

The Epidemiology of Adult Obstructive Sleep Apnea

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Obstructive sleep apnea is a chronic condition characterized by frequent episodes of upper airway collapse during sleep. Its effect on nocturnal sleep quality and ensuing daytime fatigue and sleepiness are widely acknowledged. Increasingly, obstructive sleep apnea is also being recognized as an independent risk factor for several clinical consequences, including systemic hypertension, cardiovascular disease, stroke, and abnormal glucose metabolism. Estimates of disease prevalence are in the range of 3% to 7%, with certain subgroups of the population bearing higher risk. Factors that increase vulnerability for the disorder include age, male sex, obesity, family history, menopause, craniofacial abnormalities, and certain health behaviors such as cigarette smoking and alcohol use. Despite the numerous advancements in our understanding of the pathogenesis and clinical consequences of the disorder, a majority of those affected remain undiagnosed. Simple queries of the patient or bed-partner for the symptoms and signs of the disorder, namely, loud snoring, observed apneas, and daytime sleepiness, would help identify those in need of further diagnostic evaluation. The primary objective of this article is to review some of the epidemiologic aspects of obstructive sleep apnea in adults.

Keywords: obstructive sleep apnea; sleep-disordered breathing; epidemiology

Obstructive sleep apnea is being increasingly recognized as an important cause of medical morbidity and mortality. It is a relatively common sleep disorder that is characterized by recurrent episodes of partial or complete collapse of the upper airway during sleep. The ensuing reduction of airflow often leads to acute derangements in gas exchange and recurrent arousals from sleep. The health consequences of obstructive sleep apnea are numerous. If left untreated, it leads to excessive daytime sleepiness, cognitive dysfunction, impaired work performance, and decrements in health-related quality of life. Observational and experimental evidence also suggests that obstructive sleep apnea may contribute to the development of systemic hypertension (1), cardiovascular disease (2), and abnormalities in glucose metabolism (3). Obstructive sleep apnea is insidious and patients are often unaware of the associated symptoms. Cardinal manifestations include loud snoring, witnessed breathing pauses during sleep, fitful sleep quality, and excessive daytime sleepiness. Early recognition and appropriate therapy can ameliorate the neurobehavioral consequences and may also have favorable effects on cardiovascular health (4).

Clinical descriptions of obstructive sleep apnea can be found in numerous reports published in the medical literature over the last century (5). However, it was not until the 1980s that the clinical ramifications of disorder became more widely appreciated

by the medical community. Although public awareness of obstructive sleep apnea has steadily increased since then, a majority of those affected still remain undiagnosed. Thus, primary care physicians and specialists across various medical disciplines should be sufficiently knowledgeable to identify those affected with this disease. In this article various epidemiologic aspects of adult obstructive sleep apnea are considered, with a particular emphasis on issues related to the population prevalence, natural history, and factors that increase the predisposition for the disorder. Before embarking on these issues, the methods used to identify and diagnose the condition are briefly reviewed.

DISEASE DEFINITION AND DIAGNOSIS

The overnight polysomnogram is the standard diagnostic test for obstructive sleep apnea. It involves simultaneous recordings of multiple physiologic signals during sleep, including the electroencephalogram, electrooculogram, electromyogram, oronasal airflow, and oxyhemoglobin saturation. Collectively, these recordings allow identification and classification of sleep-related apneas and hypopneas. An apnea is defined as the complete cessation of airflow for at least 10 seconds. Apneas are further classified as obstructive, central, or mixed based on whether effort to breathe is present during the event. A hypopnea is defined as a reduction in airflow that is followed by an arousal from sleep or a decrease in oxyhemoglobin saturation. Commonly used definitions of a hypopnea require a 25% or 50% reduction in oronasal airflow associated either with a reduction in oxyhemoglobin saturation or an arousal from sleep (6). Sleep apnea severity is typically assessed with the apnea-hypopnea index (AHI), which is the number of apneas and hypopneas per hour of sleep. Several additional measures of disease severity that characterize the degree of nocturnal hypoxemia (e.g., average oxyhemoglobin desaturation) and extent of sleep fragmentation (i.e., arousal frequency) are also used in the clinical and research arenas.

Although considered as a “gold-standard,” the polysomnogram is not without limitations. It requires an overnight stay in a sleep laboratory staffed with qualified personnel that can collect and interpret complex physiologic data. The process is time consuming, labor intensive, and can be costly. Moreover, despite recent attempts at standardization, inconsistencies in the collection, analysis, and interpretation of the polysomnogram across different laboratories have made it difficult to compare various studies on health-related consequences associated with obstructive sleep apnea. Issues such as abbreviated monitoring, night-to-night variability, and the “first-night” effect explain some of the variability in results across different studies. While some of aforementioned factors have modest effects, others can have a serious impact. For example, the oxyhemoglobin desaturation threshold (e.g., 3% or 4%) used for defining hypopneas can lead to varying estimates of disease severity. Awareness of such factors is vital to better understand how distinct studies with relatively comparable designs produce widely discrepant estimates of prevalence or measures of association. Methodologic issues notwithstanding, substantial advancements have been made in our knowledge of the health risks imposed by obstructive sleep apnea. In the sections that follow, this article will provide a nonexhaustive review of the prevalence, natural history, and risk factors of adult obstructive sleep apnea.

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PREVALENCE

Despite the increasing recognition that obstructive sleep apnea is a relatively common condition, population data sets to estimate disease prevalence in the United States and abroad did not exist until about 15 years ago. Since the 1990s much has happened to quantify the health burden of obstructive sleep apnea in various populations. A number of studies using large samples representative of the general population are now available and provide prevalence estimates for obstructive sleep apnea in countries such as the United States (7–9), Australia (10), Spain (11), China (12, 13), Korea (14), and India (15). However, as previously noted, synthesis of the available experience is burdened with a number of methodologic limitations. Differences in sampling schemes, disparities in techniques used for monitoring sleep and breathing, and variability in definitions, can alter disease prevalence and potentially preclude a comprehensive estimate of true burden of symptomatic and occult disease. While some of the initial studies were plagued with most, if not all, of the above limitations, relatively consistent estimates of disease prevalence across several population cohorts have emerged. Based on available population-based studies that are summarized in Table 1, the prevalence of obstructive sleep apnea associated with accompanying daytime sleepiness is approximately 3 to 7% for adult men and 2 to 5% for adult women in the general population. Disease prevalence is higher in different population subsets, including overweight or obese people, those of a minority race, and older individuals. The fact that prevalence estimates of obstructive sleep apnea from North America, Europe, Australia, and Asia are not substantially different suggests that this disease is common not only in developed but also in developing countries. Moreover, given the widespread under recognition of this disorder by the medical and lay communities, the public and personal health care costs globally are likely to be enormous. Finally, it is now apparent that the available estimates of disease prevalence are likely to be lower than the true burden considering that even subtle breathing abnormalities during sleep (i.e., respiratory effort-related arousals) may be of clinical significance (6). Systematic surveys, however, that characterize the continuum of disordered breathing during sleep and the associated health impairment in the general population are not yet available.

NATURAL HISTORY AND DISEASE PROGRESSION

Observational studies, particularly those using a cross-sectional design, are fraught with problems of uncertainty, bias, and confounding. Longitudinal cohort studies, on the other hand, which explicitly embody the dimension of time, can be quite informative despite their observational nature. The historical dimension in such studies is the only means through which we can attain a clear perspective of the natural history of a chronic disease and define the key factors associated with an increased risk. In contrast to the wealth of prevalence data, information on obstructive sleep

apnea incidence and progression is greatly limited. Longitudinal data collected by the Wisconsin Sleep Cohort Study over a 4-year period have shown that weight change is an important determinant of disease progression and regression (16). Compared with participants with a stable weight, those that have a 10% increase in their weight had on average a 32% increase in their AHI and a sixfold risk of developing moderate to severe obstructive sleep apnea. On the other hand, a 10% decrease in weight was associated with a 26% decrease in the AHI. Changes in other body composition measures (e.g., waist or neck circumference) were not associated with an increase (or decrease) in the AHI after accounting for the changes in weight. Recent data from the Sleep Heart Health Study have provided corroborating evidence for body weight as an important determinant of disease evolution (17). Using a community sample of middle-aged men and women, Newman and coworkers have shown that the overall incidence of moderate-to-severe obstructive sleep apnea (AHI ≥ 15 events/h) over a 5-year period was 11.1% and 4.9% in men and women, respectively. Sex differences in disease incidence (and progression) persist even after consideration for confounding covariates. Compared with those with a stable weight over the follow-up interval, men with more than 10 kg weight gain had 5.2-fold the odds of increasing their AHI by more than 15 events per hour. In contrast, for a comparable amount of weight gain, women had 2.5-fold the odds of a similar increase in their AHI. Interestingly, even in the absence of any weight change, approximately 20% of men and 10% of women developed moderate to severe obstructive sleep apnea over the 5-year period of observation. Not surprisingly, regression of obstructive sleep apnea was associated with weight loss in a dose-dependent fashion.

Effects of body weight on disease progression have also been confirmed by the Cleveland Family Study, which showed that incidence of obstructive sleep apnea is independently determined by body weight, age, and sex. The influence of body weight and sex on disease incidence in the Cleveland Family Study diminished with increasing age with men and women being at equal risk for disease after the age of 50 years (18). Finally, it is important to note that the longitudinal changes in AHI were nonlinear functions of age and body weight, with older overweight and obese men experiencing the greatest rise in disease severity (19). The consistency of the effects of body weight on disease progression across different cohorts confirms the general clinical impression that many patients with obstructive sleep apnea present with a history of recent weight gain. Given the epidemic of obesity, the temporal coherence between weight change and disease progression heightens the concern that obstructive sleep apnea and its plethora of associated complications will inevitably impose an enormous burden on health care systems worldwide.

RISK FACTORS

It is remarkable that despite all of the clinical and scientific advancements regarding obstructive sleep apnea in the last two

TABLE 1. STUDIES ON THE PREVALENCE OF OBSTRUCTIVE SLEEP APNEA

Country	First Author (Reference)	N	Ethnicity	Diagnostic Method	Prevalence	
					Men	Women
United States	Young (7)	602	White	Polysomnography	4.0%	2.0%
	Bixler (9)	1,741	White	Polysomnography	3.9%	1.2%
Australia	Bearpark (10)	485	White	MESAM IV*	3.1%	–
India	Udwadia (15)	250	Indian	Polysomnography	7.5%	4.5%
China	Ip (12)	258	Chinese	Polysomnography	4.1%	–
	Ip (13)		Chinese	Polysomnography	–	2.1%
Korea	Kim (14)	457	Korean	Polysomnography	4.5%	2.3%

*MESAM IV (Madaus, Marburg, Germany) is a portable sleep monitoring system.

decades, a great majority (70–80%) of those affected remain undiagnosed (20, 21). The lack of an appropriate level of case identification is partially driven by the fact that patients are frequently unaware of the associated symptoms that are often identified either by a bed partner or family member. Compounding the lack of patient awareness, health care professionals in most medical specialties have not received the necessary training to help expedite case finding and institute early intervention. Knowledge of risk factors for obstructive sleep apnea is therefore crucial to properly direct diagnostic attention at those with the highest risk. In the following sections, several of the key risk factors for obstructive sleep apnea are briefly discussed.

Age

With advancing age, sleep-related difficulties become increasingly common and often manifest as subjective complaints of difficulty falling asleep, the number and duration of night-time awakenings, and the amount of night-time sleep obtained (22, 23). Epidemiologic surveys reveal that more than 50% of adults over the age of 65 years have some form of chronic sleep-related complaints (24). Moreover, one of the prevailing characteristics of sleep with advancing age is the significant variability in objective sleep parameters. The age-related variability in subjective and objective sleep parameters is, in part, related to the high prevalence of obstructive sleep apnea with advancing age. In one of the earliest studies, Ancoli-Israel and colleagues (25) reported that 70% of men and 56% of women between 65 and 99 years of age had obstructive sleep apnea defined as an AHI of at least 10 events per hour. Subsequent studies from several population-based cohorts confirm the high prevalence of SDB in older individuals. In a probability sample from two Pennsylvania counties, obstructive sleep apnea prevalence was shown to progressively increase with age (8, 9). In men, obstructive sleep apnea (AHI \geq 10 events/h) was present in 3.2%, 11.3%, and 18.1% of the 20- to 44-year, 45- to 64-year, and 61- to 100-year age groups, respectively (8). Using the youngest group as the reference category, the odds ratio for an AHI greater than or equal to 10 events per hour for those in the 65- to 100-year age group was 6.6 (95% confidence interval, 2.6–16.7). In a separate analyses of women from the same cohort, the prevalence of obstructive sleep apnea (AHI \geq 15 events/h) was 0.6%, 2.0%, and 7.0% for the 20- to 44-year, 45- to 64-year, and 61- to 100-year age groups, respectively (9). Disease prevalence was lowest in pre-menopausal women (~0.6%) and intermediate in post-menopausal women on hormone replacement therapy (~1.1%). In contrast, the prevalence of obstructive sleep apnea was relatively high (~5.5%) in post-menopausal women not on hormone replacement therapy (9). Data from the community-based Sleep Heart Health Study have shown that disease prevalence increases steadily with age and reaches a plateau after the age of 60 years (26). Similar trends with increasing age have also been noted in other cohorts in which the prevalence of moderate to severe obstructive sleep apnea (AHI \geq 15–20 events/h) remains relatively constant after the sixth decade of life (11). Mechanisms proposed for the age-related increase in prevalence include increased deposition of fat in the parapharyngeal area, lengthening of the soft palate, and changes in body structures surrounding the pharynx (27, 28).

The question of whether obstructive sleep apnea in older adults represents a distinct clinical entity than that seen in middle-aged adults remains a controversial issue. Data on morbidity and mortality attributable to obstructive sleep apnea in older adults has been inconsistent, with some studies concluding increased risk of adverse outcomes whereas others report little or no association (29). Undoubtedly, longitudinal data from representative population-based samples of older adults with adequate control for confounding covariates are needed to investigate whether obstructive sleep apnea portends excess medical risks in older people.

Excess Body Weight

Over the last 10 to 15 years, there have been dramatic increases in the number of overweight and obese adults in the United States (30). Excess body weight is a common clinical finding and is present in more than 60% of the patients referred for a diagnostic sleep evaluation (31). Epidemiologic studies from around the world have consistently identified body weight as the strongest risk factor for obstructive sleep apnea. In the Wisconsin Sleep Cohort study, a one standard deviation difference in body mass index (BMI) was associated with a 4-fold increase in disease prevalence (7). Other population- and community-based studies conducted in the United States and abroad have since confirmed that excess body weight is uniformly associated with a graded increase in obstructive sleep apnea prevalence (8–15). Moreover, longitudinal data from the Sleep Heart Health Study, Wisconsin Sleep Cohort Study, and the Cleveland Family Study show that an increase in body weight over time can certainly accelerate the progression of obstructive sleep apnea or lead to development of moderate to severe disease (16–18). Complementing the available body of observational data are studies on the effects of dietary or surgical weight loss which show that reducing obstructive sleep apnea severity is possible with a decrease in body weight. Although limited by small study samples and the lack of appropriate control groups, the unvarying observation is that weight loss by any means (i.e., surgery or caloric restriction) can improve severity of disease in many patients and may be completely curative in some (32–34).

Despite the unquestionable link between obesity and obstructive sleep apnea, controversy remains as to whether specific measures of body habitus (e.g., neck circumference, waist circumference) that reflect a central versus peripheral distribution of fat are associated with an increased risk for obstructive sleep apnea after controlling for BMI (35). The challenge in determining whether such measures of central obesity are able to better predict disease risk or severity is the modest to strong correlation between these inter-related measures (BMI, waist girth, neck circumference). Nonetheless, cross-sectional analyses of the Sleep Heart Health Study data show that, in middle-aged and older adults, moderate to severe obstructive sleep apnea, as defined as an AHI greater than or equal to 15 events per hour, is independently associated with BMI, neck circumference, and waist circumference (26). Increases in body weight can alter normal upper airway mechanics during sleep through several distinct mechanisms including: (1) increased parapharyngeal fat deposition resulting in a smaller upper airway, (2) alterations in neural compensatory mechanisms that maintain airway patency, (3) respiratory control system instability, and (4) reduction in functional residual capacity with a resultant decrease in the stabilizing caudal traction on the upper airway (36). Given that the pathophysiology of obstructive sleep apnea is intimately linked with obesity with an estimated 58% of the moderate to severe cases attributable to a BMI greater than or equal to 25 kg/m² (35), effective strategies to achieve long-term weight loss are desperately needed to curtail the concurrent epidemics of obesity and obstructive sleep apnea.

Sex

It has long been recognized that men have greater vulnerability than women toward developing obstructive sleep apnea. Clinic-based studies have shown that, in patients referred for clinical evaluation, the ratio of men to women is in the range from 5 to 8:1 (31). Epidemiologic studies have confirmed the higher prevalence of obstructive sleep apnea in men but report a lower male-to-female ratio in the range 2 to 3:1 (7, 9, 11, 37). Several explanations exist for the disparity in sex differences between clinic- and population-based studies. First, it is possible that men

and women with obstructive sleep apnea have distinct symptom profiles, with women possibly not reporting the classical symptoms, namely loud snoring, nocturnal snorting or gasping, and witnessed apneas (38). In fact, analyses from different referral centers show that that women with obstructive sleep apnea have a greater tendency to report symptoms of fatigue and lack of energy than men (39, 40). Second, differential response of the bed-partner to the symptoms of obstructive breathing during sleep may also contribute to the clinical underrecognition of the disorder in women. Although systematic evaluations of sex differences in the response to snoring and breathing pauses have not been conducted, female bed partners of male patients appear to have a lower threshold for symptom perception and reporting than male bed partners of female patients (41). Finally, it is also possible that health care providers have a lower index of suspicion for considering obstructive sleep apnea in men than women given the general expectation that the disorder predominantly affects men. Irrespective of the underlying cause, the underrecognition of obstructive sleep apnea is of public health significance given that delayed diagnosis and treatment in women can contribute to significant medical morbidity and increased health care-related costs (42). Thus, specific questioning of snoring, witnessed apneas, fatigue, and insomnia symptoms should be routinely conducted in women and in the presence of a suggestive history a referral initiated for further diagnostic testing.

In addition to the differences in prevalence, polysomnographic characteristics of sleep and breathing patterns also differ between women and men. Women tend to have a lower AHI in non-rapid eye movement (non-REM) sleep but have a similar AHI in REM sleep. Moreover, disordered breathing events in women have a shorter duration and are associated with less oxyhemoglobin desaturation than in men (43). The male predisposition for the disorder has been attributed to sex differences in anatomical and functional properties of the upper airway and in the ventilatory response to arousals from sleep (44, 45). Hormonal influences are also likely to have an important role in pathogenesis of obstructive sleep apnea, as disease prevalence is higher in post- versus pre-menopausal women (9). Furthermore, hormone replacement therapy in post-menopausal women has been associated with a lower prevalence in epidemiologic studies (9, 46). Finally, although there are limited controlled data, exogenous androgen therapy in men and women can aggravate obstructive sleep apnea severity. Without doubt, research on many different fronts is still needed to better define the biologic basis for male sex as an independent risk factor for obstructive sleep apnea.

Race

Until recently, most of the population-based studies on the prevalence of obstructive sleep apnea were focused on characterizing disease prevalence in North America, Europe, or Australia. With the increasing appreciation that obstructive sleep apnea can lead to serious medical sequelae, several studies have been undertaken to characterize the disease burden in countries including China, India, and Korea (Table 1). These studies show that the prevalence of obstructive sleep apnea in Asians is comparable to that documented in North American and European samples. An interesting and unexpected observation that has emerged is that, while Asians are less obese than whites, disease prevalence in the East is no less than in the West. Moreover, for a given age, sex, and BMI, Asians have greater disease severity than whites (47, 48). Differences in craniofacial features between Asians and whites have been demonstrated and are considered as the etiologic factors for the increased risk and greater severity of obstructive sleep apnea in Asians despite lesser degrees of obesity (49).

In African-American samples, disease prevalence in middle-aged adults is comparable to that of other racial groups (26, 50).

However, African Americans that are at least 65 years of age (51) or those less than 25 years of age (50) have been found to have a higher prevalence of obstructive sleep apnea than middle-aged African Americans and those of other racial groups. In contrast to the data on Asians and African Americans, there is a relative paucity of data on the population prevalence of obstructive sleep apnea in Hispanics. Snoring, a cardinal sign of obstructive sleep apnea, has been reported in 27.8% of Hispanic men and 15.3% of Hispanic women (52). Recent work from the Sleep Heart Health data substantiates the notion that after accounting for possible confounders, snoring is in fact more common in Hispanics than in whites (53). These data indicate that studies with representative samples of Hispanic men and women are needed to estimate the prevalence of the polysomnographically verified obstructive sleep apnea and determine whether it is higher than other racial sub-groups.

Several caveats should to be considered in the interpretation of the data linking race with an increased risk for obstructive sleep apnea. First, minority populations often have a higher prevalence of comorbid medical conditions, including obesity. These factors, in conjunction with a low socioeconomic status and disadvantages in health care, could explain the higher prevalence of obstructive sleep apnea. Thus, race may be a surrogate for other predisposing features and any additional risk documented in minority samples may disappear if confounding is adequately addressed. Second, given the mixing of different racial groups, classification of subjects to a particular group based on self-report will have some degree of error. Given the advancements in the field of genomics, better means for racial classification may provide new insight into why some groups are more predisposed than others to obstructive sleep apnea.

Craniofacial Anatomy

Several soft and hard tissue factors can alter the mechanical properties of the upper airway and increase its propensity to collapse during sleep. Static cephalometric analyses using radiography, computerized tomography, and magnetic resonance imaging have revealed a number of skeletal and soft-tissue structural differences between individuals with and without obstructive sleep apnea during wakefulness. Features such as retrognathia, tonsillar hypertrophy, enlarged tongue or soft palate, inferiorly positioned hyoid bone, maxillary and mandibular retroposition, and decreased posterior airway space can narrow upper airway dimensions and promote the occurrence of apneas and hypopneas during sleep (54). Even in the absence of clinically obvious craniofacial abnormalities, subtle differences in maxillary or mandibular size can increase the vulnerability for obstructive sleep apnea. A meta-analysis of studies investigating the craniofacial risk factors showed that mandibular body length is a craniofacial measure with the strongest association with increased risk (55).

Differences in craniofacial morphology may explicate some of the variation in risk for obstructive sleep apnea across different racial groups. Comparative analyses of whites and African Americans show that different cephalometric variables are positively correlated with measures of disease severity. For example, in whites the AHI is associated with brachycephaly (56), whereas in African Americans it is more associated with soft tissue measurements of the tongue and soft palate (50). Similar interracial comparisons between Chinese Asians and whites show that Chinese patients with obstructive sleep apnea have a more crowded upper airway and relative retrognathia compared with their white counterparts after controlling for BMI and neck circumference (49). In addition, Asians have other craniofacial features which increase disease predisposition, including a shorter cranial base and a more acute cranial base flexure (48). Collectively, such studies confirm that craniofacial abnormalities are important

in pathogenesis of obstructive sleep apnea, particularly in non-obese patients. Moreover, given that different racial groups are inclined to develop obstructive sleep apnea at varying degrees of obesity, clinicians should consider the possibility of this disorder particularly in the presence of clinically detectable craniofacial abnormalities.

Familial and Genetic Predisposition

Familial aggregation of obstructive sleep apnea was first recognized in the 1970s by Strohl and coworkers in a family with several affected individuals (57). Since then, several large-scale studies have confirmed a role for inheritance and familial factors in the genesis of obstructive sleep apnea (58). First-degree relatives of those with the disorder are more likely to be at risk compared with first-degree relatives of those without the disorder. Familial susceptibility to obstructive sleep apnea increases directly with the number of affected relatives (59). Segregation analyses of the Cleveland Family Study show that, independent of BMI, up to 35% of the variance in disease severity (i.e., AHI) can be attributed to genetic factors with possible racial differences in the mode of inheritance (60). Genome-wide association scans have identified susceptibility loci for obstructive sleep apnea and show that linkage patterns for the disorder may differ between whites and African Americans (61, 62). However, some has been argued that confounding factors, such as obesity, prohibit definitive conclusions on genetic underpinnings for obstructive sleep apnea and that additional studies are needed to further define whether the disorder truly has a genetic component (63).

If further research does confirm a genetic basis for obstructive sleep apnea, what are the intermediate traits that could mediate the increase? Craniofacial morphology, as discussed above, is important in determining upper airway collapsibility during sleep. Cephalometric abnormalities, including retroposition of the maxilla and mandible and a large soft palate, can compromise upper airway patency and tend to aggregate within families (64, 65). Heritability has also been demonstrated for volume of the lateral parapharyngeal walls, tongue, and total soft tissue structures (66). Inherited abnormalities in the control of breathing may predispose to the occurrence of disordered breathing events during sleep (67, 68). Finally, genetic determinants of obesity and regional fat distribution are also relevant, given the wealth of evidence implicating these factors in the pathogenesis of the disorder. Although the genetic basis of obstructive sleep apnea needs to be better defined, the available data suggests that inquiries about family history can certainly aid in identifying those that have the disorder but remain undiagnosed.

Smoking and Alcohol Consumption

Cigarette smoking and alcohol have been suggested as possible risk factors for obstructive sleep apnea. Epidemiologic investigations show that current smoking is associated with a higher prevalence of snoring and obstructive sleep apnea (69–72). Even exposure to second-hand smoke has been independently linked with habitual snoring (73). Because former smokers do not manifest the increased risk for obstructive sleep apnea, airway inflammation and damage due to cigarette smoke could alter the mechanical and neural properties of upper airway and increase its collapsibility during sleep.

Ingestion of alcohol before sleep has been shown to increase upper airway collapsibility and the precipitate obstructive apneas and hypopneas during sleep. Alcohol ingestion can induce apneic activity in normal or asymptomatic individuals (74–76). Alcohol intake can prolong apnea duration and worsen the severity of associated hypoxemia (74, 77, 78). The mechanisms by which alcohol induces or worsens pharyngeal collapse are not well known. Experimental studies in animals (79) and humans

(80) indicate that alcohol reduces respiratory motor output to the upper airway, resulting in hypotonia of the oropharyngeal muscles. Nonetheless, epidemiologic data on the effects of chronic alcohol use on obstructive sleep apnea risk remain discrepant with some studies reporting a positive association (81, 82) and others reporting no association (12, 15). Differences in ascertainment of alcohol use across different studies may explain the variability in the available findings.

Medical Comorbidity

Besides the unfavorable effects on daytime sleep tendency and cognitive performance, obstructive sleep apnea also has been implicated in the etiology of cardiovascular conditions, including hypertension, coronary artery disease, congestive heart failure, and stroke. Previous studies on whether obstructive sleep apnea is an independent cardiovascular risk factor were beleaguered with concerns of confounding. With the advent of large epidemiologic studies and well-controlled clinical trials, there is now substantial proof that obstructive sleep apnea does increase the risk for various cardiovascular endpoints, most notably hypertension. Although evidence for causal associations with other medical conditions is likely forthcoming, the lack of such associations with prevalent health outcomes should not annul the clinical and public health significance of obstructive sleep apnea. For example, the Wisconsin Sleep Cohort Study has shown that obstructive sleep apnea is independently associated with prevalent diabetes mellitus (83). In that study, obstructive sleep apnea was also associated with incident diabetes mellitus, but the association was not statistically significant after adjusting for BMI and waist circumference. Even if obstructive sleep apnea is eventually found not to be a harbinger of excess metabolic risk, the high prevalence of this condition in those with diabetes mellitus because of underlying obesity cannot be neglected. Identification of obstructive sleep apnea is of clinical significance, as early intervention may directly or indirectly enhance glycemic control. It is possible that intermittent hypoxemia and sleep disruption of obstructive sleep apnea are deleterious to glucose homeostasis and alleviating obstructive breathing during sleep with continuous positive airway pressure therapy has direct effects in improving hyperglycemia. Alternatively, treatment can diminish daytime fatigue, foster increase in physical activity, and thus result in improved metabolic control. Similarly, patients with other comorbid conditions such as coronary artery disease could experience direct and indirect benefits with early identification and treatment of undiagnosed disease. The potential of such improvements emphasizes the fact that in the presence of medical conditions such as uncontrolled hypertension, coronary artery disease, congestive heart failure, stroke, and diabetes mellitus, undiagnosed obstructive sleep apnea should be considered as a possible concomitant problem.

Other Risk Factors

The discussion thus far has focused on the prevailing risk factors for obstructive sleep apnea. There are, however, several other conditions that have also been associated with an increased prevalence of obstructive sleep apnea. These conditions include polycystic ovary syndrome, hypothyroidism, and pregnancy. Polycystic ovary syndrome (PCOS) is a clinical syndrome that is diagnosed in the presence of oligomenorrhea and signs of androgen excess. Cardinal features include chronic anovulation, disordered gonadotropin secretion, central obesity, insulin resistance, dyslipidemia, and presence of polycystic ovaries on ultrasonography. Prevalence of PCOS among women of reproductive age is in the range of 5 to 12% (84, 85). Although limited by small samples, a number of studies have shown a high prevalence (~60–70%) of obstructive sleep apnea in women with PCOS (86–88).

Visceral adiposity and higher androgen levels may predispose to obstructive sleep apnea by altering upper airway passive mechanical properties and neural control during sleep (87, 88).

Cross-sectional studies suggest that obstructive sleep apnea may be more prevalent in patients with hypothyroidism (89, 90). Whether the occurrence of obstructive sleep apnea is directly caused by decrease in thyroidal hormones or whether it is due to confounding factors (e.g., obesity) that are common in hypothyroidism remains controversial (90). Hypothyroidism leads to widespread accumulation of hyaluronic acid in the skin and subcutaneous tissues, which gives rise to myxedematous appearance in these patients. Such deposition of mucoproteins in the upper airway causes enlargement of the tongue and the pharyngeal and laryngeal mucous membranes, thereby increasing the propensity for upper airway collapse during sleep (91). In addition to these mechanical alterations, there is evidence to suggest that hypothyroidism leads to a decrease in central ventilatory drive (92, 93). Thus, patients with hypothyroidism may have increased susceptibility for obstructive sleep apnea due to the combined effects of mechanical abnormalities and/or suppressed central respiratory control output.

Pregnancy is also associated with a higher prevalence of snoring, particularly in the third trimester (94). While some of the physiologic changes that accompany pregnancy (e.g., higher progesterone levels, decrease in sleep time in the supine position) may protect against obstructive sleep apnea, gestational weight gain, decrease in pharyngeal luminal size, and alterations in pulmonary physiology increase the tendency for disordered breathing during sleep (95, 96). Frank obstructive sleep apnea during pregnancy may lead to lower Apgar scores and birth weights (97). Thus, early case identification during pregnancy may have implications for maternal and fetal outcomes.

CONCLUSIONS

There is now a wealth of information indicating that untreated obstructive sleep apnea is associated with an increased risk of fatal and nonfatal cardiovascular event (4), a higher propensity of sudden death during sleep (98), and a greater risk for stroke and all-cause mortality (99). The mechanisms by which obstructive sleep apnea increases medical morbidity are complex and remain a focus of intense basic and human research. As data supporting a causal role of obstructive sleep apnea in medical complications continues to increase, a concerted effort by health care professional across specialties is needed to recognize those that remain undiagnosed. By posing a few additional questions during the routine clinical interview, patients in need for further diagnostic testing can be easily identified. The threshold for a sleep center referral should be particularly lower if patient or public safety is in question or if there are co-existing medical conditions. Finally, it is imperative that medical education at all levels incorporate instruction on the risks of obstructive sleep apnea and other sleep disorders. Given the high prevalence and public health burden of obstructive sleep apnea, the implications of untreated disease for the individual and society are enormous and cannot be ignored.

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