weight conferred a 32% increase in AHI and a 6-fold increase in the risk of developing moderate-severe OSA (8). In the Sleep Heart Health Study, a multi-centre epidemiologic cohort study of cardiovascular correlates of OSA in middle-aged and older Americans, weight gain of 10 kilograms over a 5-year period conferred a 5.2- and 2.5-fold increase in the likelihood of increasing the AHI by 15 events per hour in men and women respectively (9). OSA is present in 41% of patients with a body mass index (BMI) greater than 28 and the prevalence can be as high as 78% in patients referred for bariatric surgery (10,11).

OSA is marked by repetitive collapses of the upper airway during sleep that occur due to reduced airway dilator muscle tone. Obesity may alter the normal upper airway mechanics and contribute to the pathophysiology of OSA in a number of ways (4). Parapharyngeal fat deposition can result in a reduction in calibre and a change in shape of the upper airway promoting collapsibility (12,13). Obesity is associated with a reduction in lung volumes, especially functional residual capacity, contributing to decreased tracheal tug, a decrease in upper airway size and increased airflow resistance (14). Leptin is a hormone produced by adipocytes in proportion to their triglyceride content and involved in the suppression of appetite (15). However, it also acts on the central respiratory centres to stimulate ventilation and leptin deficiency has been associated with hypoventilation (16,17). Obesity is characterised by central leptin resistance and there is blunting of the response to hypercapnia leading to worsening of hypercapnia and impairment of arousal from sleep during apneas (18).

It is postulated that the interaction between OSA and

obesity is not unidirectional, and that OSA may also have an impact on the pathogenesis of obesity (19). It is well recognized that weight gain may be preceded by the onset of OSA symptoms (20), and reduced physical activity with an associated reduction in energy expenditure due to excessive daytime somnolence in OSA can promote weight gain (21). Calorie intake in OSA patients may also be higher (22). Sleep deprivation is a feature of OSA and sleep curtailment is linked with obesity, particularly in pediatric populations (23), potentially through alterations in the hormonal regulation of diet. Finally a number of studies have demonstrated elevated leptin levels in OSA patients compared to weight-matched controls and a decrease in leptin levels following continuous positive airway pressure (CPAP) therapy (24,25), suggesting that OSA may influence leptin metabolism independently of changes in weight (26).

Weight loss should be recommended for all overweight or obese patients with OSA, as it may confer not only a benefit in reducing OSA severity, but also a positive impact on other obesity-related diseases such as type 2 diabetes mellitus (T2DM). Patients with more severe OSA derive more benefit from weight loss than those with milder disease (27). Several studies have explored weight loss as a therapeutic option for OSA and approaches evaluated include behavioral methods (dietary modification and exercise), pharmacological methods and bariatric surgery (28). The results for behavioral modification have been mixed. Johansson reported a significant reduction in AHI to such an extent that 17% were cured, no longer requiring CPAP (27). Results from other studies showed no change in AHI however (29,30). Sibutramine, an oral anorexiant, has been evaluated in a number of studies in OSA patients, but any positive benefit it may have has now been superseded by concerns related to increased cardiovascular morbidity (nonfatal myocardial infarction and stroke) associated with its use (28).

Studies on the effects of bariatric surgery appear promising. In a Swedish case-control longitudinal study of more than 3,400 obese patients, the average fall in BMI was $-9.7 \pm 5 \text{ kg}\cdot\text{m}^{-2}$ compared to $0 \pm 3 \text{ kg}\cdot\text{m}^{-2}$ in the control group (31). There was also a marked improvement in OSA symptoms and a lower 2-year incidence of T2DM and hypertriglyceridemia. Laparoscopic adjustable gastric banding in a cohort of severely obese patients with moderate to severe OSA resulted in significant weight loss and a decrease in AHI when evaluated at 17.7 ± 10.0 months after surgery (32). However, the majority of patients will still have residual OSA after surgery and care should be taken to ensure CPAP is not inappropriately discontinued (33,34).

OSA and age

The prevalence of OSA increases with age in adults (5). This age-related increase in prevalence may be attributable to parapharyngeal fat deposition, lengthening of the soft palate and changes in other anatomic parapharyngeal structures (35). The Sleep Heart Health Study demonstrated that the prevalence of OSA plateaued after the age of 60 years (36), and the increased risk of all-cause and cardiovascular mortality associated with OSA is mainly limited to middle-aged adults, especially men (37). Some researchers have suggested that the mortality risk with sleep apnea may even decrease in the elderly as a result of preconditioning cardioprotective adaptations to chronic intermittent hypoxia (38). Elderly patients with and without excessive daytime somnolence may represent different phenotypes that explain the conflicting data on mortality risk with increasing age in OSA; the presence of concomitant excessive daytime somnolence in OSA patients may increase the risk of mortality whereas the same severity of OSA without symptoms may not (39).

OSA and sex

It is well recognized that there is a higher prevalence of OSA in men than women, with most population-based studies demonstrating a 2- to 3-fold higher prevalence of OSA in men (4). Men are also more likely to be referred for clinical assessment for OSA (40), perhaps because physicians appear to have a higher index of suspicion for considering the disorder in men. This tendency may contribute to the underdiagnosis of OSA in women in clinical practice, a bias which may be compounded by the fact that women often do not present with the classical symptoms of OSA (loud snoring, witnessed apneas and excessive daytime somnolence) but instead may complain of poor energy levels and fatigue (41). Furthermore, the female bed partners of male patients may be more likely to perceive and report snoring or nocturnal breathing abnormalities than male bed partners of female patients.

Sex hormones may also play an important role in the pathogenesis of OSA. OSA is more prevalent in post-menopausal women than pre-menopausal women, and hormone replacement therapy in post-menopausal women may protect against the disorder (42,43).

Genetic aspects of OSA

Given its complexity as a disorder with multiple predisposing

factors, the likelihood of a single governing genetic factor causing OSA is extremely low. That said, it is thought that up to 40% of the risk of OSA is genetically predisposed (44). The prevalence of OSA in first-degree relatives of patients with OSA ranges from 22-84% with an odds ratio (OR) of a first-degree relative having OSA ranging from 2 to 46 (45).

Anatomic risk factors for OSA, such as obesity and upper airway soft tissue structure, demonstrate familial aggregation. Obesity often persists from early life to late middle age and twin studies on Caucasian populations demonstrate a heritability estimate of 57-86% for the trend of BMI from early adulthood to late middle age (46). A case-control study in a Scottish cohort identified a strong familial component to OSA and suggested that differences in facial structure were more important than obesity in this regard (47). The lateral pharyngeal wall volume, tongue volume and total upper airway soft tissue volume have a significant level of heritability after adjusting for sex, age, ethnic background, craniofacial properties and neck fat deposition.

A number of candidate gene associations have been investigated in OSA including different alleles for apolipoprotein E4 (ApoE4), tumour necrosis factor (TNF), and angiotensin-converting enzyme (ACE) but only one TNF polymorphism (TNFA rs1800629) was significantly associated with OSA under an allele frequency model (48).

Economic aspects of OSA

OSA has a significant economic impact on healthcare systems and society. OSA-related healthcare cost includes the direct costs of OSA diagnosis and treatment and the indirect costs of associated conditions (obesity, diabetes) and sequelae (cardiovascular disease, depression). Patients with sleep disorders are less productive workers than those without sleep disorders and have a higher level of absenteeism and decreased productivity at work due to fatigue (49). Occupational injuries are also more common in patients with OSA (50).

Several studies have shown that QOL is adversely affected in patients with OSA and that it improves with therapy (51-53). The bed partner of a patient with untreated OSA may also suffer from disrupted sleep because of the patient's snoring, gasping or witnessed apneas. The QOL of bed partners also improves significantly when OSA is treated (54,55).

Untreated patients with OSA are at an increased risk of motor vehicle accidents (MVAs). Patients with OSA have

a 2- to 10-fold increased risk of MVAs and the severity of accident may be greater compared to controls (56,57). OSA-related MVAs in the USA were estimated to involve 800,000 drivers and cost \$15.9 billion annually (58). Treatment with CPAP therapy reduces this risk in compliant patients to that of controls (59).

The results of cost-effectiveness analyses support the utilization of CPAP therapy in patients with moderate to severe OSA relative to other commonly accepted medical interventions. It is estimated that it costs \$2,000–11,000 per quality-adjusted life year (QALY) over 5 years to treat moderate to severe OSA in a sleep clinic population compared to \$5,000–19,000 for breast cancer screening and \$10,000–57,000 for hypertension control (5).

Epidemiology of co-morbidity in OSA

OSA and cardiovascular disease

OSA and hypertension

The most robust evidence supporting an independent role for OSA in promoting adverse cardiovascular outcomes is to be found in studies addressing its relationship with hypertension (1). Following on from a number of studies where snorers were more likely to also have hypertension than might otherwise be expected (60), a series of clinical and epidemiological studies identified a dose-response relationship between OSA severity and the likelihood of prevalent hypertension (61). For example, a cross sectional analysis of over 6,000 North American subjects enrolled in the community-based Sleep Heart Health Study showed that subjects with severe sleep disordered breathing had an OR of 1.37 [95% confidence interval (CI): 1.03-1.83] for prevalent hypertension following adjustment for confounding factors when compared to those with no OSA (62). Recent European data underline this association, and suggest that intermittent hypoxemia may be a key factor contributing to co-existent hypertension—among 11,900 participants in the multi-national the European Sleep Apnea Cohort (ESADA) study, OSA severity indices, and in particular the oxyhemoglobin desaturation index, were strong independent predictors of hypertension (63).

Subsequent longitudinal studies have provided convincing evidence that OSA contributes to an increased risk of clinically-relevant hypertension. Landmark findings among participants in the Wisconsin Sleep Cohort study demonstrated a strikingly increased propensity for the development of incident hypertension in subjects with sleep

disordered breathing (64). In an analysis of 709 subjects, the presence severe OSA at enrollment conferred a nearly threefold risk of being diagnosed with hypertension over a four-year follow-up period, independently of the effects of age, obesity and smoking history. More recent data from Spain have confirmed this relationship (65).

OSA and coronary artery disease (CAD)

Data from clinic and community based studies generally suggest that CAD is highly prevalent in OSA cohorts (66), and *vice versa* that subjects with CAD are more likely to also have sleep disordered breathing, even allowing for the impact of obesity and other confounding factors (67). For example, in over 6,000 participants in the Sleep Heart Health Study, the burden of self-reported CAD among these subjects increased from 9% in the lowest AHI quartile to 19% in the highest, a relationship that survived adjustment for confounding variables (68).

It is less clear if the presence and severity of OSA actually serve as independent predictors of subsequent CAD, however. While data from relatively small, but well-conducted studies of hospital patients suggest a robust dose-response relationship between the two (69), these data have not been reproduced to the same degree at a population level. A relatively modest relationship between OSA and CAD incidence was seen in a community-based study of 4,422 (56.4% female) North American subjects followed for a median of 8.7 years (37). Within this cohort, severe OSA predicted an increased risk of developing symptomatic CAD, but only in men aged 70 or less (HR 1.68; 95% CI: 1.02-2.76). However, another analysis of this cohort has shown severe OSA to be an independent predictor of death, and in particular death related to CAD (70). While this relationship was again strongest in men under 70 years of age (adjusted HR 2.09; 95% CI: 1.31-3.33), it was nonetheless seen across the entire study population (adjusted HR 1.46; 95% CI: 1.14-1.86), with similar findings seen at eighteen year follow-up in the Wisconsin Sleep Cohort study (71).

Were OSA playing a causative role in driving cardiovascular morbidity and mortality, CPAP therapy might be expected to lead to measurable reductions in adverse cardiac outcomes. In a study of 1,652 subjects attending a Spanish sleep laboratory, cardiovascular outcomes were assessed over an average of 10.1 years (72). Those with untreated severe OSA (14.2%) were more likely to die of cardiovascular disease (adjusted OR 2.87; 95% CI: 1.17-7.51) or experience cardiovascular morbidity (adjusted OR

3.17; 95% CI: 1.12-7.51) compared with healthy non-apneic subjects. In contrast, no significant increased risk of cardiac death was seen in OSA patients who had been successfully commenced on CPAP (adjusted OR 1.05; 95% CI: 0.39-2.21). As yet there are no published data from large-scale randomised trials in this area, although a number of potentially important studies with this goal are ongoing.

OSA and heart failure

Obstructive sleep apnea is highly prevalent in heart failure patients, and is independently associated with increased prevalence of clinically overt heart failure (73). In a cross sectional analysis of the Sleep Heart Health study, severe OSA was associated with increased likelihood of prevalent heart failure, with an adjusted OR of 2.20 (95% CI: 1.11-4.37) in the highest AHI quartile (68). Longitudinal follow-up in the same cohort identified a strong relationship between incident heart failure and AHI in men but not women (37). Following adjustment for demographic, anthropometric and clinical factors and medication usage, male participants with severe OSA at baseline had a 58% increased risk of developing heart failure over nearly nine years of follow-up. When present, OSA appears to lead to increased risk of mortality in heart failure cohorts (74).

OSA and cardiac arrhythmia

Subjects with OSA are at increased risk of atrial fibrillation (AF); in a nested case control study involving 566 participants in the Sleep Heart Health study, severe sleep disordered breathing was associated with a four-fold odds of prevalent AF, following adjustment for age, gender, obesity and the presence of CAD (adjusted OR 4.02; 95% CI: 1.03-15.74) (75). The presence of OSA predicts an increased likelihood of risk factors for AF, such as increased left atrial diameter (76), and furthermore is associated with an increased risk of recurrence of AF and failure of chemical cardioversion measures (77,78). Moreover, recurrence of AF becomes less likely with the initiation of CPAP treatment (77). Sleep disordered breathing is also an independent predictor of ventricular arrhythmia, particularly in subjects with heart failure (75).

OSA and cerebrovascular disease

Sleep disordered breathing is significantly more common in patients who have had a stroke or transient ischaemic attack (TIA) than in the general community, occurring in between 32-63% of stroke patients, and is associated with increased mortality and worse functional outcomes in these patients

(79,80). Furthermore, cerebrovascular disease prevalence appears to increase with increasing OSA severity. Among 6,089 subjects in the Sleep Heart Health Study, 2.7% in the lowest AHI quartile had a prior stroke or TIA, compared with 5.3% in the most severe quartile, a relationship which persisted following adjustment for relevant confounders (adjusted OR 1.58; 95% CI: 1.02-2.46) (68). A number of prospective studies suggest that the presence and severity of sleep disordered breathing predicts incident stroke (81-84). For example, among 5,422 North American subjects followed for a median of 8.7 years, those in the most severe AHI quartile had an adjusted HR 2.86 (95% CI: 1.1-7.4) for stroke over the study period (83) (*Table 1*).

OSA and metabolic disease

The complex relationship between OSA, obesity and metabolic disease, and in particular insulin resistance, glucose intolerance and T2DM is the subject of a forthcoming review in *Journal of Thoracic Disease*, and will not be discussed in detail here. Briefly, it does appear that OSA severity has a direct bearing on metabolic health. For example, in a large study of over 6,000 subjects attending European sleep laboratories, severe OSA was associated with an almost twofold increase in likelihood (adjusted OR 1.87) of concomitant T2DM, even following adjustment for the confounding effects of obesity, age and other variables (85). Moreover, diabetic patients with severe OSA within this cohort had higher HbA1c levels, and were more likely to have poorly controlled T2DM than non-apneic diabetics. Similarly, in an historical cohort study of 8,678 Canadian sleep clinic patients, followed for a median time period of 67 months, a diagnosis of severe OSA conferred a 37% increase in risk for incident T2DM, following statistical adjustment for confounding factors (86).

Insulin resistance and glucose intolerance also appear to be more common in OSA populations. In a large North American community-based cohort, severity of nocturnal hypoxemia and the presence of at least moderately severe OSA were both associated with an increased odds of insulin resistance (87), while a study of over 5,000 non-diabetic European sleep clinic patients found that HbA1c levels increased in parallel with AHI, irrespective of the influence of obesity (88).

Once again, the ability of CPAP to make a meaningful difference to metabolic health in patients with OSA remains unproven. A number of well-conducted, if relatively small, randomised trials have generally failed to identify anything

Table 1 Selected population studies of associations between OSA and cardiovascular disease

Authors	Participants	Study design	Outcome measures	Findings
OSA and hypertension				
Nieto <i>et al.</i> (62)	6,132 subjects	Cross sectional	Relationship of OSA severity with prevalent hypertension	Severe OSA associated with increased odds of prevalent hypertension (AOR 1.37)
Tkacova <i>et al.</i> (63)	Community based 11,911 subjects	Cross sectional	Hypertension prevalence	AHI and ODI both independently predict prevalent hypertension
Peppard <i>et al.</i> (64)	Clinic based 709 subjects	Observational	Hypertension incidence	Stronger relationship between ODI and hypertension Increased hypertension incidence with increasing OSA severity
Marin <i>et al.</i> (65)	Community based 1,889 subjects Clinic based	4-8 years follow-up Observational 12.2 years median follow-up	Hypertension incidence Analysis stratified by CPAP prescription and compliance	AOR 2.89 for AHI >15 vs. AHI 0 OSA associated with increased risk of hypertension Increase in incidence abrogated by CPAP use
OSA and coronary artery disease				
Gottlieb <i>et al.</i> (37)	1,927 men 2,495 women Community based	Observational 8.7 years median follow-up	CAD disease incidence	No relationship between OSA severity and CAD in women HR 1.68 in men aged 40-70 with AHI \geq 30
OSA and stroke				
Redline <i>et al.</i> (83)	5,422 subjects Community based	Observational 8.7 years median follow-up	Stroke incidence	HR 2.86 in men in highest AHI quartile Non-significant relationship with OSA severity in women
OSA and cardiovascular mortality				
Young <i>et al.</i> (71)	1,522 subjects Community based	Observational 18 years follow-up	Cardiovascular mortality	HR 5.2 with severe OSA in subjects who did not use CPAP
Marin <i>et al.</i> (72)	1,651 subjects Clinic based	Observational 10.1 years mean follow-up	Cardiovascular mortality Analysis stratified by CPAP use	HR 2.87 for fatal cardiovascular events with severe OSA CPAP use associated with incidence similar to controls

AHI, apnoea-hypopnoea index; AOR, adjusted odds ratio; ODI, oxyhemoglobin desaturation index; CAD, coronary artery disease; HR, hazard ratio; OSA, obstructive sleep apnea; CPAP, continuous positive airway pressure.

more than a minor impact from CPAP therapy on a range of metabolic variables (89-92).

OSA and malignancy

Sleep disordered breathing generates a molecular environment which is certainly markedly pro-atherogenic (93), but could also potentially promote the development of cancer. A recognition that OSA causes tissue hypoxia, systemic inflammation, oxidative stress and immune dysregulation (93), all factors associated with oncogenesis, lead a number of investigators to examine the effects of intermittent hypoxia in a rodent model of malignant melanoma. Data from these animal models suggested that exposure to IH may increase tumor progression, and appears to promote tumor metastasis (94,95).

A number of longitudinal studies have since suggested that an association between OSA, nocturnal hypoxemia and cancer may not be confined to rodents living in laboratories. In an analysis of 1,522 subjects enrolled in the community-based Wisconsin Sleep Cohort, severe sleep disordered breathing was associated with an almost five-fold risk of cancer death (96). Similarly, in a cohort of nearly 5,000 Spanish patients attending sleep clinics, severity of nocturnal hypoxemia predicted incident cancer, even following rigorous adjustment for confounding variables (97). Conversely, a large retrospective cohort study of Canadian sleep found that any relationship between OSA and cancer incidence could be attributed to conventional, established risk factors for malignancy (98); however, even within this population an independent association was seen between smoking-related cancer and severity of nocturnal hypoxemia. To date, there are no published data examining the effect of CPAP therapy on cancer outcomes, but potentially ground-breaking clinical trials are ongoing in this area.

Conclusions

OSA is an increasingly common disorder, with a particularly intimate relationship with obesity. OSA leads to impaired QOL, an increased risk of MVAs and impaired workplace performance. Furthermore, it contributes to development of clinically overt cardiovascular disease, and may also lead to increased risk of metabolic disease and cancer. Consequently, OSA represents a significant, evolving public health challenge in both the developed and developing world.

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