State of the Art

Epidemiology of Obstructive Sleep Apnea
A Population Health Perspective

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Population-based epidemiologic studies have uncovered the high prevalence and wide severity spectrum of undiagnosed obstructive sleep apnea, and have consistently found that even mild obstructive sleep apnea is associated with significant morbidity. Evidence from methodologically strong cohort studies indicates that undiagnosed obstructive sleep apnea, with or without symptoms, is independently associated with increased likelihood of hypertension, cardiovascular disease, stroke, daytime sleepiness, motor vehicle accidents, and diminished quality of life. Strategies to decrease the high prevalence and associated morbidity of obstructive sleep apnea are critically needed. The reduction or elimination of risk factors through public health initiatives with clinical support holds promise. Potentially modifiable risk factors considered in this review include overweight and obesity, alcohol, smoking, nasal congestion, and estrogen depletion in menopause. Data suggest that obstructive sleep apnea is associated with all these factors, but at present the only intervention strategy supported with adequate evidence is weight loss. A focus on weight control is especially important given the expanding epidemic of overweight and obesity in the United States. Primary care providers will be central to clinical approaches for addressing the burden and the development of cost-effective case-finding strategies and feasible treatment for mild obstructive sleep apnea warrants high priority.

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

CONTENTS

The basic epidemiological features of obstructive sleep apnea (OSA), a condition characterized by repeated episodes of apnea and hypopnea during sleep, are well established. Undiagnosed OSA is common in adults, the severity spectrum is wide, and the cardiovascular and behavioral morbidity seen in patients with OSA is also associated with undiagnosed OSA (1–3). There is no controversy regarding the need for better recognition and treatment of severe, symptomatic OSA, but critical questions remain regarding what clinical and public health approaches are needed to address mild to moderate OSA, for which the prevalence is particularly high (3–6). Should case finding or population screening be encouraged? Are risk factor intervention strategies feasible means of reducing the incidence and progression of mild OSA? Formulating answers to these questions requires a greater understanding of the natural history and morbidity attributable to OSA over its severity spectrum and identification of modifiable factors that initiate OSA and affect its progression. In this review we focus on data from population-based epidemiology studies, with the goal of addressing some of the questions raised by the high prevalence of undiagnosed OSA.

Brief History of Undiagnosed Obstructive Sleep Apnea

Obstructive sleep apnea was clinically recognized more than 30 years ago (7), but awareness of this condition outside the field of sleep medicine was slow to develop. The situation changed drastically when population-based studies uncovered an unexpectedly high prevalence of OSA in adults (8–11). Health care systems around the world were not prepared to cope with the extremely large number of people expected to have OSA, and attention appropriately turned to the health significance of nightly exposure to frequent episodes of apnea and hypopnea.

Findings from early clinical and community cross-sectional studies of OSA and hypertension, myocardial infarction, and other cardiovascular disease were mixed and generated considerable controversy (6, 12, 13). It was clear from the low clinical recognition of sleep apnea that only a small fraction of all cases even of severe OSA was being diagnosed (1, 14), so selection bias in studies of patients with sleep apnea was a serious con-

cern. Furthermore, the validity of most studies was questioned because of small samples, inadequate control for obesity and other potential confounding factors, and other methodological limitations. The need for population-based, longitudinal studies of the natural history and adverse health consequences of OSA was widely recognized and large cohort studies were initiated (8, 10, 11, 15–19). Findings from these studies relevant to the significance of undiagnosed OSA are now emerging, and progress has been made toward overcoming methodological drawbacks of case-based and cross-sectional investigations of this condition. The major cohort studies discussed in this review are described briefly in the APPENDIX.

Interpretation of Observational Studies of Obstructive Sleep Apnea

In reviewing and synthesizing findings, we were mindful of the general limitations inherent in observational studies of a chronic condition with unknown onset or time course as well as the need to consider methodological issues of particular relevance to OSA. These include variability in measurements, definitions, sample construction, and statistical techniques used for analyses.

In most epidemiology studies, and accordingly in this review, OSA is defined by the number of obstructive apnea and hypopnea episodes per hour of sleep (apnea–hypopnea index, AHI), reflecting the degree of departure from the normal physiology of breathing during sleep. The term "OSA syndrome" will be used to indicate a clinical entity defined by an elevated AHI in conjunction with hypersomnolence or related problems in daytime function and is synonymous with the term "obstructive sleep apnea–hypopnea syndrome." The spectrum of sleep-related obstructed breathing is considered by many researchers to include increased upper airway resistance manifested as snoring without frank apnea or hypopnea events (20) and episodic flow limitation terminating in central nervous system arousals—often called "upper airway resistance syndrome" (21). These conditions may represent the earliest stages of OSA and may be important in investigating disease progression or may be distinct conditions, but to date there are few epidemiological data based on objectively measured nonapneic snoring or on respiratory effort-related arousals.

Although a detailed discussion of the pathophysiology of airflow obstruction in OSA is outside the scope of this review, it is clear that upper airway collapse most often results from a combination of anatomic factors that predispose the airway to collapse during inspiration plus neuromuscular compensation that is insufficient during sleep to maintain airway patency. The relative contribution of anatomic versus neuromuscular factors is likely to vary greatly among individuals and may vary considerably among groups defined on the basis of age, sex, body habitus, race, and ethnicity, although there are no data from epidemiological studies with which to address this. In contrast to OSA, central sleep apnea is characterized by repeated episodes of apnea or hypopnea resulting from decreased neural output to respiratory motoneurons, without airflow obstruction. There may be some overlap in the pathophysiology underlying these conditions, as reducing neural output to both the diaphragm and pharyngeal dilator muscles may lead to central apnea or hypopnea if the upper airway is not anatomically prone to collapse, but to obstructive apnea or hypopnea if the airway is more collapsible (22). In general, however, the pathophysiology, epidemiology, and clinical characteristics of central and obstructive sleep apnea are distinct, and this review addresses only the latter. It is important to note that the methods employed in most epidemiological studies, and indeed in many sleep laboratories, although good at distinguishing central from obstructive apneas, cannot reliably discriminate between central and obstructive hypopneas. Hypopneas, which are in general much more common than apneas, are typically included in the AHI and assumed to reflect obstructive respiratory events, although the validity of this assumption, particularly in subgroups of the population such as the elderly, remains to be demonstrated.

Epidemiology studies have used a variety of methods to measure OSA, including in-laboratory polysomnography; unattended in-home polysomnography; unattended polygraphic or other recording of a few physiological parameters; and self-report data on markers of OSA, such as habitual snoring. Studies using objective measures of apnea and hypopnea have employed variable respiratory event definitions, with differing requirements for fractional decrease in airflow, oxyhemoglobin desaturation, or associated evidence of cortical or autonomic arousal. Moreover, there has been no standardization in the methodology used to quantify airflow, with methods such as thermistry, inductance plethysmography, and nasal cannula/pressure transducer systems providing different sensitivities to changes in airflow. Like other conditions based on a severity continuum, the definition of the units of the continuum and the ultimate thresholds used to designate the presence of OSA will affect the magnitude of prevalence and estimates of associations with risk factors and outcomes. The use of more restrictive definitions of apnea and hypopnea, higher AHI cutpoints, or an additional requirement for symptoms of sleepiness will obviously lower prevalence estimates and affect values expressing associations, such as odds ratios (23–25). The traditional use of the AHI, while having substantial face validity as a summary parameter of OSA, does not reflect a large body of empiric data demonstrating that the AHI fully and succinctly captures those physiologic aspects of OSA that are most germane to the pathogenesis of adverse consequences of OSA. Certainly it is possible that the AHI and other parameters, such as duration of hypoxemia or degree of sleep fragmentation, are of varying relative importance among the many sequelae of OSA, such as sleepiness, cognitive impairment, and hypertension. Although there has been interest in developing alternatives to the AHI, event frequency was used as the basis for describing OSA by a task force with the aim of standardizing measurement techniques and syndrome definitions for sleep-related breathing disorders (26). Recommended diagnostic criteria for OSA syndrome include an AHI of 5 or more, determined by overnight monitoring, and evidence of disturbed or unrefreshing sleep, daytime sleepiness, or other daytime symptoms. The task force suggested AHI cutpoints of 5, 15, and 30 events/hour to indicate mild, moderate, and severe levels of OSA. These recommendations were acknowledged to be an expert consensus statement based on a paucity of objective data, and intended to stimulate further research to identify the optimal approach to quantifying sleep-related breathing disorders.

Precision is often neglected when comparing findings of various studies, and a false sense of disagreement among studies can occur when only the point estimates are considered. Measurement error and sample size affect the precision of prevalence and other point estimates and, consequently, confidence intervals are necessary to interpret findings. Less importance can be placed on a point estimate when confidence intervals are wide or unreported.

Finally, findings from both case-based and population studies can be seriously flawed by inappropriate sample sources, participation bias, and loss to follow-up. In particular, a spurious estimate of prevalence or the association of interest can result if selection, participation, or dropout is related to the study factors. For example, in a case–control study, choosing a

sample of patients with OSA from sleep clinics where referral from cardiovascular clinics is high would lead to an overestimation of the association of OSA and cardiovascular disease (CVD). A similar bias would result in a population-based study if participation rates were higher for snorers with hypertension, compared with that of snorers without hypertension. To assess and correct possible bias due to sample construction, a probability sample drawn from a sampling frame that provides some information about participants as well as nonparticipants is needed.

OCCURRENCE OF OBSTRUCTIVE SLEEP APNEA

Prevalence

Understanding disease prevalence, that is, the proportion of a population with the condition, is critical to anticipating health care needs and allocating appropriate resources. In addition, comparisons of prevalence by demographic factors may yield etiological clues and identify subgroups at particularly high risk for targeted case finding. Prevalence studies conducted over the past decade provide considerable data from diverse populations to estimate the health burden of OSA and to explore interesting aspects of its occurrence. However, prevalence estimates are extremely vulnerable to the methodological issues discussed above.

Previous reviews of OSA prevalence have taken some of these issues into account by roughly adjusting for differences in definitions or by comparing results from studies with similar study designs. Davies and Stradling (27) analyzed 12 studies of OSA prevalence in Western populations and, using conservative approaches to account for methodological differences, estimated that 1 to 5% of adult men have OSA syndrome (i.e., frequent apnea and hypopnea episodes and daytime sleepiness). Lindberg and Gislason (2) considered prevalence estimates for undiagnosed OSA syndrome from nine studies that all used two-stage sampling procedures in which sleep studies were conducted on subsets of participants drawn from large-sample surveys. A strength of this type of study design is that subsets are drawn from a defined probability sample, permitting some evaluation of participation bias. Furthermore, the two-stage design, with oversampling of important subgroups and weighting of results to the survey sample, increases study efficiency and allows extrapolation of the subgroup-specific prevalence estimates to populations of different composition. Prevalence of undiagnosed OSA syndrome in these studies ranged from 0.3 to 5%; samples from countries with lower mean body mass index (BMI) tended to yield lower prevalence estimates. However, some of these estimates are based on the extremely conservative assumption that all survey participants who did not report snoring and sleepiness were free of OSA. This assumption is almost certainly false and could lead to a serious underestimation of prevalence.

Thus, up to 5% of adults in Western countries are likely to have undiagnosed OSA syndrome, and hence be candidates for treatment. Consequently, in addressing the burden of OSA, the resources to identify and treat up to 5% of middle-aged adults with OSA constitute a minimum need. Not counted in this estimate is the large proportion of adults with OSA, defined by frequent episodes of apnea and hypopnea, who do not report sleepiness. At present, the clinical significance of OSA without overt daytime symptoms is controversial and the public health significance remains to be determined. Many studies, however, have shown adverse health outcomes to be associated with OSA regardless of the presence of sleepiness (discussed in the following section) and, consequently, the prevalence of OSA as determined solely by abnormal breathing

during sleep is extremely important in understanding the potential OSA burden in the population.

Prevalence estimates from studies with probability samples range, for OSA of at least mild severity (defined by AHI $\geqslant 5$), from 3 to 28%; for OSA of at least moderate severity (defined by AHI $\geqslant 15$), estimates range from 1 to 14% (8–11, 15–17, 28). The wide range of these estimates precludes adequate assessment of the population burden of OSA because feasible means to reduce the burden are different for the extremes (i.e., 1 and 28%). When only those studies with in-laboratory polysomnography conducted on large samples are compared, however, the prevalence estimates are in closer agreement. Results from studies of cohorts in Wisconsin (11), Pennsylvania (15, 16), and Spain (17) are given in Table 1 (see the APPENDIX for descriptions of these and other large population-based cohorts). Because all three studies used two-stage stratified probability sampling with appropriate weighting techniques and used similar measurement methods and definitions of hypopnea and AHI cutpoints, their concurrence is particularly reassuring. On the basis of the average of prevalence estimates from these studies of predominantly white men and women with mean BMI of 25 to 28, we estimate that roughly 1 of every 5 adults has at least mild OSA and 1 of every 15 has at least moderate OSA.

Ethnicity. OSA prevalence has been established in few populations other than those of Western nations, and therefore the worldwide importance of OSA, as well as potentially important racial or ethnic prevalence patterns, are poorly understood. Epidemiologists have traditionally investigated geographical distributions of disease occurrence to find etiologic clues, but it is often hard to disentangle environmental risk factors, including cultural differences in diet and lifestyle, from genetic factors. When there are large differences in disease prevalence between countries, studies of whether the rates change in migrant populations and their succeeding generations have often been enlightening. At present, data from studies of groups other than white subjects are too sparse even to determine with confidence if prevalence differs worldwide.

Population-based studies suggest that OSA prevalence is as high or higher in African-Americans compared with Caucasians. Ancoli-Israel and coworkers (29) studied community dwelling adults, age 65 years or greater, by in-home monitoring, and found that the odds of having an AHI of 30 or higher was 2.5 times greater in African-Americans relative to Caucasians, controlling for BMI and other confounding factors. In the Cleveland Family Study, a racially heterogeneous sample of families with one index OSA case and neighborhood control subjects, Redline (30) found that in participants less than 25 years of age, the prevalence of OSA (adjusted for BMI and other potentially confounding factors) was higher in African-

TABLE 1. PREVALENCE OF OBSTRUCTIVE SLEEP APNEA FROM THREE STUDIES WITH SIMILAR DESIGN AND METHODOLOGY

Study Location	n	Age Range (*years*)	Estimated Prevalence of AHI $\geqslant 5$ events/hour (% [95% CI])		Estimated Prevalence of AHI $\geqslant 15$ events/hour (% [95% CI])	
			Men	Women	Men	Women
Wisconsin*	626	30–60	24 (19–28)	9 (6–12)	9 (6–11)	4 (2–7)
Pennsylvania†	1,741	20–99	17 (15–20)	Not given	7 (6–9)	2 (2–3)
Spain‡	400	30–70	26 (20–32)	28 (20–35)	14 (10–18)	7 (3–11)

Definition of abbreviation: AHI = apnea–hypopnea index.
* Young and coworkers (11).
† Bixler and coworkers (15, 16).
‡ Durán and coworkers (17).

Americans than in Caucasians. On the basis of in-home polysomnography on more than 6,000 participants in the multicenter Sleep Heart Health Study, however, the prevalence of OSA was not higher in African-Americans compared with Caucasians after adjustment for age, sex, and BMI (31). Unfortunately, there are no data about OSA prevalence in African countries for comparison.

Ip and colleagues (32) reported the first estimates of OSA prevalence in an Asian population, using two-stage sampling methodology and in-laboratory polysomnography. From a survey sample of 784 Hong Kong men, 30 to 60 years of age, 153 completed polysomnography studies; of these, 25% had AHI of 15 or more events per hour, but the authors found evidence of self-selection of men most likely to have OSA. To account for this bias, the authors made a conservative assumption that there were no cases of OSA among the nonparticipants, and estimated the prevalence of OSA defined as an AHI of 15 or more to be 5%, and of OSA syndrome defined as an AHI of 5 or more plus excessive daytime sleepiness to be 4%. Preliminary data from a similar study of Chinese women in Hong Kong indicated a conservative estimate of OSA syndrome prevalence of 2% (33).

The similarity of the estimates from the Hong Kong studies with those reported from Western nations are provocative because obesity, a strong risk factor for OSA, is prevalent in white populations, but is relatively uncommon in Asian countries. Ip and coworkers (32) noted that whereas BMI and other measures of body habitus were associated with OSA in the Hong Kong study, the correlations were weaker than those seen in studies of white subjects. In view of the higher than expected prevalence, these investigators hypothesized that other strong OSA risk factors that are more prevalent in Chinese relative to Western populations, such as craniofacial features that compromise the upper airway, must exist. Some, but not all, clinical observations of Asian patients with OSA support this hypothesis (34–36).

Other studies suggest that correlates of OSA may differ by race. Redline and coworkers (37) found that the association of BMI with OSA in younger participants was stronger in Caucasians than in African-Americans in the Cleveland Family Study. Furthermore, associations of head form and craniofacial measures with OSA in this sample were stronger in Caucasians (37, 38). Race-specific risk factors were also reported from a comparison of patients with OSA in New Zealand (39). Again, BMI was a stronger predictor of OSA severity in Caucasians compared with Polynesians, and the specific craniofacial risk factors associated with OSA severity differed by race.

More information is clearly needed about the distribution of OSA in countries in Africa, Asia, and the South Pacific to understand the worldwide burden of OSA. Furthermore, because environmental and genetic risk factors for OSA vary considerably among these and Western countries, studies of OSA risk factors in resident populations, as well as in migrants and their offspring born in Western nations, would be illuminating.

Sex. In most population-based studies that have estimated sex-specific prevalence, a 2- to 3-fold greater risk for men compared with women has been reported (1), but little progress has been made in understanding the reasons for the risk difference. Most hypotheses to account for the disparity focus on a role of sex hormones in OSA pathogenesis (40). However, administration of estrogen and progesterone to men (or postmenopausal women) has not been shown to reduce AHI (41). Although male sex is a striking risk factor for OSA, the prevalence of many chronic disorders of middle and older age are higher in men compared with women. Investigations of sex differences in other chronic diseases have gone beyond a focus

on estrogen and have shown that sex-based phenotypes including physical features, occupational and other environmental exposures, and health behavior put men at higher risks for disease (42). Clear sex differences in upper airway shape and genioglossal muscle activity during the awake state, in craniofacial morphology, and pattern of fat deposition have been proposed to account for a higher male risk of OSA (42). However, no conclusive findings have emerged from the few studies that have investigated differences in upper airway dimensions and upper airway fat deposits in small samples of men and women (43–47). Sex differences in exposure to exogenous potential risk factors, such as occupational exposures or smoking, have not been investigated as explanatory factors for the sex disparity in OSA.

Pregnancy may be a period of particular risk for OSA in women. In a survey completed by 350 women at two U.S. Army hospitals during the second or third trimester of pregnancy and by 110 nonpregnant women, 14% of the pregnant women reported snoring often or always, compared with only 4% of the nonpregnant women (48). Both frequency and loudness of snoring, and episodes of awakening with a choking sensation, appear to increase during pregnancy, with half of the women in one study reporting snoring and 14% reporting choking awakenings at 35 to 38 weeks of gestation, versus 37 and 4%, respectively, at 8 to 12 weeks of gestation (49). A questionnaire administered to 502 Swedish women at the time of delivery found that 23% reported snoring often or always during the week before delivery, whereas only 4% reported snoring before pregnancy. Most of the increase in snoring occurred in the third trimester (50). There is evidence that the impact of pregnancy on snoring resolves within several months after delivery (51).

The high prevalence of snoring and choking awakenings during pregnancy suggests that pregnancy may be associated with OSA; however, there are few data regarding the prevalence of OSA during pregnancy. In the largest reported study, polysomnography was performed in 11 snoring women early in the third trimester. All had an AHI less than 5, although all had evidence of increased upper airway resistance characterized by either crescendo respiratory effort or abnormal sustained increases in respiratory effort, occurring more commonly than in nonsnoring control subjects (51). The mechanisms underlying the increase in snoring during pregnancy are uncertain, but may include excess weight gain (50, 52), diffuse pharyngeal edema of pregnancy (53), or the effect of sleep deprivation on pharyngeal dilator muscle activity.

Age. OSA prevalence appears to increase steadily with age in midlife, but age trends in childhood, adolescence, and older age do not indicate a simple positive correlation of OSA with age. A multimodal distribution of prevalence by age is often indicative of distinct disease subtypes with different etiology and health sequelae. There is controversy, however, regarding the occurrence and significance of OSA in older people and its relationship to OSA that occurs in middle age. Childhood OSA was the topic of a State of the Art review in this journal by Marcus (54) and is reviewed here only briefly. Although OSA in children shares elements of pathophysiology and consequences with OSA in adults, it differs sufficiently regarding etiology and associated morbidity that it has been accorded a separate section in this review.

Several studies have found OSA to be highly prevalent in people older than age 65 years. In the first large population-based study of older people, Ancoli-Israel and coworkers (55) conducted in-home polygraphy on a probability sample of 427 men and women 65 to 95 years of age. OSA defined as an AHI of 10 or more occurred in 70% of the men and 56% of

the women, approximately 3-fold higher than the prevalence estimates for OSA in middle age given in Table 1.

Four subsequent cohort studies have samples with wide age ranges, allowing internal comparisons of prevalence in broad categories of older age and middle age without the problem of interstudy methodological differences, such as measurement and definition of OSA. Bixler and coworkers found that in both men and women, those 65 to 100 years of age had a prevalence of OSA that was approximately twice as high as the upper bounds of the 95% confidence interval (95% CI) for OSA prevalence in middle age, shown in Table 1 (15, 16). The largest prevalence difference between middle and older age was found in the Vitoria-Gasteiz, Spain Cohort (17, 56). For ages 71–100 years, the prevalence of AHI $\geqslant$ 5 was 80% (95% CI = 74 to 86%) for women and 81% (95% CI = 76 to 86%) for men. The prevalence for an AHI of $\geqslant$ 15 was 49% (42 to 56%) for women and 57% (95% CI = 50 to 63%) for men. When compared with the prevalence estimates for the middle-aged participants in this cohort (given in Table 1), the prevalence in older age appears to be nearly three times higher for an AHI $\geqslant$ 5 and more than four times higher for an AHI $\geqslant$ 15. Age- and sex-specific prevalence of an AHI $\geqslant$ 15 in the Cleveland Family Study (30) showed a higher prevalence for subjects over 60 years of age, compared with those 25 to 60 years of age. In women, the prevalence was 4 and 32% in the younger and older groups, respectively, and for men it was 22 and 42%, respectively. Similarly, in the Sleep Heart Health Study (31), the proportion of people with an AHI $\geqslant$ 15 events per hour was approximately 1.7-fold higher in older (60 to 99 years) versus younger (40 to 60 years) participants.

These observations raise two critical questions: does aging over the middle to older years per se have an etiological role in OSA, and what is the significance of the high prevalence of OSA in older age? A higher prevalence of OSA in older versus middle age does not necessarily mean that physiological changes associated with later life cause an increase in the OSA incidence rate: The prevalence of an unremitting, nonfatal disease would be expected to increase with age as cases accumulate from a constant or even declining incidence rate. Differences in age-specific prevalence beyond what would be expected by accumulation of cases would indicate that changes in OSA mortality rate, incidence rate, or both occur with aging. Because we do not know the incidence or mortality rate of OSA at any age, we can only speculate as to why the prevalence of OSA is high in older people.

If aging actually leads to an increase in OSA incidence, we would expect prevalence to continue to rise over the older age range; however, the studies by Ancoli-Israel and coworkers (55), Bixler and coworkers (15, 16), and the Sleep Heart Health Study (31) all suggest that most of the age-related prevalence increase occurs before age 65 (Figure 1). A plateau in OSA prevalence at some point after age 65 years necessitates a new perspective on the occurrence of OSA in older people. Unless incidence drops with older age, either the mortality rate of persons with OSA relative to those without OSA must increase, or else OSA must remit. Certainly the mortality rates of many chronic diseases increase with age, but at present there is no solid evidence that OSA causes death. Similarly, there is no evidence for remission of OSA with aging.

Some data suggest that OSA in older age may be a condition distinct from that of middle age. Several studies of OSA in older populations report little or no association of OSA with sleepiness, hypertension, or decrements in cognitive function (57–61), all common correlates of OSA in middle age. Eighteen-year follow-up data from the San Diego sample of older adults indicated that changes in BMI were weakly associated with change in AHI (62) and that the association of obesity with AHI was

weaker in older compared with middle-aged participants in the Sleep Heart Health Study (31). Furthermore, despite the high prevalence of OSA, the prevalence of self-reported snoring, a strong marker for OSA, clearly decreases past middle age (15, 63). One possible explanation for this paradox is that bed partners may no longer be alive or may be unable to report validly on snoring, owing to age-related conditions such as hearing loss. Alternatively, older compared with younger adults may be more likely to have central sleep apnea or a prominent central neuromuscular component to their OSA. Central apnea and hypopnea are not associated with snoring and may be less likely to elicit daytime symptoms. Data to evaluate this theory are sparse, but findings from the cohort of Bixler and colleagues (15) offer some support. Central sleep apnea, defined by 20 or more central apnea events/hour of sleep, was nonexistent before age 65 years, but occurred in 5% of the sample over age 65 years. In contrast, despite the higher prevalence of OSA in those over age 65 years, the prevalence of OSA *syndrome*, defined as an AHI of 10 or more plus symptoms (including daytime sleepiness and hypertension), was actually lower in those over 65 years (1.7%) than in those age 45 to 64 years (4.7%), although the difference was not significant.

In summary, the occurrence of OSA in older people is more complex than previously appreciated. The scant data available suggest that instead of a continual rise in prevalence with age due to accumulating cases, prevalence tends to level off after age 65 years. This trend, if correct, implies either a relative increase in the mortality rate from OSA or a remission of OSA with aging. However, it is possible that biases, including poor measurement of OSA in older people or birth cohort effects, explain some or all of the age-related prevalence trends seen in cross-sectional studies. More importantly, a better understanding of sleep-related breathing disorders in older age and how they differ, if at all, from the typical OSA of middle age is crucial for proper clinical management of older patients. Prospective data to investigate sleep-related breathing disorders and aging, as well as the role of OSA in increased mortality, are clearly needed.

Incidence and Progression

Whereas there are considerable prevalence data from Western countries, little is known about incidence (i.e., the occurrence of new cases over a given time interval) or progression (i.e., worsening over time) of OSA. Incidence assessment is susceptible to all the problems that plague attempts to measure OSA prevalence and, in addition, there are special problems in identifying representative disease-free cohorts in which to measure new occurrences of OSA. Night-to-night variability in AHI and measurement error lead to difficulties in valid classification of OSA status that can cause systematic biases in estimating incidence, for example, due to regression to the mean across
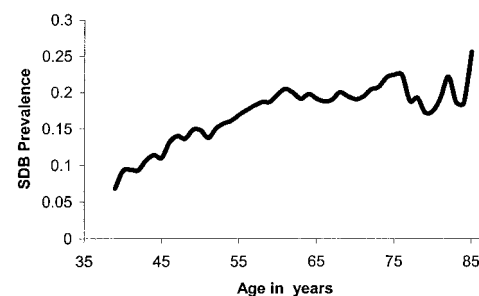

Figure 1. Prevalence of OSA by age in the Sleep Heart Health Study (31). SDB = Sleep-disturbed breathing.

arbitrary disease-defining cutpoints. Accordingly, the few studies that have prospectively examined OSA in defined populations have focused on OSA progression, usually measured as changes in AHI over time, rather than on incidence.

Only preliminary findings of OSA progression are currently available from population studies. Data from baseline and 8-year follow-up studies of 282 participants in the Wisconsin Sleep Cohort show a significant increase in OSA severity over this interval (Table 2): The overall mean AHI increased by 2.6 events/hour, from 2.5 at baseline to 5.1 at follow-up. There were significant increases in mean AHI in all strata of sex, BMI, age, and snoring. Whereas the change in mean AHI was not significantly greater in men compared with women, progression was significantly greater in obese compared with non-obese, older compared with younger, and habitually snoring compared with nonhabitually snoring subjects. In Figure 2, AHI at 8-year follow-up is plotted against baseline AHI. Although there is a considerable amount of scatter in the plot, two patterns are evident. First, consistent with the elevation in mean AHI, there are more persons whose AHI increased than decreased. Second, many people who had an AHI of 1 or less at baseline increased to an AHI greater than 1 at follow-up, whereas few individuals with an AHI over 1 at baseline decreased to an AHI of 1 or less at follow-up.

Preliminary data from the Cleveland Family Study demonstrate trends similar to the Wisconsin data. Redline and coworkers (64) monitored 232 participants from the Cleveland Family Study with AHI less than 5 at baseline and reported a 5-year increase from a baseline mean (SD) AHI of 2.0 (1.4) to a follow-up AHI of 6.2 (7.9). Significant predictors of higher AHI at follow-up were excess body weight, central obesity, cardiovascular disease, and diabetes. Because of the lack of older participants, neither the Wisconsin Sleep Cohort nor the Cleveland Family provides insight into disease progression beyond age 65 years, but 18-year follow-up data from the San Diego Older Adult cohort showed little change in AHI with
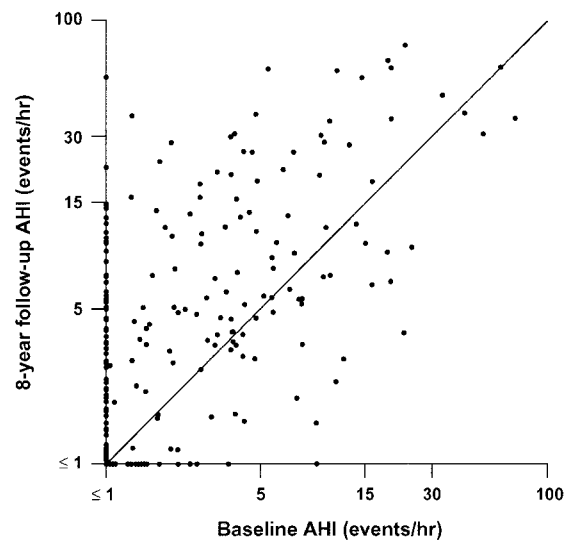

Figure 2. Eight-year follow-up apnea–hypopnea index (AHI) versus baseline AHI in the Wisconsin Sleep Cohort Study (n = 282). Note that the axes are log-scaled.

aging (62). In follow-up studies with small sample sizes (n = 11 to 55) of community-dwelling persons monitored for 3 to 8 years, most (65–67), but not all (68), found evidence of progressive increase in AHI over time.

In two studies of patients with mild to moderate OSA who had refused treatment and were later restudied, significant progression was found (69, 70); however, in a study of patients with severe OSA (mean AHI = 52), no net progression, and some individual regression, was seen after 5 years (71). The validity of these studies may have been compromised by incomplete follow-up and, in the clinic-based studies, by regression to the mean resulting from the selection of participants with evidence of substantial OSA. However, the available data from both population and clinic studies suggest that change in severity, mostly toward progression, does occur in individuals with mild or moderate OSA.

The available epidemiological evidence suggests that substantial progression of OSA can occur over relatively short time periods. An efficient method of recognizing individuals likely to develop severe OSA would allow interventions to reduce or reverse OSA progression before the development of significant morbidity. It appears that habitual snoring and obesity may be useful markers of risk for OSA progression, although data remain limited. One particularly difficult methodologic issue in characterizing OSA incidence and progression is the worsening epidemic of obesity in the United States (72). Any temporal nonuniformity among studies or differences among sex, race, and age subgroups in secular trends in obesity will likely be reflected in progression trends of OSA. Thus, researchers attempting to characterize underlying age-related natural history patterns of OSA face the difficult task of separating these patterns from contemporaneous secular trends in obesity prevalence. In any event, as the overall prevalence of obesity increases, it is reasonable to expect an increase in prevalence and severity of OSA beyond the high levels already seen.

OUTCOMES: WHAT IS THE COST OF OBSTRUCTIVE SLEEP APNEA IN THE POPULATION?

Obstructive sleep apnea is associated with conditions that account for the leading causes of mortality in adults: hyperten-

TABLE 2. MEAN 8-YEAR INCREASES IN THE APNEA–HYPOPNEA INDEX BY SUBGROUP IN THE WISCONSIN SLEEP COHORT STUDY

	n	Baseline AHI (mean)	Follow-up AHI (mean)	8-year AHI Increase (mean ± SD [SE])	95% CI for Increase
All participants	282	2.5	5.1	2.7 ± 8.2	(1.7, 3.6)
Women	121	1.5	3.8	2.3 ± 6.1	(1.2, 3.4)
Men	161	3.3	6.3	3.0 ± 9.4	(1.5, 4.5)
Difference, men − women		1.8	2.5	0.7 (1.0)	
Not obese, BMI < 30*	179	1.5	3.0	1.6 ± 5.4	(0.8, 2.3)
Obese, BMI > 30*	103	4.8	10.1	5.2 ± 12	(2.8, 7.7)
Difference, obese − not obese		3.4	7.0	3.7 (1.0)†	
Age 30–45 years*	137	1.8	3.4	1.7 ± 6.5	(0.6, 2.7)
Age 45–60 years*	145	3.2	6.9	3.7 ± 9.5	(2.1, 5.2)
Difference, older − younger		1.5	3.5	2.0 (1.0)†	
Not habitual snorer*	134	1.3	2.6	1.3 ± 5.1	(0.6, 2.0)
Habitual snorer*	148	5.5	11.8	6.3 ± 9.7	(4.1, 8.4)
Difference (habitual snorer − not)		4.2	9.2	5.9 (1.0)†	

Definition of abbreviations: AHI = apnea–hypopnea index; BMI = body mass index; CI = confidence interval.
* At baseline.
† Significant difference (p < 0.05) in mean AHI increase between subgroups.

sion, cardiovascular, and cerebrovascular diseases. In addition, several neurobehavioral morbidities that are of potentially great public health and economic importance are linked with OSA, including daytime sleepiness and impaired cognitive function that may, in turn, contribute to motor vehicle crashes and job-related accidents (73).

Hypertension

Apnea and hypopnea episodes during sleep cause acute, transient blood pressure perturbations, inducing elevations of 30 mm Hg or more in mean arterial pressure (74, 75). Nightly episodes of hypoxia, arousals, and swings in intrathoracic pressure due to OSA may lead to sustained elevation of blood pressure via pathophysiologic mechanisms that include chronically elevated sympathetic tone, alterations in baroreceptor function, and cardiovascular remodeling (13, 76–79). Until more recently, however, research linking OSA to hypertension has been equivocal.

Most earlier epidemiological studies assessing the OSA–blood pressure association reflected a trade-off between state-of-the-art OSA assessment in inherently unrepresentative clinic samples (80–88) and methodologically more rigorous population-based studies that employed OSA assessment instruments with poor or unknown validity (e.g., self-report of OSA symptoms or at-home nocturnal oximetry) (89–95). Collectively, these studies shed little light on the connection between OSA and hypertension, with findings ranging from no association whatsoever to strong associations. Reviewers of this earlier research concluded that because of the varying results and the potential biases due to the use of clinic samples, crude assessment of OSA, or inadequate control of important confounding factors, an independent association had not been established (12, 77, 96, 97).

Since those earlier reviews, several epidemiologic studies have consistently found positive associations between OSA and hypertension. These studies, described below, have used a variety of designs, but most have had large samples and all have attempted to rigorously account for important confounding factors such as obesity, age, and sex. The uniformity of these positive results has lead some researchers to conclude that OSA should be considered a cause of secondary hypertension (98) and that the controversy over the presence of a causal association is passé (78). These most recent findings and the related question of whether treating OSA can lower blood pressure are the focus of this section.

Four large cross-sectional population-based studies and one prospective population-based study have estimated associations between polysomnographically assessed AHI and daytime hypertension (use of antihypertensive agents or systolic blood pressure $\geq$ 140 mm Hg or diastolic blood pressure $\geq$ 90 mm Hg) while controlling for multiple potential confounding variables including, minimally, age, sex, and BMI. Durán and colleagues (17) measured the cross-sectional association in 555 men and women from the Spanish city of Vitoria-Gasteiz. Even among subjects with an AHI of less than 5 events per hour, those with AHI greater than zero had increased odds of hypertension (odds ratio, 2.5; 95% CI, 1.1 to 5.8) relative to those with an AHI of zero. The odds of hypertension were also increased in more severe AHI categories, but not significantly so, and without a clear dose response. After adjustment for multiple potential confounding variables, Nieto and coworkers (99) found a significant association between AHI and hypertension in a cross-sectional sample of 6,132 men and women participating in the Sleep Heart Health Study. Relative to an AHI less than 1.5, the odds ratios were 1.1, 1.2, 1.3, and 1.4 for AHI categories of 1.5 to 5, 5 to 15, 15

to 30, and 30 or greater, respectively. There was a significant increasing trend in the odds ratios, and all but the lowest odds ratio were significantly greater than one. Bixler and coworkers (100) also found a significant cross-sectional association between OSA and hypertension in a sample of 1,741 men and women in the Pennsylvania cohort. The associations were complex and generally indicated a stronger relationship between OSA and hypertension in younger and less obese participants than in older, heavier participants. These findings correspond well with those of Young and coworkers (101), who also found a stronger cross-sectional association of OSA and hypertension in less obese participants in the Wisconsin Sleep Cohort, and those of Nieto and coworkers, who found a stronger association in younger subjects (99).

Although these four studies have had compatible results, because of their cross-sectional design, none has been able to demonstrate that OSA predated hypertension. This issue was addressed in a prospective analysis from the Wisconsin Sleep Cohort (102, 103). Even minimally elevated AHI at baseline (0 < AHI < 5 events per hour) was associated with 42% (95% CI, 13 to 78%) increased odds of developing hypertension over a 4-year follow-up period. A dose–response relationship was observed for more severe categories of AHI, with an odds ratio of 2.9 (95% CI, 1.5 to 5.6) for an AHI of 15 or greater versus an AHI of zero events per hour. However, although the dose–response trend was significant, there appeared to be a plateau in the hypertension response at high levels of OSA severity. Such a plateau was also suggested by the cross-sectional analyses from Spain (17) and from the Sleep Heart Health Study (99).

The results of these studies are also consistent with those seen in other studies of OSA with different study designs. In a longitudinal analysis of the large Nurses' Health Study (n = 73,231), Hu and coworkers (104) found that self-reported snoring at baseline moderately increased the risk of subsequent development of hypertension over an 8-year follow-up period. Grote and coworkers (105) and Lavie and coworkers (106) found significant associations between polysomnography-assessed OSA and increased blood pressure or the occurrence of hypertension in large samples of sleep clinic patients. Davies and coworkers (107) assessed 24-hour ambulatory blood pressure in 45 persons with OSA and 45 persons without OSA, matched on several factors including age, BMI, alcohol and cigarette use, and heart disease. The patients with OSA had higher daytime and nighttime blood pressures and demonstrated an attenuated nighttime reduction in blood pressure compared with the matched participants without OSA. Finally, in a large community-sample British study, Stradling and colleagues (108) found that the degree of overnight reduction in blood pressure (evening minus morning blood pressure) was stunted in proportion to the severity of oxygen desaturation and excess respiratory effort during sleep. This finding is consistent with an earlier study examining the evening-to-morning blood pressure difference in patients with varying degrees of OSA (84) and findings of attenuated nighttime blood pressure "dipping" in patients with OSA (86, 107, 109).

Although the associations found in observational studies suggest a causal, albeit not strong, relationship between OSA and elevated blood pressure, the potential for remediating hypertension by treating OSA is unclear. This is a particularly important issue given the finding that patients with severe OSA may be relatively likely to have hypertension that responds poorly to pharmacotherapy (110). The effectiveness of reducing blood pressure by treating OSA with continuous positive airway pressure (CPAP) has been addressed in numerous intervention studies (21, 81, 87, 98, 111–121). These studies showed mixed results. However, few of them used appropriate placebo-controlled

comparison groups, an important consideration given the demonstration of a placebo response of blood pressure to sham CPAP (115). Among studies using placebo control groups, results have also been inconsistent. Barbé and coworkers (114) found no effect after 6 weeks of CPAP on 24-hour blood pressure measures in a study of 29 treatment and 25 sham CPAP-control patients with OSA. Three other placebo-controlled studies found small to moderate effects of CPAP on ambulatory blood pressure that varied in degree depending on time of day (i.e., sleeping or awake) or among subsets of treated patients (116, 117). Thus, it remains uncertain to what degree CPAP use can lower daytime blood pressure in most patients with OSA. This may reflect methodologic issues such as inadequate study power, given the fairly modest magnitude of the effect of OSA on blood pressure. A more important consideration, however, is the possibility that chronically elevated blood pressure due to OSA leads to vascular damage, which causes hypertension to persist even when the OSA is treated. Whether long-term CPAP therapy might result in reduced blood pressure in such patients is unknown.

There is a growing consensus that OSA is an important risk factor for hypertension independent of excess weight and other potentially confounding factors. An association appears to be present even at the mild end of the OSA severity spectrum. Despite the generally modest magnitude of the association, the high prevalence of OSA implies that it may be responsible for a substantial portion of the population burden of hypertension. However, the potential for remediating hypertension by treating OSA remains unclear.

Cardiovascular Morbidity and Mortality

If OSA does cause hypertension, then OSA should also contribute to cardiovascular and cerebrovascular morbidity and mortality, given their incontrovertible link to hypertension. Nonetheless, important questions remain regarding the degree to which cardiovascular outcomes are related to OSA, and whether there are mechanisms other than hypertension by which OSA may influence these outcomes. As previously noted, obstructive respiratory events cause profound temporary cardiovascular disturbances that may lead to long-term cardiovascular remodeling. In addition to chronically elevated blood pressure, a number of possible mechanisms by which OSA might affect cardiovascular function have been hypothesized, including vascular injury and acceleration of atherosclerosis due to episodic hypoxemia (122), chronic sympathetic hyperactivity (123–126), elevated fibrinogen (127) and homocysteine (110); elevated pulmonary blood pressure and consequent risk for right heart hypertrophy (128) and heart failure (129); and increased risk of plaque ruptures and subsequent cardiovascular or cerebrovascular events (79).

Several case–control studies of patients assessed for OSA after myocardial infarction (MI) support an association between the two conditions, with odds ratios generally in the range of 4.1 to 4.5 in both men and women (130–132). The odds ratio for MI associated with OSA was as high as 23 in one study (133); however, the confidence interval was wide (95% CI, 4 to 140). Although these case–control studies all demonstrated strong associations between OSA and MI, they also share an important limitation: OSA status in cases was assessed after an MI, and therefore may be a poor surrogate for OSA severity during the relevant etiologic time frame before the occurrence of MI. This is especially true if the MI itself could affect OSA severity, by virtue of changes in cardiac function, medication use, or peri-infarction sleep deprivation.

Cross-sectional epidemiologic studies of objectively measured OSA or self-reported snoring and cardiovascular disease (CVD) have found a positive association, although of considerably smaller magnitude than that observed in case–control studies. Schmidt-Nowara and coworkers (94), in a population sample of 1,222 Hispanic Americans, found an elevated odds of self-reported CVD in snorers that was of borderline significance (odds ratio, 1.8; 95% CI, 0.9 to 3.6). Olson and coworkers (134) assessed OSA by in-home monitoring and found a nonsignificant elevated odds of self-reported CVD in an Australian sample (n = 441). The adjusted odds ratio for coronary artery disease in persons classified as having OSA versus nonsnorers without OSA was 1.4 (95% CI, 0.4 to 4.5). In both these studies, lack of significance could have been a result of insufficient study power. Shahar and coworkers (135) found a significant cross-sectional association of OSA with prevalent CVD in persons undergoing in-home polysomnography in the Sleep Heart Health Study. Among the 6,424 participants, those in the upper quartile of AHI (11.0 events or more per hour) had a 42% (95% CI, 13 to 78%) greater odds of prevalent CVD (including coronary heart disease, stroke, and congestive heart failure) than participants in the lowest quartile (AHI less than 1.3 events per hour), after adjusting for multiple potential confounders. Additional analyses examining the association of OSA and CVD along the entire spectrum of OSA severity suggested that most of the elevation in risk of CVD occurs as the AHI rises from zero to 10 events per hour. The analysis included adjustment for hypertension, suggesting that hypertension is not the only mechanism by which the risk of cardiovascular sequelae is heightened in persons with OSA. If confirmed, this would seem to imply that pharmacologic treatment of hypertension would not fully insulate these patients from heightened cardiovascular risk.

The only prospective data on OSA and CVD come from three large population-based studies of snoring and incident CVD. In two of these studies, the magnitude of the increased risk of CVD in regular snorers was similar to that observed in the cross-sectional studies. In a report from the Nurses' Health Study, Hu and coworkers (136) found significant associations between self-reported snoring and CVD among nearly 72,000 women monitored for up to 8 years. Adjusting for several possible confounding factors, regular snorers had a 33% (95% CI, 6 to 67%) elevation in risk of incident CVD relative to nonsnorers. Koskenvuo and coworkers (137) surveyed 3,847 male participants, 40 to 69 years of age, on snoring status and then ascertained CVD status with hospital discharge data and mortality records 3 years later. The odds ratio (95% CI) for new ischemic heart disease was 1.4 (1.2 to 1.7), for regular versus infrequent snorers, independent of BMI, age, smoking, alcohol, and hypertension. Jennum and coworkers (138) conducted a similar large prospective study (n = 2937) with participants aged 54 to 74 years surveyed on snoring and then monitored for CVD outcomes through hospital and mortality records for up to 6 years. In this study, snoring was not related to CVD (adjusted relative risk, 1.0; 95% CI, 0.6 to 1.6). The disparity in results from these two Scandinavian studies with similar study methods and large, well-constructed samples is puzzling. Although this could simply be due to sampling variability (the confidence intervals overlap substantially), it is also consistent with the interpretation that the association of OSA and CVD is present only in younger men, below the age range of the Jennum and coworkers study (138), but not below the age range of the Koskenvuo and coworkers study (137) (i.e., less than 54 years old).

Stroke has been linked to OSA in cross-sectional and case–control studies. In the Sleep Heart Health Study, Shahar and coworkers (135) found a stronger association between stroke and OSA than between total CVD and OSA; the odds ratio of

prevalent stroke in persons in the upper OSA quartile compared with those in the lowest quartile, adjusted for several possible confounding factors, was 1.58 (95% CI, 1.02 to 2.46). In case–control studies of stroke patients and hospital control subjects (139, 140) or control subjects selected from cases' friends or family (141), snorers were found to have substantially elevated odds of stroke (significant odds ratio ranged from 2 to 10). More definitive assessment of the causal role of OSA in stroke awaits data from prospective designs in which it can be determined that OSA precedes stroke, and that associations are not influenced by recall bias, choice of control groups, or stroke-related breathing disturbance.

Several studies of mortality in sleep clinic patients suggest that OSA results in increased CVD mortality. He and coworkers (142) attempted to ascertain the vital status of 706 patients with sleep apnea. Mortality in treated versus untreated patients was compared in the 385 patients (only 55% of the original sample) who were successfully tracked. Conservatively treated patients (e.g., weight loss was advised) had a significantly higher death rate than did patients treated by tracheostomy. Using a similar study design, Partinen and colleagues conducted a 5-year mortality follow-up (143) and 7-year morbidity (144) analysis of 198 patients with sleep apnea. Extensive tracking determined that conservatively treated patients, compared with those treated by tracheostomy, had more than two times the risk of new vascular disease and nearly five times the risk of cardiovascular or stroke-related death. Also, in separate 5-year prospective Swedish studies of patients with coronary artery disease, OSA was found to increase the risk of mortality in one study (145) and increase the composite risk of occurrence of death, MI, or cerebrovascular event (stroke or transient ischemic attack) in the other study (146).

The association between snoring or AHI and all-cause or cardiovascular mortality has also been examined in several population-based studies. In a study from Sweden, data on snoring, excessive daytime sleepiness, and other factors were obtained by mailed questionnaire from 3,100 men (ages 30 to 69 years). Lindberg and colleagues (147) tracked mortality outcomes of the complete sample over a 10-year period. An overall association between snoring and mortality was not observed. However, in the subset of men less than 60 years of age, those with snoring and excessive daytime sleepiness were approximately twice as likely to die over the study period as men without those symptoms (relative risk, 2.2; 95% CI, 1.3 to 3.8), after adjustment for several possible confounding factors. In a community sample, Ancoli-Israel and coworkers (148) conducted an 8- to 10-year follow-up of 426 older persons by in-home nocturnal polygraphy-assessed breathing disturbance. In unadjusted analyses, severe respiratory disturbance (AHI ≥ 30 events per hour) was a predictor or shortened survival, but in a multiple regression model that adjusted for age, sex, BMI, and history of CVD, respiratory disturbance was not a significant predictor of mortality. Adjustment for CVD (a putative mechanism by which OSA hastens death) in the model may have led to an underestimate of a true association. Also in follow-up studies of older persons, Bliwise and coworkers (63) and Mant and coworkers (149) did not find significant associations between AHI and age-adjusted cardiovascular mortality. However, both of these studies monitored fewer than 200 participants.

These few data preclude firm conclusions about the magnitude of the associations between OSA and mortality. The clinic-based studies indicate that people with untreated OSA are at greater risk for early mortality. However, without randomization to treatment groups, it is possible that observed differences at follow-up merely reflect differences in baseline health. It might be expected that the patients with the most severe OSA would be treated aggressively, and indeed comparisons of AHI, weight, and other factors in the studies by He and coworkers (142) and Partinen and coworkers (143) support this. As this should bias the studies toward a null result, the observed associations do provide evidence consistent with a role for OSA in excess mortality. Because these studies were conducted with patients experiencing severe OSA, however, the findings may not be applicable to mild or moderate OSA. In contrast to the clinic-based studies, population studies have not demonstrated strong associations between OSA and mortality. This may, in part, reflect an association of OSA with mortality only in younger to middle-aged adults, as the data from Lindberg and coworkers suggest. It is possible that OSA in older persons represents a less noxious disease than OSA in younger populations, as previously discussed, or that older persons with OSA are constitutionally resistant to its adverse consequences, having survived a selection process that claimed their less resistant contemporaries.

In summary, although it appears that OSA is likely to increase moderately the risk of cardiovascular morbidity and mortality, strong empirical evidence of that conclusion and precise estimates of the magnitude of the association will have to await incidence data from several ongoing population-based cohort studies of objectively assessed OSA. It remains to be demonstrated whether increased CVD risk is truly independent of the effects of OSA on blood pressure and whether treatment of OSA (e.g., with CPAP) can reduce cardiovascular risk. This important issue will be more difficult to address than the relationship of OSA treatment and elevated blood pressure because of the large samples and lengthy follow-up periods required to assess those outcomes.

Sleepiness

Excessive daytime sleepiness is a cardinal feature of the OSA syndrome, and numerous studies including oral placebo- or sham CPAP-controlled studies in clinically identified patients with OSA have demonstrated an improvement in daytime sleepiness after treatment of OSA (150, 151). Patients presenting for evaluation and treatment of OSA are unrepresentative of subjects with elevated AHI in the general population, however, as asymptomatic individuals are less likely to be evaluated for the presence of OSA than are those who complain of sleepiness. Although many details of the relationship between sleepiness and OSA in the general population are poorly understood, there is evidence that both OSA and non-apneic snoring are important causes of daytime sleepiness. Among subjects participating in the Wisconsin Sleep Cohort Study, approximately 23% of women and 16% of men with an AHI of 5 or more reported experiencing three measures of sleepiness (excessive daytime sleepiness plus awakening unrefreshed no matter how long they had slept plus uncontrollable daytime sleepiness that interfered with daily living) 2 days or more per week compared with only 10% of nonsnoring women and 3% of nonsnoring men with an AHI less than 5 (11). Among subjects participating in the Sleep Heart Health Study, there was a significant, progressive increase in Epworth Sleepiness Scale (ESS) score with increasing AHI, from a mean of 7.2 in subjects with an AHI less than 5 to 9.3 in subjects with an AHI of 30 or greater (152). The percentage of subjects with excessive sleepiness, defined as an ESS score ≥ 11, increased from 21% in subjects with an AHI less than 5 to 35% in those with an AHI of 30 or greater. The association of AHI with sleepiness was similar in subjects older and younger than age 65 years and was independent of sex, BMI, or evidence of insufficient sleep time. The relationship of AHI to sleepiness was

also independent of race, although even this large study had little power to explore modification by race of the effect of AHI on sleepiness.

Notwithstanding the strong association of AHI with self-reported sleepiness, the majority of subjects with an AHI of 5 or greater in each of these studies did not report excessive sleepiness. Indeed, the mean ESS score in Sleep Heart Health Study subjects with "severe" OSA, defined as an AHI 30 or greater, was lower than the mean ESS score previously reported for clinically identified cases of "mild" OSA, defined as an AHI from 5 to 15. Although self-report measures may underestimate the severity of sleepiness in the setting of chronic hypersomnolence, it is likely that many, if not most, individuals with polysomnographic evidence of OSA have minimal daytime sleepiness. This implies that there is considerable inter-individual variation in susceptibility to sleepiness resulting from OSA and indicates the potential magnitude of the bias inherent in attempting to extrapolate to the general population from studies of clinical cases. As reviewed elsewhere, sleep fragmentation due to repeated arousals from apneas and hypopneas is thought to be the cause of excessive sleepiness in patients with OSA (153). In the Sleep Heart Health Study, however, differences in the frequency of arousals, defined by American Sleep Disorders Association Atlas Task Force criteria (154) did not explain the observed variation in resultant sleepiness (152). More detailed study of subjects with OSA with and without excessive sleepiness, drawn from the same population, is needed to explain the factors underlying individual differences in susceptibility to daytime sleepiness.

A number of epidemiological studies have evaluated the relationship between snoring and daytime sleepiness and almost all have found a significant association. As snoring is a strong marker of the presence of OSA, the association of snoring with sleepiness might be due to their joint association with OSA; however, several studies suggest that snoring is independently associated with excessive sleepiness. Stradling and coworkers (155) found that the report of snoring "often" was associated with 5-fold increased odds of subjects reporting that they fall asleep during the day against their will after adjusting for the severity of OSA as measured by the frequency of 4% dips in blood oxygen saturation during the night. On each of the three questions quantifying sleepiness in the Wisconsin Sleep Cohort Study, subjects with an AHI less than 5 who reported habitual snoring (three or more nights per week) had a prevalence of daytime sleepiness approximately midway between those of subjects with an AHI less than 5 who did not report habitual snoring and subjects with an AHI 5 or more (11). Among 5,777 subjects participating in the Sleep Heart Health Study, there was a progressive increase in sleepiness as measured by the Epworth Sleepiness Scale across five categories of snoring frequency, from a mean of 6.4 in current non-snorers to 9.3 in subjects who snored 6 to 7 nights per week (156). The prevalence of excessive daytime sleepiness, defined as an ESS score 11 or more, increased from 15% in never-snorers to 39% in those who snore 6 to 7 nights per week. The relationship of snoring to sleepiness was seen at all levels of AHI, with no significant change in the relationship of snoring to ESS score after adjustment for AHI in multivariate models.

These studies suggest that snoring without frank apnea and hypopnea episodes is associated with daytime sleepiness independent of AHI. If so, the very high prevalence of snoring in the adult population suggests that public health burden of snoring-related sleepiness might well exceed that of overt OSA. One must interpret the available data with caution, however, as the mechanism underlying the association of snoring with sleepiness is unclear. While snoring-related arousal due to in-

creased upper airway resistance or snoring noise is possible, an increased arousal frequency, measured using American Sleep Disorders Association criteria, did not explain the observed association in the Sleep Heart Health Study (156). Similarly, although Stradling and coworkers (157) found an association between snoring and sleepiness, as measured by the Epworth Sleepiness Scale, this was not explained by an increase in either arousals or increased inspiratory effort as measured using pulse–transit time. As there is well-documented night-to-night variability in the measurement of AHI, it is possible that among subjects without elevated AHI on a single night of monitoring, habitual snoring is an indicator of a higher "usual" AHI. Confounding by the effects of voluntary sleep restriction, which is a cause of both snoring (158) and sleepiness, could contribute to the observed association, although in one study the relationship of snoring to sleepiness was independent of self-reported sleep restriction (156). A true association of snoring with sleepiness is suggested, however, by the observation that habitually snoring subjects with an AHI less than 5 in the Wisconsin Sleep Cohort Study had 3-fold increased odds of experiencing multiple motor vehicle accidents during a 5-year period compared with subjects without habitual snoring (159).

Cognitive Function

Population-based studies of the effect of OSA on cognitive function are few and the existing findings are somewhat weaker than results from clinic-based studies (160, 161). This is not surprising because selective referral of the most impaired patients for sleep laboratory evaluation is likely to bias the clinic study findings toward stronger associations. In the Wisconsin Sleep Cohort Study, psychomotor function and memory factors derived from a neuropsychological test battery were investigated as OSA outcomes (162). OSA severity, indicated by the AHI, was significantly but weakly related to diminished psychomotor efficiency, a factor reflecting the coordination of fine motor control with sustained attention and concentration. The association of OSA and psychomotor efficiency, adjusted for age and education, was not explained by measures of fatigue or daytime sleepiness. OSA was not related to the memory factor. In extrapolating the regression findings, the effect of an increase in AHI of 15 was approximately equivalent to the effect of 5 years of aging on psychomotor function. Similar findings were reported from a study of 848 participants in the Danish MONICA (*Monitoring Trends and Determinants in Cardiovascular Disease*) cohort: AHI of 5 or greater was significantly associated with self-assessed concentration problems but not with memory (163). Weak but significant associations of OSA and neuropsychological function were also found in a study of 100 self-reported snorers recruited from public advertisements and clinic referrals, screened to exclude comorbidity related to cognitive function (164). However, in contrast to the two cohort studies, OSA was associated with factors reflecting memory as well as signal discrimination.

Health-related Quality of Life

Efforts to develop an instrument to measure disease-specific quality of life for obstructive sleep apnea–hypopnea syndrome and sleepiness are underway (165), but to date, population-based investigations of OSA have been limited to general health-related quality of life measured with the SF-36, a widely used short form of the Medical Outcomes Study (166). The Wisconsin Sleep Cohort Study (167) and the Sleep Heart Health Study (168) both demonstrated a linear association of OSA severity with decrements on the eight SF-36 scales, but pain and emo-

tional role scales were not statistically significant in the Wisconsin study and only the vitality scale was significant in the Sleep Heart Health Study. In the Sleep Heart Health Study data, associations with scales other than vitality were significant only when OSA was defined as an AHI of 30 or more and when dichotomous outcomes rather than standardized scores for the SF-36 scales were used. In addition to differences in analytic techniques, the samples of the two studies differ in age and comorbidity. Compared with the Wisconsin Sleep Cohort sample, the Sleep Heart Health sample is older and has more comorbidity, and thus competing causes of poor quality of life may have diminished the magnitude of any association between OSA and quality of life. Both studies, however, concluded that undiagnosed OSA affects quality of life on a par with other chronic disorders of moderate severity. Stepnowsky and coworkers (169) also demonstrated an association of OSA and quality of life in a sample of older black volunteers with self-reported sleepiness or snoring. Obstructive sleep apnea was related to general physical and mental function over the range of AHI from 1 to 15 events per hour, but there was no further worsening of score beyond an AHI of 15. The findings may indicate a threshold effect at a moderate level OSA in older black subjects, but aspects of the sample construction and the small sample size limit interpretation.

Motor Vehicle Crashes and Occupational Accidents

Several studies have shown that patients with OSA syndrome have high motor vehicle crash rates, based on crash records as well as self-report and poor performance on driving simulators (170–175). Because traffic safety is under governmental regulation, there are legal implications for both private and commercial drivers if OSA is a significant cause of impaired driving. The need to understand the role of undiagnosed sleep apnea in motor vehicle crashes is further heightened because unlike other outcomes of sleep apnea, motor vehicle crashes put lives other than the driver's at risk. Consequently, this potential outcome of OSA is of unique importance to society in general.

Although the associations of OSA and motor vehicle crashes demonstrated in sleep clinic samples are alarming, there is great potential for overestimation of risk in clinic patient samples due to selection bias. However, two population studies of undiagnosed OSA and objectively measured motor vehicle crashes also suggest that the association is strong. Young and coworkers (159) investigated 5 years of state records of reported motor vehicle accidents and OSA in the Wisconsin Sleep Cohort. Men, but not women, with an AHI $\geq$ 5 or habitual snoring (compared with nonhabitual snorers and an AHI $<$ 5) were significantly more likely to have at least one crash in a 5-year period, but the magnitude of the association did not differ by severity of OSA. Both men and women with an AHI of 15 or greater (compared with an AHI less than 5 and no habitual snoring) had an odds ratio of 7.3 (95% CI, 2 to more than 25) for multiple crashes in a 5-year period (adjusted for age and miles driven per year). Terán-Santos and coworkers (176) compared OSA severity in incident motor vehicle crash victims from two hospitals and control subjects from primary care health centers and found that the odds ratio (95% CI) of having OSA (AHI $\geq$ 5) in crash cases compared with control subjects was 6.3 (2.4 to 16.2). In both studies, self-assessed sleepiness did not explain the associations of OSA and motor vehicle crash history.

Most recently, similar findings of an association of OSA with motor vehicle crash history, independent of sleepiness, were reported from a novel study conducted in Spain (177). From a survey of a random population sample (n = 4,000),

subjects reporting that they often felt so sleepy while driving that they feared falling asleep were identified. Laboratory polysomnography, including esophageal pressure recording to identify episodes of upper airway resistance, was conducted on a subsample. Of these sleepy drivers, those with self-reported motor vehicle crashes in the previous 5 years, compared with those without crashes, were twice as likely to have OSA defined as an AHI of 5 or more, but the association was not significant. When arousals due to upper airway resistance were taken into account in the definition of OSA, associations were stronger and significant: the odds ratio (95% CI) for 15 or more respiratory events per hour, compared with fewer than 15 events per hour, was 8.5 (1.3 to 62).

Although the population studies do appear to support for a role for undiagnosed OSA in vehicle crashes, it is important to stress the wide confidence intervals for the odds ratios reported. The lack of finding sleepiness as an explanatory factor in the OSA–motor vehicle crash association is disconcerting because it may indicate that drivers with OSA do not perceive performance impairment and thus may not be likely to take extra precautions when driving. A more precise estimate of the magnitude of crash risk associated with OSA based on prospective data is critically needed to determine the risk of motor vehicle crashes attributable to OSA at different severity levels and identify vulnerable subgroups.

No large population-based study of OSA measured by polysomnography and occupational accidents has been conducted; however, Lindberg and colleagues found support for this association based on self-reported snoring and sleepiness as an indicator of OSA. In a cohort of men in Uppsala (n = 2,724), the authors found baseline snoring and sleepiness was significantly related to occupational injuries as recorded in 10 years of government records (odds ratio, 2.2; 95% CI, 1.3 to 3.8). In another study in Sweden, using the same source of occupational injury data, clinic patients with OSA syndrome or heavy snoring were 2- to 3-fold as likely to have had an occupational injury in the past 10 years than were employed control subjects from the general population. The clinic sample, however, is likely to reflect selection bias of men with OSA who are most impaired, and so the association may be overestimated.

Impact on Pregnancy

There are conflicting data regarding the potential impact of OSA on pregnancy outcomes. Case reports of OSA during pregnancy suggest a possible association with both intrauterine growth retardation and pre-eclampsia (178). A study of 11 women hospitalized for severe pre-eclampsia found that none of the women had frank OSA, based on an AHI less than 10; however, all the women had evidence of mild inspiratory flow limitation, affecting on average 72% of breaths during sleep (179). Elimination of the flow limitation with continuous positive airway pressure for one night was associated with a decrease in nocturnal blood pressure. Unfortunately, no control pregnant women without pre-eclampsia were studied, and it is therefore not known whether this pattern of flow limitation is associated with pre-eclampsia or is simply a normal feature of respiration during sleep in late pregnancy.

There are few epidemiologic data concerning the association of OSA with pregnancy outcomes. Loube and coworkers (48) found no significant differences in birth weight, Apgar score, or frequency of perinatal complications between infants born to women with or without frequent snoring during the second or third trimester of pregnancy. In contrast, Franklin and coworkers (50) found that women who reported snoring often or always during the week before delivery were more than twice as likely to have pregnancy-induced hypertension

(14 versus 6%) and pre-eclampsia (10 versus 4%) as were women without frequent snoring, and were more than twice as likely to give birth to an infant small for gestational age (7.1 versus 2.6%) or with an Apgar score less than 7 at both 1 and 5 minutes. After adjusting for maternal age, weight, and smoking habits, odds ratios for associations with frequent snoring were 2.0 for pregnancy-induced hypertension, 2.2 for pre-eclampsia, and 3.5 for intrauterine growth retardation.

RISK FACTORS WITH PARTICULAR POPULATION HEALTH SIGNIFICANCE

Several factors have been hypothesized to have a role in the development and progression of OSA. Potential causes of OSA most relevant to the questions central to this review are those that are prevalent and have the potential to be ameliorated by relatively simple, noninvasive, and preferably population-based interventions: excess body weight, smoking, alcohol consumption, nasal congestion, and hormonal changes during menopause.

Excess Body Weight

Overweight and obesity are highly and increasingly prevalent in the United States (72, 180, 181) and have long been known to be associated with OSA. There have been many cross-sectional clinic-based (83, 182–189) and population-based studies (8, 11, 28, 59, 91, 92, 94, 190–192) of correlates of OSA. Almost all have found significant associations between OSA and measures of excess body weight. There seems to be little controversy that the associations seen in observational studies represent a causal role of excess weight in OSA. However, there are several important questions regarding the nature of the association that continue to merit examination, including the magnitude of the association and variability of response of OSA to excess weight; the role of excess weight in the natural history of OSA; the usefulness of weight control as a preventive measure or as a treatment for OSA; the importance of excess weight in subgroups defined by sex, ethnicity, and age; and the importance of specific distribution of excess fat in the body. It is beyond the scope of this review to address all these issues in depth, and in keeping with the goals of this review this section focuses on the important clinical and public health question of how change in weight affects the occurrence of OSA.

Excess body weight has been hypothesized to affect breathing in numerous ways, including alterations in upper airway structure (e.g., altered geometry) or function (e.g., increased collapsibility), disturbance of the relationship between respiratory drive and load compensation, and by exacerbating OSA events via obesity-related reductions in functional residual capacity and increased whole-body oxygen demand (193, 194). These putative mechanisms suggest that specific anatomical locations of excess fat deposition may be important. A variety of body habitus measures including neck morphology (8, 28, 182–185, 188, 192, 195), general obesity (8, 11, 186, 187, 191), and central obesity (8, 11, 83, 187, 189, 191) have been cross-sectionally associated with OSA. Presently, there is no consensus that a particular habitus phenotype is most important in the pathophysiology of OSA. It is possible that different types of distributions (e.g., central versus upper-body or neck obesity) are more important in specific subgroups defined by factors such as sex. Because alternative habitus measures tend to be highly correlated and measured with varying degrees of accuracy, contemporary epidemiologic methodologies may be ill-suited to determine whether there is a "most-important" body habitus phenotype. In any event, clinical and public health strategies attempting to manage OSA are likely to focus directly on weight control, and nearly all intervention studies of obesity and OSA have assessed weight or BMI reductions, as opposed to changes in body fat distribution.

The effect of weight change on OSA has been most commonly examined in clinical weight loss studies of morbidly obese patients. Typically, these studies assessed indices of OSA before and after either surgical or dietary weight loss. Only two studies included an appropriate control group (i.e., at a minimum with comparable weight and OSA). In the only randomized study, Smith and coworkers (196) monitored a treatment (dietary weight loss instruction) group of 15 obese men and women for an average of 5 months, and a control group (no weight loss instruction) of 8 obese men and women over an average of 9 months. The treatment group experienced a mean weight loss of 9% and a significant mean reduction of 47% in the frequency of apneas (from 55 to 29 events/hour). The control group slightly increased mean weight, and experienced a nonsignificant increase in apnea frequency. In the other controlled study, Schwartz and coworkers (197) examined dietary weight loss in 13 obese patients and 13 age- and weight-matched obese control subjects (all men). Over an approximate 1.5-year period, the weight loss group dropped from a mean BMI of 42 to 35 kg/m^2 (a 17% reduction) and the control group remained at a mean BMI of 38 kg/m^2. The weight loss group experienced a significant reduction in AHI, from 83 to 33 (a 60% reduction), whereas the control group experienced no significant reduction in AHI. These results were mirrored in several uncontrolled dietary (198–205) and surgical (202, 206–209) weight loss studies of obese patients with OSA. Sample sizes in the studies were small (n < 40), follow-up times were short (typically several months, some up to 2 years), and the majority of subjects were men. The relationship between mean weight change and mean AHI reduction among the weight change studies is depicted in Figure 3. Generally, there was greater relative weight loss (i.e., mean percent reduction from baseline weight) in the studies of surgical weight loss (Figure 3, *circles*) than in those of dietary loss (Figure 3, *triangles*). Accordingly, the surgical studies tended to show a greater mean reduction in AHI. Overall, across the several studies, Figure 3 shows a clear and consistent trend in the relationship of mean weight loss and mean reduction in AHI.

An association of weight gain and OSA is usually inferred from the multitude of cross-sectional studies demonstrating greater severity and prevalence of OSA in persons with greater excess weight. However, only one population-based observational study of the association between weight change (gain or loss) and OSA progression has been published. An analysis from the Wisconsin Sleep Cohort Study (210) examined this association over a 4-year period in 690 men and women. Over the follow-up period, mean weight increased from 85 to 88 kg and mean AHI from 4.1 to 5.5 events/hour. Logistic regression modeling estimated that, in persons with an AHI less than 15 at baseline, a 10% weight gain increased 6-fold (95% CI, 2 to 17) the odds of developing moderate or worse OSA (AHI ≥ 15) relative to persons with stable weight. In persons with some degree of OSA, linear regression modeling adjusting for sex, age, and cigarette smoking indicated that an approximate 3% (95% CI, 2 to 4%) increase (decrease) in the AHI is expected for each 1% increase (decrease) in body weight. Note that, among those that lost weight, the relationship between weight loss and AHI reduction was generally consistent with the effect observed in the clinical studies of patients with OSA, as can be seen in Figure 3, where the solid line depicts the estimated percent AHI reduction associated with weight loss in the cohort participants.

Three observational studies of weight change in samples of patients with OSA (69, 71) or persons at high risk for OSA
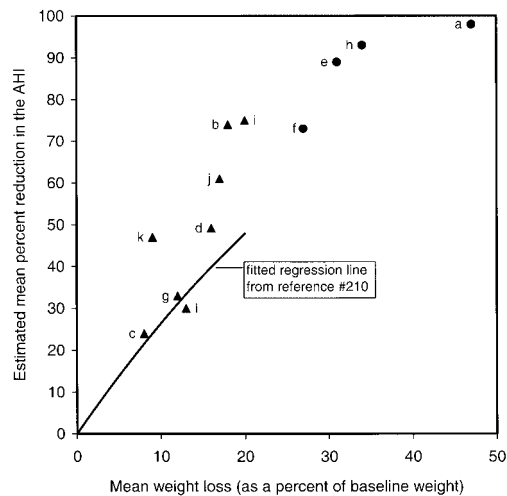
Figure 3. Estimated mean AHI reduction (as a percentage of baseline AHI) associated with mean weight loss (as a percentage of baseline weight) from clinical studies of dietary weight loss (*triangles*), surgical weight loss (*circles*), and one population-based observational study of weight change (*fitted regression line*). Note that the *regression line* is fitted to individual observations from Peppard and coworkers (210) and is not fitted to the points (representing other studies) in the figure. Letters indicate the following references: *a* (207), *b* (200), *c* (201), *d* (275), *e* (208), *f* (209), *g* (202), *h* (202), *i* (203), *j* (197), *k* (196), *l* (205).

(66) were conducted. No significant associations were found between weight change and AHI change over several months to several years of follow-up. However, none of these studies reported significant changes in mean BMI, and the studies likely had too few subjects (n $\leqslant$ 55) to measure a significant association.

Although none of the weight change studies rose to the rigorous standards of a large randomized clinical trial, interpretation of the results seems straightforward: weight loss is an effective means of reducing OSA severity in overweight persons with OSA. Weight gain appears to greatly increase the chances of developing OSA in persons without OSA, and to accelerate progression of OSA in persons already afflicted. However, consistent though these general findings are, there are important limitations to their interpretation. Although the studies uniformly demonstrated weight loss–OSA associations, OSA was rarely completely abolished, individual study participants showed substantial variability in AHI response to weight loss, and the impact on OSA symptoms was generally not evaluated. Moreover, most studies focused on obese men with severe OSA and covered periods ranging only months to a few years. The coevolution of obesity and OSA over a lifetime is likely to be considerably more complicated than can be assessed in short-term studies. Further, the clinical studies usually examined weight loss due primarily to reduced caloric intake. Studies of weight loss due to increased caloric output (e.g., more exercise) are lacking, and it is possible that increased exercise may produce more favorable OSA-related outcomes than expected from diet-associated weight loss alone. There continues to be a need for both randomized studies and rigorous observational prospective studies of exercise, weight loss, or weight control in persons with a wide spectrum of body habitus and OSA severity that include more women and have extended follow-up periods. Effective diet and exercise modification programs exist that can yield long-term weight loss (211). Thus, it seems clear that weight control is likely to be the best nonmedical means of treating or arresting the progression of OSA in clini-

cal settings, and reducing the prevalence of OSA and its associated sequelae in a public health context.

Alcohol

Alcohol ingestion has been demonstrated to acutely increase nasal and pharyngeal resistance in awake subjects (212), and it is reasonable to hypothesize that this effect may compromise breathing during sleep. Studies of the association of alcohol use and OSA have taken two basic approaches: experiments examining the effect of acute administration of alcohol on nocturnal respiratory disturbance, and epidemiologic studies examining correlations between self-reported typical alcohol use patterns and OSA. Most (213–218) but not all (219, 220) studies in which defined quantities of alcohol were administered to healthy subjects or patients with OSA before bedtime have demonstrated harmful effects on nocturnal respiration, including increased number and duration of hypopnea and apnea events. In one CPAP-titration experiment (215), but not another (221), moderate alcohol consumption near bedtime increased the level of nasal pressure necessary to prevent apneas and hypopneas in patients with OSA.

Population-based cross-sectional epidemiologic studies have not consistently demonstrated significant associations between self-reported typical alcohol consumption and OSA, with some finding significant associations with snoring (59, 91, 92, 222) or OSA (28), but others failing to demonstrate associations (89, 94, 192). Although the studies that involve administration of alcohol near bedtime imply an adverse acute impact on breathing during sleep, the effect of long-term alcohol use patterns on the occurrence of OSA is unknown.

Smoking

Smoking is often mentioned as a risk factor for OSA, but few studies have been conducted to investigate this association. There may be several mechanisms by which smoking affects OSA, including smoking-related increases in sleep instability and airway inflammation. Sleep instability, which has been linked to OSA (223), may be increased by overnight reductions in nicotine blood levels. Further, a "rebound effect" may occur in which the acute effects of nicotine that favor increased upper airway tone are reversed during overnight nicotine withdrawal (224). In addition, smoking-related airway inflammation and disease may increase vulnerability to OSA.

Several (28, 91, 92, 94, 222, 224) cross-sectional epidemiologic studies of OSA have found positive associations with cigarette smoking. In the only epidemiologic study to focus on smoking, Wetter and coworkers (224) found that current smokers were three times (95% CI, 1.4 to 6.4) more likely to have OSA than never-smokers. However, former smokers were not more likely to have OSA than never-smokers. Lindberg and colleagues (225) found smoking to predict development of snoring in younger (less than 60 years), but not older men in a 10-year follow-up study. Curiously, an analysis from the Sleep Heart Health Study (191) found an inverse association between current smoking and OSA: After adjusting for several factors including age and BMI, current smokers had significantly fewer respiratory disturbance events as assessed by in-home polysomnography. The authors speculated that the inverse association might indicate that persons with severe OSA may have been more prone to quit smoking. However, there was no association between past smoking and OSA.

Although there is biological plausibility for a causal role of smoking in OSA, it is not yet firmly established as a risk factor. Thus, studies capable of determining the importance of smoking in OSA development and progression should be a research priority.

Nasal Congestion

Although reported correlations between AHI and nasal congestion, as measured by rhinometry during wakefulness before sleep, have been inconsistent (226–229), findings from one study comparing AHI in patients with seasonal rhinitis when symptomatic and symptom free have indicated a role for nasal congestion in OSA (230). Some experimental studies of the effect of nasal packing on breathing during sleep have supported a causal association (231, 232). A biological basis for nasal congestion during sleep as a cause of OSA lies in the importance of nasal breathing to the pressure differential between the atmosphere and intrathoracic space, with increased pressure difference predisposing to airway collapse (233). Understanding the role of allergy-related nasal congestion in OSA is of particular importance because this condition can be diminished by desensitization, allergen avoidance, or pharmacological therapy.

A nasal congestion–OSA link has been tested in depth in only one epidemiology study. In the Wisconsin Sleep Cohort, nasal airflow measured by anterior rhinometry and data from self-reported frequency of acute, seasonal, and chronic nasal congestion at night were collected before overnight polysomnography (229). Nasal congestion was associated with OSA indicated by an AHI of 5 or greater, but was most strongly related to habitual snoring regardless of AHI. The odds ratio for habitual snoring and chronic severe nasal congestion at night was 3.3 (1.8 to 6.2). Longitudinal data demonstrated that the odds of habitual snoring increased over a 5-year study period in people with chronic, severe nasal congestion compared with no congestion (234).

As discussed in the section on OSA incidence and progression, snoring is an important risk factor for increases in AHI over time, and therefore the strong association of nasal congestion with nonapneic snoring raises the possibility that early intervention to decrease nasal congestion, a prevalent condition, may be a promising approach to decrease OSA prevalence. Controlled intervention trials with adequate sample sizes are needed.

Menopause

Early clinical observations that OSA was more prevalent in men compared with women, and extremely rare in premenopausal women led to the hypothesis that hormonal changes during menopause play a role in OSA etiology (40, 235). Although menopause has long been considered an established risk factor for OSA, no study to date has provided solid support for this belief. Findings from clinical observations, examination of age trends in OSA prevalence in women, experimental studies, and small trials of estrogen and progesterone hormone replacement have been inconclusive (41). However, published findings and preliminary data from two population-based epidemiology studies provide the first substantial support for a role of menopausal changes in OSA.

Bixler and coworkers (16) studied the relationship of menopause to OSA in the Hershey, Pennsylvania cohort with menopause defined by self-reported amenorrhea for 12 months or more. Odds ratios for the presence of OSA (AHI $\geqslant$ 15), adjusted for several potential confounding factors, were estimated from logistic regression models in which men, postmenopausal women with hormone replacement therapy (HRT), and postmenopausal women without HRT were compared with premenopausal women. Postmenopausal women with HRT were not at increased risk for OSA (odds ratio, 0.9; 95% CI, 0.1 to 5.8), but postmenopausal women without HRT had a 4-fold risk of OSA (odds ratio, 4.3; 95% CI, 1.1 to 17.3).

Conclusions are difficult to draw from these findings, however, because men were included in the control group. The authors noted that when the analysis was performed with men excluded from the sample, the results were similar but not significant.

Preliminary analyses on 541 women, 30 to 60 years of age, enrolled in the Wisconsin Sleep Cohort Study also support an effect of menopausal status on OSA. The odds ratios for AHI of 15 or more, adjusted for age, body habitus, and other potential confounders, for menopausal (defined by menstrual and gynecological surgery histories) relative to premenopausal women, were 1.5 (0.5 to 4.0) for menopause with HRT use and 2.8 (1.2 to 6.4) for menopause with no HRT use. These estimates are lower than those of Bixler and coworkers (16), but fall within their confidence intervals. Together these studies support the hypothesis that menopause is independently related to OSA and suggest that HRT may be a protective factor. However, it is important to note that the confidence intervals for estimates in both studies are wide, that is, the odds ratios are of borderline significance.

The lack of definitive estimates from these analyses is not surprising in view of the limitations of the underlying models used in both studies. Both studies express the "exposure" of menopause as a dichotomy of pre- and postmenopausal status and neither consider a latent period between exposure and onset of OSA or account for patterns of HRT use. Furthermore, it is likely that control for confounding was incomplete. These limitations, illustrated in Figure 4, are discussed below.

Menopause, defined as the permanent cessation of menstruation due to loss of ovarian function, is preceded by a transition that spans an average of 4 years, throughout which hormone levels decline and other changes occur (236, 237). Although other changes with menopause may be relevant in OSA, most of the focus has been on estrogen and progesterone depletion as the exposure of interest. Several investigations have shown that estrogen and progesterone begin to drop 4 years before menopause, reach a level that is approximately 20% of the premenopausal level at menopause, and continue to drop in the first few years of postmenopause (236, 238–240) (see Figure 4). Consequently, misclassification with respect to the degree of hormone depletion is likely when a simple dichotomy of pre- versus postmenopause is used to categorize women. Identifying stages of the menopausal transition may be critical in adequate classification of exposure. On the other hand, as depicted in Figure 4, hormonal and other menopausal changes may affect OSA indirectly, through metabolic and other physiological changes that persist or continue to increase over time, such as anatomic changes associated with bone loss. Thus, there may be a "latent" period for the effects of menopause such that exposure is better captured by the duration of postmenopause.

Classification of the menopausal exposure is complicated further by the use of HRT. Within hours of administration, estradiol and other active estrogenic compounds are increased to the lower values of the range of estradiol in premenopausal women; with discontinuation of HRT, there is an acute drop to the previous levels of hormones. Thus, depending on HRT use pattern, acute and large fluctuations in hormone levels may occur, superimposed on the slow decline experienced over the menopausal transition.

Assessing menopause–OSA associations independent of age is a formidable challenge. The menopausal transition is tightly correlated with age, which in turn is associated with increased OSA. Controlling for age depends on adequate overlap of age in premenopausal and postmenopausal women, but in reality there is little overlap outside of the range of 45 to 55
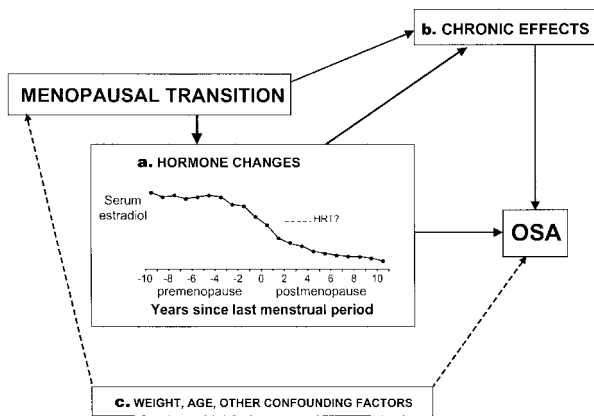
Figure 4. Conceptual model of the role of menopausal changes in OSA. The pattern of hormonal changes, illustrated by the decline of estradiol over several years, (*a*) and modification by hormone replacement therapy (HRT), (*b*) demonstrates the limitation of using the simple dichotomy of premenopause and postmenopause to define the menopausal transition. The effects of hormonal change may be acute or chronic, (*c*) demonstrating the need to consider the length of postmenopause and pattern of hormone replacement therapy. Increased age and weight are strongly associated with both menopausal changes and OSA and, along with other potential confounding factors, must be taken into account in study design and analyses.

years. Thus, the assumption that the findings from the Wisconsin Cohort (presented above) and Bixler and coworkers (16) studies are "adjusted for age" is only partially correct.

Body composition is associated in complex ways with midlife aging, with menopause, and with sleep apnea (241), making control for confounding due to increased weight and fat deposition difficult. In midlife, the most significant changes appear to be in the deposition of body fat and loss of lean weight. However, body composition also influences menopause, with lean women reaching menopause at a younger age. Furthermore, HRT use is associated with increases in weight and body fat (242, 243).

The correlations of both HRT use and OSA with psychosocial and biological factors represent other important sources of potential confounding in the studies of HRT and OSA. HRT use tends to be greater in healthier women (244), and this would contribute to an overestimation of the protective effect of HRT. HRT is commonly discontinued a few years past menopause, when menopausal vasomotor symptoms are likely to have disappeared, and therefore HRT use may be a marker for women in the earlier stages of the menopausal transition. Controlling for factors related to HRT use, many of which are unmeasureable, is extremely important but methodologically challenging.

The implications of a menopausal role in OSA that is lessened with HRT use are profound. HRT use for other than vasomotor symptoms of menopause is controversial (245, 246). Because there are health risks associated with HRT use, solid estimates of the benefit with respect to reducing OSA in women are critical. For this, prospective studies with multiple measures over time are needed to overcome many of the difficulties discussed above.

OBSTRUCTIVE SLEEP APNEA IN CHILDREN

Prevalence

There are few published studies of the prevalence of sleep-related obstructed breathing in children, most using parent-completed questionnaires. In seven studies from Europe and the United States of children 6 years of age or younger, approximately one-third were reported to snore at least occasionally, whereas in most studies 10 to 14% were reported to snore frequently (range, 3 to 38%) (247–253). It appears that older children are less likely than younger children to snore (252, 254, 255). Witnessed apneas were reported in approximately 5% (range, 0.5 to 9%) of children (250, 251, 253, 255). Differences in the populations studied, the questionnaires employed, and perhaps in cultural factors influencing the perception of loud or noisy breathing as "snoring" may underlie the large variation in reported snoring and apnea frequency in these populations.

Obtaining reliable estimates of the prevalence of objectively measured OSA in children is problematic, as the interpretation of polysomnography findings is controversial and based on scant normative data (256) and there is little consistency in the definition of obstructive respiratory events (257), which may have a major impact on prevalence estimates (258). Moreover, the use of respiratory event counts such as the AHI may be inappropriate for childhood OSA, which is often characterized by prolonged obstructive hypoventilation with few discrete apneas or hypopneas (256, 259, 260). Among 213 children, 2 to 7 years of age, with polysomnography evidence of sleep-related obstructed breathing, only 24% had OSA based on an obstructive apnea frequency at least 1 event per hour or an AHI of 5 events or more per hour (260). Several studies from the United States and Europe, including children of various ages from infancy through adolescence, have yielded minimum prevalence estimates for OSA from 1 to 10% (247, 249, 250, 255, 261). These studies employed widely varying sampling strategies, respiratory monitoring techniques, definitions of respiratory events, and threshold event frequencies defining abnormality, and all but one used event counts to identify OSA. It is thus not possible at present to accurately estimate the prevalence of childhood OSA, although a minimum prevalence of 2 to 3% is likely, with prevalence as high as 10 to 20% in habitually snoring children.

Risk Factors

Because of the limited epidemiological data regarding childhood OSA, assessment of risk factors must be inferred in part from published case series, with their inherent risk of bias. These series suggest that the peak incidence of OSA occurs between 2 and 5 years of age (262, 263), consistent with the available epidemiological data on snoring prevalence. In contrast to the male predominance of OSA in adults, epidemiological studies and case series find a similar prevalence of snoring and OSA in boys and girls (247, 248, 250, 251, 254, 261). Although obesity is clearly a less important risk factor in children than in adults, snoring and other symptoms of sleep-related obstructed breathing are two to three times more common in obese than in nonobese children (251, 253). In one study, obese children were four to five times as likely as nonobese children to have polysomnography evidence of moderate to severe OSA (261). Sleep position, which has a large impact on the frequency of obstructive respiratory events in adults, appears much less important in children. In contrast to the adverse impact of supine sleep position in adults, childhood sleep apnea appears to be most severe in the prone position, with little difference between supine and side sleep positions (264). Race may be an important risk factor for sleep-disordered breathing (251, 253, 261, 262), although there are too few data to draw firm conclusions in this regard.

Consequences

Although a less common manifestation of OSA in children than in adults, daytime sleepiness is reported in one-fourth to one-

third of children in most case series (259). Sleepiness appears to be more common in older children, although it may be that sleepiness is simply not recognized in younger children, for whom napping is considered normal. Epidemiological studies have also noted an association of snoring and other symptoms of sleep-related obstructed breathing with daytime sleepiness (247, 250, 253), with approximately a two- to three-fold increased risk of sleepiness in children who snore most nights.

Cardiovascular morbidity has been reported in case series of childhood OSA, including both left and right ventricular dysfunction and hypertension, although there are no epidemiological studies establishing the prevalence of these conditions in association with OSA. Cor pulmonale was present in $\sim 20\%$ of patients in two early case series (265, 266), although cor pulmonale is considered a rare manifestation of childhood OSA at present, possibly because of earlier recognition and treatment of severe OSA (256). In a series of 67 children referred for evaluation of suspected sleep apnea, Marcus and colleagues found that the age-adjusted diastolic blood pressure was 8 mm Hg higher in those with OSA than in those without OSA during both wakefulness and sleep, with no difference in systolic blood pressure (267).

Early case series identified "hyperactivity" and aggressive or rebellious behavior in 22–48% of children with OSA (263, 266, 268), and poor school performance in 16–71% (266, 268), although Brouillette and coworkers found no difference between patients with OSA and control subjects in parentally reported aggressive or hyperactive behaviors (265). Stradling and coworkers evaluated 61 snoring children, mean age 5 years, before and 6 months after adenotonsillectomy for recurrent tonsillitis, and compared them with 31 apparently healthy control subjects of similar age and sex distribution (269). Parents of children referred for adenotonsillectomy were substantially more likely to report that their children were often hyperactive (28 versus 0%) or often aggressive or rebellious (31 versus 0%); these frequencies fell by more than half at the time of the 6-month follow-up. Using standardized neurobehavioral tests, Ali and coworkers (270) compared 12 children with OSA and 11 snoring children without OSA who were referred for adenotonsillectomy with a control group of 10 children undergoing unrelated minor surgical procedures. Several months after surgery, the children with OSA showed improvements in measures of aggression, inattention, hyperactivity, and vigilance, whereas no improvement was seen in the control children. The children with nonapneic snoring showed an intermediate degree of improvement.

Few data are available from population-based studies on the neurobehavioral consequences of OSA in children. Two studies found that children with snoring and other signs of obstructed breathing scored higher on standardized tests of aggression, inattention, and hyperactivity (247), and were more likely than children without these symptoms to have academic problems or symptoms of attention deficit–hyperactivity disorder (271). Using questionnaire plus overnight pulse oximetry, Gozal (272) evaluated 297 first-grade students whose school performance was in the lowest decile of their class; he found evidence of OSA in 54 children, all of whom were given a recommendation to seek medical intervention. In 24 undergoing adenotonsillectomy, grades improved significantly during the following year, whereas there was no improvement seen in those not seeking treatment or in those without evidence of OSA.

It thus appears likely that OSA in children is associated with daytime sleepiness, although this effect is less prominent than in adults. Impairment of behavioral regulation may be a particularly important consequence of OSA in children, whereas the cardiovascular impact of childhood OSA remains poorly elucidated. Because of the paucity of epidemiological studies of childhood OSA, the magnitude of the potential contribution of OSA to cardiovascular and neurobehavioral impairment is unclear, and the mechanisms underlying these associations are not known.

CONCLUSION

OSA with daytime impairment, that is, OSA *syndrome*, is estimated to occur in 1 of 20 adults, is usually unrecognized and undiagnosed, and results in behavioral and cardiovascular morbidity. Minimally symptomatic or asymptomatic OSA is estimated to occur in one of five adults, is rarely recognized, and is likely to result in a large population-level burden of morbidity. If current secular trends of increasing overweight continue, the occurrence, and consequently the clinical and public health burdens of OSA, will increase accordingly. There are two different strategies to address this burden: identification and treatment of undiagnosed OSA syndrome via case finding based on primary care or population screening, and population-based interventions to prevent the development or halt the progression of OSA.

The effectiveness of case finding as a means of reducing the burden of OSA across its severity spectrum is hampered by the lack of adequate clinical resources to meet even current demands, problems with patient acceptance of the available treatment modalities, and uncertainty regarding the benefits from treatment of mild or asymptomatic OSA. It is unlikely that these obstacles will be overcome in the near future. However, with current knowledge that treatment of symptomatic OSA will reduce known serious health risks, there is an ethical imperative to implement strategies to identify undiagnosed OSA syndrome cases considered to be clinically significant according to current clinical practice. At a minimum, this includes those patients with otherwise unexplained daytime sleepiness who have an elevated frequency of apnea and hypopnea during sleep.

Primary care providers will be key to successful case finding. Unfortunately, both pre- and postdoctoral medical education generally fails to provide training in the recognition and treatment of sleep disorders (273). Therefore, changes in medical school and postgraduate medical education are essential to promote an understanding of the signs, symptoms, and risk factors for OSA. Simple questions about snoring frequency and loudness, witnessed nocturnal apneas, and daytime sleepiness should become a routine component of the review of systems in the general medical history interview. As there is a high prevalence of snoring and sleepiness, the hallmarks of OSA, in the general population, the greatest challenge for primary care providers will lie in determining which patients with these symptoms warrant further evaluation. Patients who report frequent sleep-related breathing abnormalities, unsatisfactory sleep, or unexplained daytime sleepiness would clearly be candidates for referral.

What should be done with snorers without explicit daytime complaints? Most patients with OSA snore, but most snorers do not have frank OSA. Given the lack of a simple clinical test with a low "false-positive" rate, clinical judgment must be used in identifying patients for referral, if the resources for evaluation and treatment of OSA are not to be overwhelmed. More detailed questioning of noncomplaining snorers should be undertaken to be certain that symptoms suggestive of OSA syndrome are not being minimized, as often occurs in the setting of adaptation to a chronic condition. In the absence of significant daytime symptoms, a prudent approach in most cases would be to instruct the patient about the potential for OSA

to develop, with special attention to factors such as weight gain that may influence progression. In the patient with hypertension that is difficult to control, or cardiovascular disease, a lower threshold for referral may be appropriate, although it is as yet uncertain that treatment of OSA per se is more effective than drug therapy in reducing blood pressure in such patients, or in reducing the risk of complications of cardiovascular disease.

What is the cost of failure to identify mildly symptomatic or asymptomatic OSA? A growing body of evidence from methodologically sound population-based cohort studies supports a causal role, albeit small, of mild OSA in the development of hypertension and cardiovascular morbidity. Although less consistent, findings also point to associations of undiagnosed mild OSA and nonapneic snoring with decrements in daytime performance. Given the modest magnitude of the adverse health consequences of mild OSA, the impact on an individual appears small from a clinical perspective. However, because mild and seemingly asymptomatic OSA is a chronic condition occurring in approximately 20% of adults, even a small increase in average blood pressure, cardiovascular disease incidence, or behavioral morbidity attributable to OSA would lower the overall health and well-being of a population—from a public health standpoint, the impact could be profound.

Thus, the magnitude of the burden of mild OSA and the strategies to reduce it are different when seen from the varied perspectives of clinical care and population health. Strategies to address mild OSA are needed from both perspectives. A clinical strategy to reduce the morbidity associated with mild OSA would require appropriate diagnostic criteria and the availability of an efficacious treatment. For prevalent conditions with a wide severity spectrum, such as OSA, the level recognized as a diagnosable disorder is often influenced by the type of therapy available. Even if CPAP treatment of all patients with mild or asymptomatic OSA were economically feasible, it is likely that the personal burden of nightly CPAP use would preclude widespread use. The advent of new therapies to feasibly treat mild OSA would be of enormous benefit in reducing its overall morbidity. However, until a low-cost, effective treatment with high patient acceptance is available, the direct clinical role in lessening the burden of mild to moderate OSA will be limited.

The reduction or elimination of causal or contributing factors through public health initiatives with clinical support is warranted. Potentially modifiable risk factors for OSA considered in this review are overweight and obesity, alcohol, smoking, nasal congestion, and estrogen depletion in menopause. Data suggest that OSA is associated with all these factors, but at present the only intervention strategy supported with adequate evidence is weight loss. Interventions to reduce overweight and obesity through both population- and clinic-based programs hold the greatest promise for reducing the burden of mild OSA. Overweight and obesity are widely recognized correlates of OSA and new prospective data show that moderate weight gain in the general population leads to an increase in the incidence and progression of OSA. Although weight loss is difficult to achieve, evidenced by an epidemic of overweight and obesity in most Western nations, effective diet and exercise modification programs can yield long-term weight loss (211).

Overweight and obesity are well-recognized strong risk factors for a constellation of serious morbidities, and there are already mechanisms in place for population-based weight reduction interventions as means of decreasing the risk of hypertension, heart disease, some cancers, and diabetes. Disorders recognized in government-sponsored public health initiatives receive considerable attention in prevention and primary care clinic settings, and when they are declared the target of an intervention they often have the additional benefit of surveillance to track changes in disease prevalence, to assess the impact of the intervention, and to monitor public and practitioner awareness of the disorder. It is therefore unfortunate that recognition of OSA as a serious outcome of overweight is lacking in high-profile health promotion initiatives, such as Healthy People 2010 (274). Recognition of the importance of OSA in such health promotion initiatives would be a valuable step toward implementing population-based strategies to reduce OSA prevalence.

It is critical that the level of suspicion for OSA be increased in primary care settings; that primary care providers refer patients suspected to have OSA syndrome to sleep specialists for further evaluation; that resources be increased for OSA diagnosis and therapy; and that public health initiatives specifically target OSA, across its severity spectrum, for recognition, prevention, and surveillance. Although we believe these recommendations for addressing the burden of OSA accurately reflect the current state of knowledge, new and continuing rigorous investigations into the natural history, causes and consequences of OSA are warranted and necessary.

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APPENDIX

Several large population-based cohort studies, using full or partial polysomnography (PSG) to characterize OSA, are described. Available information about start date, sampling scheme, sampling frame for PSG, sample size, response rate, PSG method, definitions, current status, and key reference are included.

1. San Diego Older Adult Cohort (1981): probability sample of men and women, 65 years of age or older at baseline, n = 427 (55).

Random digit dialing was used to recruit older adults for in-home interviews and overnight PSG with four-channel

modified Medilog (Oxford Instruments, Witney, Oxfordshire, UK)/Respitrace (Noninvasive Monitoring Systems, Miami Beach, FL) system (23% response rate). Wrist actigraphy was used to indicate sleep/wake state. Apnea and hypopnea events were defined by decreased amplitude of respiratory signal ($\geqslant$ 90% and 50 to 90%, respectively) for 10 seconds or more. Follow-up studies of participants with more severe sleep-disordered breathing were conducted at 2-year intervals. Several cross-sectional and prospective studies of OSA occurrence, progression, morbidity, and mortality have been published.

2. Wisconsin Sleep Cohort Study (1989): two-stage probability sample of men and women, 30 to 60 years of age at baseline, n = 1,490 (11).

In Stage 1, state employees (with full range of job classifications) in south central Wisconsin, identified by payroll data, were surveyed by mail. In Stage 2, a subsample weighted on habitual snoring was recruited from survey respondents for full in-laboratory polysomnography (Grass, Quincy, MA) at 4-year intervals (51% response rate). Apnea was defined as no airflow for 10 seconds or more and hypopnea was defined as a discernible decrease in calibrated respiratory signal accompanied by a 4% oxyhemoglobin desaturation for 10 seconds or more. Several cross-sectional and prospective studies of OSA occurrence, risk factors, and outcomes have been published. Follow-up is ongoing.

3. Cleveland Family Cohort (1990): nonprobability sample, 15 to 86 years of age at baseline, n = 932 (17).

Sleep apnea patients (n = 85) and their family members (n = 510) and members of other families (n = 337) identified by the patient were studied by in-home monitoring with a four-channel recorder (EdenTec; Mallinckrodt, Hazelton, MO). Apnea and hypopnea events were defined as a decrease in airflow or breathing accompanied by a 2.5% oxyhemoglobin desaturation for 10 seconds or more. Several studies of familial aggregation and genetics have been published. Follow-up is ongoing.

4. Sleep Heart Health Study (1997): nonprobability sample, men and women, 40 to 98 years of age at baseline, n = 6,642 (18).

Participants from six ongoing cohort studies were recruited by various methods for in-home polysomnography (Compumed-

ics, Abbotsford, Victoria, Australia). Apnea and hypopnea events were defined as decreases in airflow or respiratory signal ($\geqslant$ 75% for apnea and 30 to 75% for hypopnea) for 10 seconds or more with a 4% oxyhemoglobin desaturation. Several cross-sectional studies of risk factors and outcomes have been published. Follow-up is ongoing.

5. Vitoria-Gasteiz, Spain Cohort (1993): two-stage probability sample, men and women 30 to 100 years of age, n = 445 (19).

In Stage 1, adults were recruited from a probability sample of households drawn from census data for in-home interviews and screening with a four-channel recorder (MESAM 4; Madaus Medizin Elektronik, Munich, Germany). In Stage 2, those with suspected OSA (n = 380) and without OSA (n = 165) were studied by standard laboratory PSG (response rate, 81%). Apnea and hypopnea events were defined as a reduction in airflow or respiratory signal (100 and 50%, respectively) with a 4% oxyhemoglobin desaturation or microarousal. Studies of prevalence and hypertension have been published.

6. Southern Pennsylvania Cohort (1996): two-stage probability samples for men and women 20–100 years of age, n = 1,741 (15, 16).

In Stage 1, random digit dialing was used to recruit for survey participation. In Stage 2, survey respondents were recruited for in-laboratory full PSG (Grass) with oversampling on snoring, sleepiness, obesity, and hypertension for men (n = 741) and, in addition, oversampling on postmenopause for women (n = 1,000) (response rate, 66% for women and 68% for men). Apnea and hypopnea events were defined as decreased airflow at the nose or mouth (100 and 50%, respectively) with a 4% oxyhemoglobin desaturation for 10 seconds or more. Studies of prevalence, sex, and hypertension have been published.

7. Hong Kong Chinese Men (1997): probability sample, men 30–60 years of age, n = 153 (32).

Employees at three Hong Kong agencies were recruited on site for survey and in-laboratory PSG (Alice 3) (response rate, 20%). Apnea and hypopnea events were defined as decreased airflow (100% and discernible reduction, respectively) with 4% oxyhemoglobin desaturation for 10 seconds or longer.