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HIGHLIGHTED TOPIC | *Physiology and Pathophysiology of Sleep Apnea*

Excess weight and sleep-disordered breathing

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Young, Terry, Paul E. Peppard, and Shahrads Taheri. Excess weight and sleep-disordered breathing. *J Appl Physiol* 99: 1592–1599, 2005; doi:10.1152/jappphysiol.00587.2005. Excess weight is a well-established predictor of sleep-disordered breathing (SDB). Clinical observations and population studies throughout the United States, Europe, Asia, and Australia have consistently shown a graded increase in the prevalence of SDB as body mass index, neck girth, or other measures of body habitus increases. Clinical studies of weight loss and longitudinal population studies provide strong support for a causal association. The role of excess body weight, a modifiable risk factor, with SDB raises many questions relevant to clinical practice and public health. The topic takes on added importance with the alarming rate of weight gain in children as well as adults in industrialized nations. Among adults ages 30–69 yr, averaging over the estimated United States 2003 age, sex, and BMI distributions, we estimate that ~17% of adults have mild or worse SDB (apnea-hypopnea index ≥ 5) and that 41% of those adults have SDB “attributable” to having a body mass index of ≥ 25 kg/m². Similarly, we estimate that ~5.7% of adults have moderate or worse SDB (apnea-hypopnea index ≥ 15) and that 58% of those adults have SDB attributable to excess weight. Clearly, if the expanding epidemic of obesity seen in the United States continues, the prevalence of SDB will almost certainly increase, along with the proportion of SDB attributable to obesity.

apnea-hypopnea index; body mass index

THE LINK BETWEEN EXCESS WEIGHT or obesity and obstructive sleep apnea has long been appreciated. In 1956, obstructive sleep apnea was recognized as a disease of obesity and hypoventilation: the Pickwickian syndrome (3). Since then, observations of patients diagnosed with obstructive sleep apnea and findings from population studies have overwhelmingly supported a strong and likely causal role of overweight in this condition, more broadly described as sleep-disordered breathing (SDB).

The commonest form of SDB is obstructive sleep apnea, in which there is repetitive collapse (apnea) or partial collapse (hypopnea) of the upper airway during sleep (6). This results in decreases and pauses in breathing during sleep and intermittent transient hypoxia. These events are often terminated in arousals from deeper sleep, and the resulting sleep fragmentation can lead to excessive daytime sleepiness. The gold standard diagnostic investigation of SDB is nocturnal polysomnography to detect apnea and hypopnea events and determine whether they are obstructive or due to abnormal control of breathing. In population screening studies, the severity range is wider than seen in clinic settings, with a higher proportion of cases at the milder end of the spectrum. Usually, no distinction is made between obstructive events and those due to abnormal control of breathing, and the condition is termed SDB. To be consistent, SDB is the term used

in this review, with the assumption that it reflects, in most cases, obstructive sleep apnea. The commonly used measure for SDB is the apnea-hypopnea index (AHI; the number of apnea and hypopnea events per hour of sleep).

The important association of excess body weight, a modifiable risk factor, with SDB raises many questions relevant to clinical practice and public health. The topic takes on added importance with the alarming rate of weight gain in children as well as adults in industrialized nations. Although there are multiple established factors that predispose one to SDB, ranging from genetic makeup to upper airway abnormalities and to various craniofacial phenotypes, excess weight is the strongest contributing factor (57). It is therefore expected that the prevalence of SDB will increase in parallel with obesity. Recently, interest has expanded to include intermediary mechanisms by which excess weight and SDB may interact. Particularly important are the associations of SDB, obesity, and metabolic hormones. In this review, we first describe the associations of excess weight in the occurrence and progression of SDB and estimate the overall burden of SDB that may be attributed to excess weight. Next, we discuss mechanisms, including hormonal changes, that explore the excess weight-SDB link.

QUANTIFYING THE ROLE OF EXCESS WEIGHT IN SDB
Cross-Sectional Studies

The high prevalence of obesity and morbid obesity in patients diagnosed with sleep apnea is well established (43).

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Table 1. Prevalence of sleep-disordered breathing by BMI and other body habitus strata in several community studies

Study (Ref.)	Sample	Definition of SDB	Body Habitus Variable and Strata	Prevalence, %
Bixler et al. (4)	Pennsylvania, <i>n</i> = 1,000 W 20–100 yr	AHI ≥15, Laboratory	BMI <32.3	1.1
		PSG	≥32.3	7.2
Bixler et al. (5)	Pennsylvania, <i>n</i> = 741 M 20–100 yr	AHI ≥15, Laboratory	BMI <32.3	2.0
		PSG	≥32.3	13.8
Young et al. (56)	Multisite (Sleep Heart Health Study) <i>n</i> = 5,615 M, W 40–98 yr	AHI ≥15 In-home PSG	Quartiles, BMI	
			1 (16–24)	10
			2 (24–28)	13
			3 (28–32)	17
		4 (32–59)	32	
		Waist-to-hip girth ratio		
		1 W (0.53–0.82); M (0.68–0.92)	12	
		2 W (0.82–0.89); M (0.92–0.97)	14	
		3 W (0.89–0.96); M (0.97–1.01)	19	
		4 W (0.96–1.34); M (1.01–1.50)	26	
Neck girth, cm				
1 W (10.2–13.0); M (11.8–15.4)	10			
2 W (13.0–13.8); M (15.4–15.9)	12			
3 W (13.8–14.6); M (15.9–16.9)	18			
4 W (14.6–19.5); M (16.9–23.2)	29			
Ip et al. (19)	Hong Kong <i>n</i> = 106 W 3–60 yr	AHI ≥5 Laboratory	BMI <23	0.9
		PSG	≥23	8.8
Ip et al. (17)	Hong Kong <i>n</i> = 153 M 30–60 yr	AHI ≥5 Laboratory	BMI <23	0.9
		PSG	≥23	14.5
Carmelli et al. (7)	California (Western collaborative) <i>n</i> = 281 M 75–91 yr	AHI >5	BMI <28	26
			≥28	36

M, men; W, women; PSG, polysomnography; AHI, apnea-hypopnea index; BMI, body mass index.

Similarly, SDB has been reported to occur in 50–77% of obese patients in other clinical settings (51). The type of body fat distribution seen in obese and overweight SDB patients has led to hypotheses that large neck girth and a high waist-to-hip circumference ratio are stronger predictors of SDB, compared with weight-based measures such as body mass index (BMI) (9, 16). However, due to selection biases favoring the referral of the stereotypical “Pickwickian” patient (i.e., obese, sleepy, middle-aged man with a thick neck) for sleep evaluations, studies based on population samples continue to be important in characterizing the excess weight-SDB link.

For the past 15 yr, population studies throughout the United States, Europe, Asia, and Australia have consistently shown a high prevalence of medically undiagnosed sleep apnea in adults (55). Notably, studies have generally shown a graded increase in prevalence as BMI, neck girth, or other measures of body habitus increases (Table 1). Although the absolute values of these prevalence estimates vary somewhat due to differences in measurement techniques, definitions, and cut points, the consistency in the dose-response nature of the associations is striking. The obesity-SDB link first seen in clinical populations is clearly present in undiagnosed SDB in the general population as well. Some studies express the excess weight-SDB association with a comparison of mean BMI by AHI categories. As shown in Table 2, BMI is higher in persons with AHI of ≥5 compared with AHI of <5. Of particular importance, findings from the population studies include a wider range of body habitus values, compared with the higher weight range

and morbid obesity seen in clinic patients, and demonstrate that SDB is not just a problem of morbid obesity.

With the use of statistical modeling techniques, attempts have been made to determine which body habitus measure is the best or most important predictor of SDB. However, methodological issues, including important gender differences in ranges of anthropometric measures such as neck girth, different degrees of measurement error, and high correlations between

Table 2. Mean BMI by sleep-disordered breathing categories (AHI <5, ≥5) in Asian, African American, and Caucasian population samples

Study, SDB Measurement, Sample Characteristics	Mean BMI by SDB Category, kg/m ²	
	AHI <5	AHI ≥5
Kim et al. (21), laboratory PSG Korean men and women 40–70 yr	24	27
Udwadia et al. (48), laboratory PSG Indian men, 35–65 yr	27	31
Ip et al. (17), laboratory PSG Chinese men, 30–60 yr	25	27
Ip et al. (19), laboratory PSG Chinese women, 30–60 yr	23	27
Redline et al. (35), in-home PSG monitor, Cleveland Family Study: men and women, 2–86 yr		
African American	25	32
Caucasians	25	33

SDB, sleep-disordered breathing

these parameters, make results difficult to interpret. At present, a “best” or most predictive body habitus measure has not been identified. Some findings from studies with large sample sizes suggest that BMI, neck girth, and central fat patterning may independently contribute to SDB (56).

Longitudinal Studies

Most descriptive studies, both clinical and population, on obesity and SDB have been based on cross-sectional data that only allow interperson comparisons to suggest temporal dynamics of the association. For example, cross-sectional data may indicate that a person with a higher BMI, compared with a person of the same age and sex but lower BMI, is more likely to have SDB. But data on changes within individuals over time, from prospective studies, are needed to understand how SDB varies with weight loss or gain to determine how long it takes for weight fluctuations to have an effect and to project the impact of the current trend of increased obesity on sleep apnea prevalence in the future. Some findings regarding the effect of weight change on SDB are available from clinical studies of extremely obese patients undergoing surgical procedures and from longitudinal epidemiology studies begun several years ago.

Despite small sample sizes and often the lack of control groups, clinical studies of weight loss in sleep apnea patients have shown a consistent trend: an ~3% reduction in AHI is associated with each 1% reduction in weight (55). With the current increase in bariatric surgery (even among adolescents), data on how weight loss affects SDB are becoming more abundant (22, 50). In the most recent study (12), polysomnography was performed before gastric banding and at 1–4 yr after this surgery in 25 severely obese patients. The mean weight loss was 45 kg, and the mean AHI fell from 62 to 13.

A few population studies have investigated the role of weight change in SDB occurrence and progression over time. Findings consistently point to the importance of body habitus in predicting the occurrence and progression of SDB. In the Wisconsin sleep cohort, 690 men and women were studied with laboratory polysomnography at baseline and at 4-yr follow-up (29); a 10% weight gain was associated with a sixfold increase in the odds of developing moderate or worse SDB (AHI ≥ 15). Similar to the findings from clinical studies, each 1% change in weight was associated with a 3% change in AHI. The 5-yr incidence of SDB was investigated in the Cleveland Family Study (47). Of 286 men and women (mean age = 36.8 yr) who had no SDB (indicated by AHI < 5) at baseline, the incidence of new SDB (defined by developing AHI > 15 at follow-up) was 3.3% for those whose baseline BMI was < 24 and 22% for those whose baseline BMI was ≥ 31 . Most recently, longitudinal data from the Sleep Heart Health Study were used to examine 5-yr changes in weight and AHI based on in-home polysomnography of 2,968 men and women ages 40–95 yr (27). Results indicated that, although weight loss predicted a decrease in AHI, the effect was weaker than that of weight gain on an increase in AHI. For example, in men, the odds ratio for a 5-yr increase in AHI of ≥ 15 with a gain of at least 10 kg was 5.2, but the odds ratio for a loss in AHI of at least 15 with a loss of ≥ 10 kg was 2.9.

Association of Excess Weight and SDB by Gender, Age, and Race

Understanding special vulnerabilities to the effects of excess weight on SDB is important in targeting population subgroups that may be at high risk. Gender, age, and race or ethnicity have been characteristics of interest in looking for interaction effects. In investigating interactions, samples are stratified on the characteristic of interest, and the measures of association (e.g., odds ratios for BMI and AHI) in each strata are compared to determine whether any differences are statistically significant. Although few in number, some cross-sectional and prospective studies have addressed the possibility of differences in the nature of the obesity-SDB link by gender, age, and race.

Gender. Before the publication of population-based studies of SDB that included both women and men, gender differences in SDB occurrence and risk factors were poorly understood. SDB was believed to be rare in women, particularly those who had not reached menopause. The few premenopausal women diagnosed with SDB were reported to be strikingly more obese than the men or postmenopausal women diagnosed with this condition (26, 52). These observations suggested that women were less vulnerable to the effects of weight on SDB, particularly before menopause. Population-based studies have now shown that the increased SDB prevalence associated with male sex and menopause are significant but smaller in magnitude compared with those expected from clinical observations. Although the gender differences are less striking than once thought, there is considerable interest in understanding whether body habitus differences explain gender and menopausal differences.

A greater male vulnerability to SDB from obesity has been reported in some but not all studies. In a study of progression of SDB in the Cleveland Family Study, the interaction of age, sex, and BMI was significant in predicting changes in AHI (34). In women, the increase in AHI with increased weight was less than that observed in men, regardless of age and baseline BMI. Similar findings were reported by Newman et al. (27) in the recent analysis of 5-yr prospective data of the Sleep Heart Health Study. AHI was more likely to increase in men compared with women for a given weight increase. For a weight gain of ≥ 10 kg, the odds ratio (95% confidence interval) for a progression in AHI of ≥ 15 was 5.2 (2.4, 11.5) for men and 2.6 (1.0, 6.6) for women. In two cross-sectional community studies on middle-aged Chinese men and women in Hong Kong, men, compared with women, had higher AHI at any given BMI (17, 19).

Although suggestive, a statistically significant interaction of gender and BMI or other obesity marker on SDB (e.g., a higher odds ratio for SDB and BMI in men vs. women) was not found in two other large population studies (4, 5, 29). The lack of agreement among the various study findings may be due in part to the precision of estimates in the BMI-gender strata when other factors, such as age and menopausal status, are accounted for. For example, Bixler and colleagues (4) noted that, in the Pennsylvania cohort sample (5), all of the premenopausal women with SDB (AHI > 15) were obese (BMI ≥ 32), compared with only 42% of postmenopausal women who were not using hormone replacement therapy. In a report from the Wisconsin cohort, at any given BMI, prevalence of SDB (indicated by AHI ≥ 5) was higher in postmenopausal com-

pared with menopausal women, but SDB did occur in both post- and premenopausal women who were not obese (53). Clinical reports of greater obesity of premenopausal women, compared with postmenopausal women, suggest that association between excess weight and SDB is stronger for menopausal women. Thus both population and clinical studies indicate that BMI has a weaker effect on SDB in premenopausal women compared with postmenopausal women as well as with men.

Age. Investigation of an interaction of age in adults and obesity on SDB is limited by the small number of studies with a sufficient sample size at the higher range of the age spectrum, i.e., over age 75 yr. Ancoli-Israel and colleagues (2) reported on an 18-yr follow-up of community-dwelling adults age >65 yr at baseline. Interestingly, BMI at baseline and change in BMI over time, but not aging, were predictive of changes in AHI. In the Western Collaborative Group study of 281 men, ages 75–91 yr, AHI was measured with an in-home monitor and correlated with data collected during the previous 30 yr on BMI and waist girth (7). The prevalence of AHI of ≥ 5 was 26 and 35% in men with BMI of ≤ 28 and >28 , respectively. The authors found that, of the body habitus measures, only midlife waist girth and subsequent increases over 30 yr were independently associated with AHI in older age. The authors commented that neck girth in elderly men may be a weaker correlate of SDB than it is in younger men.

Cross-sectional studies with samples that include a wide age range have generally shown that the association of obesity and SDB appears to weaken with increasing age. In the Sleep Heart Health Study, SDB in people age 70 yr or older was only weakly related to BMI or other measures of body habitus (56).

Race and ethnicity. Studies of sleep apnea prevalence in Western nations, Eastern nations, and of populations in the United States with a diversity of ethnic groups show BMI or other measure of excess weight to predict SDB (17, 19, 21, 35, 48). Few studies, however, report data that can answer the question of whether there is a special vulnerability of a race or particular ethnic group to the effects of excess weight on sleep apnea.

EASTERN POPULATIONS. Recent studies of men and women in Hong Kong (17, 19) and Korea (21) and men in India (48) have reported prevalences of sleep apnea similar to those of Western nations and positive association of BMI and SDB, with odds ratios similar to those seen in reports of Western nations. Based on these population studies, the increased odds for AHI ≥ 5 with one standard deviation increment in BMI (~ 3 – 4 BMI units) are 4.0 for Korean men and women (21), 5.7 for Indian men (48), and 2.4 and 3.0 for Chinese men and women in Hong Kong, respectively (17, 19). The magnitude of increased odds from these studies on Asian populations is strikingly similar to the increased odds seen in the United States. The increased odds for AHI ≥ 5 with one standard deviation increment in BMI (~ 5 kg) was 4.0 in the Wisconsin sleep cohort (54). Most striking is that the similarities in the excess weight-SDB link exist despite the relatively lower BMI in Eastern compared with Western nations (as shown in Table 2). In addition to lower mean values and ranges of BMI, cut points for what is considered obese is lower (i.e., BMI > 23) in Eastern compared with Western nations (i.e., BMI > 30). Li and colleagues (25) have previously noted that far-east Asian men with sleep apnea are nonobese compared with white patients and hypoth-

esized that the interaction of craniofacial anatomy and obesity may differ in Eastern and Western populations. In support of this interaction, craniofacial parameters were a stronger correlate of SDB in leaner men in a study of largely Caucasians in the United States (11).

AFRICAN HERITAGE. There have been no studies to date on SDB in African populations. In most of the studies in the United States that include African Americans, prevalence estimates are commonly adjusted for BMI, and thus subgroup vulnerability cannot be ascertained. However, in the Sleep Heart Health Study longitudinal study of weight change and SDB (27), the authors noted that no significant interaction of race and BMI with SDB was found. Similarly, although BMI was a risk factor for SDB in African Americans in the Cleveland Family Study, the effect did not differ in magnitude from the effect in Caucasians in the same study (35).

Prevalence of SDB Attributable to Overweight and Obesity

What proportion of cases of SDB might be attributable to excess weight? The answer depends on the presence of a causal association between excess weight and SDB, the magnitude of the association, and the prevalence of excess weight in the population. Here, we describe a “ballpark estimate” of the proportion of SDB disease resulting from overweight and obesity. We use data from the US Centers for Disease Control and Prevention’s Behavioral Risk Factor Surveillance System (8), the US census, and our own data from the Wisconsin sleep cohort for the calculation.

METHODS

Although several research groups have presented prevalence estimates for SDB by age and sex, no published data are available at the resolution necessary (age- and sex-specific estimates within multiple categories of excess weight) to make reasonable attributable prevalence calculations. Thus we performed new analyses of in-laboratory overnight polysomnography data from the population-based Wisconsin Sleep Cohort Study (54) to perform estimates of SDB prevalence. We chose to use cross-sectional attributable prevalence estimates rather than more traditional attributable risks because 1) SDB is reversible and appears to change rapidly in response to weight change (loss or gain as discussed in *Longitudinal Studies*) and 2) attributable prevalence per se (the amount of SDB disease in a population at a point in time attributable to excess weight) is a population health parameter of significant interest.

We estimated the prevalence of SDB [“mild or worse SDB” (AHI ≥ 5) and “moderate or worse SDB” (AHI ≥ 15)] attributable to excess body weight in a multistep process.

We graphically examined the relation between BMI and SDB prevalence in age- and sex-specific groups. Prevalence of SDB did not rise with increasing BMI among persons with BMI less than ~ 25 kg/m² but did with increasing BMI beyond that point (data not shown). Thus we chose BMI of <25 kg/m² as the reference group for which to estimate prevalence ratios within age- and sex-specific categories.

We examined several variables that may covary with the relation between excess weight and SDB, such as alcohol and cigarette use. These were not found to be important confounders of the association.

We calculated prevalences of SDB by categories of age, sex, and BMI (<25 , 25–29, 30–39, and ≥ 40 kg/m²).

As with standard attributable risk estimation (39), the prevalence of SDB in the BMI < 25 kg/m² category was assumed to be a baseline level of SDB prevalence that would be expected in a population for which all persons had “normal weight” (BMI < 25 kg/m²). Excess

Table 3. Estimated prevalence and 95% confidence intervals of mild or worse SDB (AHI ≥ 5 events/h) and moderate or worse SDB (AHI ≥ 15 events/h) by sex, age, and BMI category

BMI category	Men		Women	
	30–49 yr	50–69 yr	30–49 yr	50–69 yr
AHI ≥ 5 events/h				
<25 kg/m ²	9.3 (6.8, 13)	26 (19, 36)	2.5 (1.6, 3.8)	8.2 (5.2, 13)
25–29 kg/m ²	17 (14, 21)	37 (30, 44)	4.8 (3.4, 6.8)	13 (9.1, 17)
30–39 kg/m ²	33 (28, 39)	52 (46, 59)	11 (8.3, 15)	21 (16, 27)
≥ 40 kg/m ²	72 (60, 81)	77 (65, 86)	39 (28, 51)	46 (31, 61)
AHI ≥ 15 events/h				
<25 kg/m ²	2.0 (1.2, 3.2)	6.4 (3.9, 10)	0.5 (0.2, 1.2)	1.8 (0.9, 3.8)
25–29 kg/m ²	4.6 (3.1, 6.6)	10 (7.3, 14)	1.3 (0.6, 2.5)	3.0 (1.6, 5.4)
30–39 kg/m ²	13 (10, 18)	18 (14, 23)	4.0 (2.3, 6.8)	5.6 (3.4, 9.2)
≥ 40 kg/m ²	55 (40, 68)	42 (26, 59)	24 (15, 37)	16 (8.6, 29)

Values are percentages, with 95% confidence intervals in parentheses.

prevalence in age- and sex-specific categories of increasing BMI, beyond that seen in the baseline category, was calculated and “attributed” to excess weight.

Finally, the age-, sex-, and BMI category-specific prevalences were extrapolated to the US distribution of adults aged 30–69 yr old (the age span represented in the Wisconsin sleep cohort). Sex and age distribution data were from 2003 census estimates (49). US population distribution of BMI categories within age and sex groups were calculated using 2003 data available from the US Centers for Disease Control’s Behavioral Risk Factor Surveillance System (8).

RESULTS

Table 3 presents the prevalence estimates for SDB by sex, age, and BMI category. In each age and sex group, SDB prevalence increases steeply with increasing BMI. Generally, SDB is more prevalent in men and older persons.

Using the prevalence of SDB in persons with a BMI of <25 kg/m² to calculate excess SDB in the higher BMI categories and weighting over the estimated US population distribution of

BMI categories within each age and sex group, Fig. 1 demonstrates age- and sex-specific estimates of US prevalences of SDB and the proportions attributed to overweight and obesity. Generally, a greater proportion of SDB is attributable to excess weight in younger persons relative to older persons. A greater proportion of more severe SDB prevalence (AHI ≥ 15), compared with SDB indicated by AHI of ≥ 5 , which includes the milder part of the spectrum, is attributable to excess weight.

Among adults ages 30–69 yr, averaging over the estimated US 2003 age, sex, and BMI distributions, we estimate that ~17% of adults have mild or worse SDB (AHI ≥ 5) and that 41% (7% of the total population) of those adults have SDB attributable to having a BMI of ≥ 25 kg/m². Similarly, we estimate that ~5.7% of adults have moderate or worse SDB (AHI ≥ 15) and that 58% (3.3% of the total population) of those adults have SDB attributable to excess weight. Note that these are rough estimates that depend on sampling error vari-

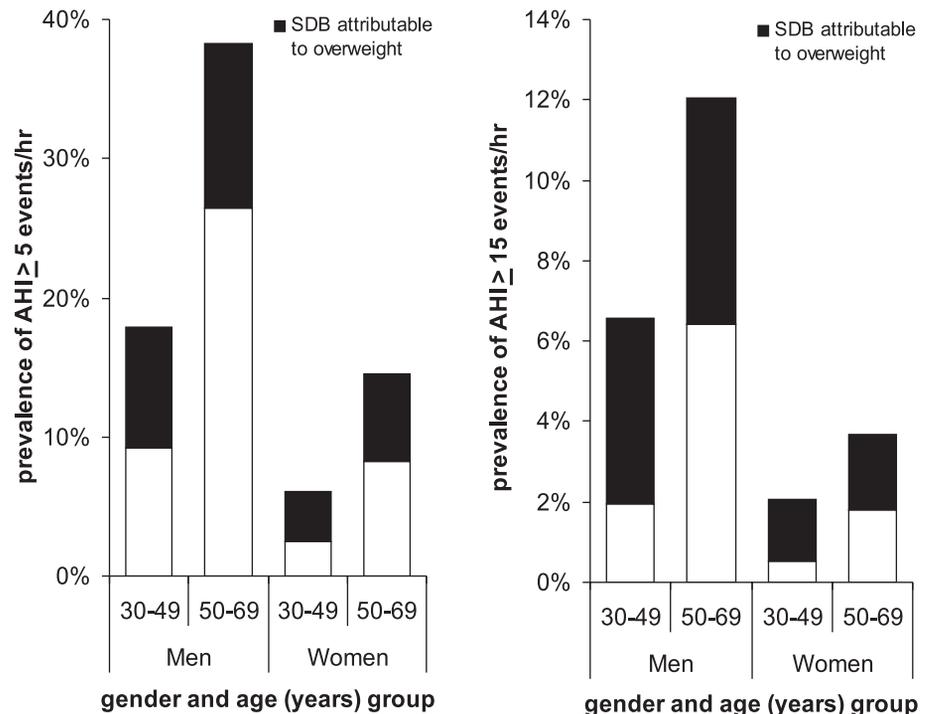


Fig. 1. Estimated prevalence of mild or worse sleep-disordered breathing [SDB; apnea-hypopnea index (AHI) ≥ 5 events/h] and moderate or worse SDB (AHI ≥ 15 events/h) and prevalence of SDB attributable to excess weight (body mass index of ≥ 25 kg/m²) by sex and age.

ance not only from the Wisconsin sleep cohort estimates but also from the census (for an intercensal year, 2003) and Centers for Disease Control and Prevention data.

The prevalence of SDB in persons with BMI of $<25 \text{ kg/m}^2$, although much less than in higher BMI categories, is still of substantial public health importance, with the prevalence of mild or worse SDB ranging from 2.5% in normal weight younger women to 26% in normal weight older men. However, much mild or worse SDB seen in the population (41% by our conservative estimate) might be due to the excess weight in persons with BMI of $\geq 25 \text{ kg/m}^2$ (~2 out of 3 US adults ages 30–69 yr in 2003, and growing). Furthermore, we estimate that most (58%) of more severe SDB (AHI ≥ 15 events/h) is due to overweight and obesity among US adults.

We present these attributable prevalences as rough estimates because the calculations are fraught with difficulties and assumptions, including sampling errors in several different underlying parameters, concerns about making causal interpretations, and extrapolating estimates from one study population to a more heterogeneous US population. For two important reasons, we expect that these attributable proportions are likely to be conservative underestimates. First, we use BMI as an imperfect proxy for whatever underlying body habitus parameters are most important in impacting SDB. This was necessary since population estimates of BMI distribution are available, whereas other population distribution patterns of, perhaps, more salient parameters such as fat deposition patterns in the upper airway are not available. Second, the amount of data available to us to examine SDB prevalence by categories of BMI, age, and sex allowed for only a few BMI categories, which imposed a type of “round-off” error. Both of these issues are likely to have resulted in underestimates of the proportion of SDB attributable to excess weight. Clearly, if the expanding epidemic of obesity seen in the United States continues, the prevalence of SDB will almost certainly increase, along with the proportion of SDB attributable to obesity.

Excess Weight and SDB: What Explains the Association?

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), reduced chest wall compliance, disturbance of the relationship between respiratory drive and load compensation (43), and exacerbation of obstructive sleep apnea events via obesity-related reductions in functional residual capacity and increased whole body oxygen demand. These putative mechanisms suggest that specific anatomical locations of excess fat deposition may be important (9, 14, 16, 24, 26, 37, 38). As discussed in *Longitudinal Studies*, longitudinal population and clinical studies have demonstrated a fairly rapid response of SDB, as indicated by AHI level, to actual change in weight. Little is known about how changes in physical activity levels, and resulting characteristic changes in body fat distribution and fitness, affect SDB apart from changes in weight. One study has demonstrated an inverse association of weekly exercise and SDB, independent of body weight (28). It is also possible that the fatigue and sleepiness that are often symptomatic of SDB disinclines afflicted persons to physical activity, further exacerbating weight gain, and thus SDB, in a feedback cycle. The

potential for such behavioral feedback mechanisms in SDB is largely unexplored.

Hormones, including those that influence sex characteristics and metabolism, may have a diverse role in the development or exacerbation of SDB. Clinical and epidemiological studies have demonstrated an increase in prevalence of SDB in menopausal, compared with premenopausal women (55). It is generally believed that depletion of estrogen and progesterone is responsible for an increased vulnerability to SDB, but data relevant to pathophysiological mechanisms are sparse. Progesterone stimulates breathing, but experimental studies have failed to show a protective effect regarding upper airway collapse. Hormonal changes in the menopausal transition may indirectly contribute to SDB by increasing body fat, specifically abdominal or central fat deposition, which are known risk factors for SDB. Although menopause is indeed associated with increased central body fat, it is unlikely that this mechanism can account for all of the increased SDB risk. In the Wisconsin sleep cohort, menopausal compared with premenopausal women had a higher prevalence of SDB regardless of BMI or indicators of central fat distribution (53). However, a negative interaction of menopause and BMI was demonstrated in the Pennsylvania cohort study, in which the effect of BMI was lower in premenopausal women (i.e., SDB only occurred in obese premenopausal women) (4), indicating a greater susceptibility related to increased BMI with menopause. Data in support of a direct role of female hormones in SDB comes from the Sleep Heart Health Study, showing a decrease in SDB prevalence in postmenopausal women who do take hormone replacement therapy compared with those who do not (40). However, in most clinical trials, hormone replacement therapy has not resulted in a significant drop in AHI (32).

Recently, there has been great interest in a putative interaction between SDB, insulin resistance, and metabolic hormones, thus suggesting that SDB is an important new facet of the metabolic syndrome. Particular attention has been paid to hormones released from fat cells (adipocytes), the adipocytokines. Because metabolic hormones are closely associated with body weight, investigators, using different approaches, have attempted to examine whether SDB and related hypoxemia are independently associated with the levels of these hormones. This is important because treatment of SDB may help reverse metabolic abnormalities. Other studies have suggested that changes in metabolic hormones that occur with obesity may aggravate/alleviate breathing in SDB.

One adipocytokine recently studied in association with SDB is leptin (30). Leptin is a 16-kDa hormone that is released by adipocytes to signal fat stores to the hypothalamus (23). Leptin therefore tends to reduce appetite. Leptin levels are higher in obese individuals, suggesting that leptin resistance exists in obesity. A mechanism for the leptin resistance in obesity may be transfer of leptin across the blood-brain barrier. It has been reported that SDB is associated with higher leptin than would be expected based on BMI alone (30). Leptin has also been associated with obesity hypoventilation and responses to hypercapnea (31). It has been proposed that SDB patients have greater leptin resistance than commonly seen in obesity and that this further impairs their breathing. Increased leptin and insulin resistance, as seen with SDB, may in turn contribute to perpetuating obesity. SDB is associated with sleep fragmentation and therefore short sleep duration at night. It is of interest

that laboratory sleep restriction in young volunteers (42) and short sleep duration in our population study (45) are paradoxically associated with low leptin levels.

SDB is closely associated with visceral obesity, which is key to insulin resistance, Type 2 diabetes, and the metabolic syndrome. Studies investigating the association between SDB and insulin resistance have used multiple approaches. Population studies have been mainly cross sectional. Studies include associations between symptoms (snoring and witnessed apneas) (1, 13, 15, 20, 36) or objective measures of SDB (AHI, oxygen desaturation) (10, 18, 24, 33, 45, 46) and insulin resistance. Both population and case-control studies have been carried out. Measures of insulin resistance have mainly included self-reported diabetes, fasting glucose and insulin, glucose levels in an oral glucose tolerance test, and surrogates of insulin sensitivity such as the homeostatic model assessment. Various mechanisms proposed for the relationship between SDB and insulin resistance include alterations in adipocytokines, decreased sleep duration due to sleep fragmentation (resulting in alterations in insulin secretion and sensitivity, decreased growth hormone, and increased cortisol) (41), increased sympathetic nervous system activity, and direct effect of intermittent hypoxia on the glucose homeostatic system.

Considerable disagreement exists between studies, which have reported either no association between SDB and insulin sensitivity or an association ranging from minor to highly significant. A large number of studies have not sufficiently controlled for possible confounding factors (especially body weight) or have been sufficiently powered to answer questions related to the association between SDB and insulin sensitivity. Recently, our laboratory investigated the above-discussed relationships in a large population-based sample from the Wisconsin Sleep Cohort Study (45). We examined possible associations between habitual sleep and polysomnographic sleep duration and serum leptin, insulin, glucose, QUICKI, homeostatic model assessment, and adiponectin. Adiponectin is an adipocyte-derived hormone associated with insulin sensitivity. All analyses were corrected for age, sex, and BMI, and if any associations were noted, further correction was carried out for identified potential confounding factors, including AHI. We found a significant association between sleep duration and serum leptin. Short sleep duration was associated with low leptin levels, suggesting that it may predispose to increased appetite and potentially obesity. However, we did not find any association between sleep duration and measures of insulin sensitivity. We also examined associations between AHI and the above measures, independent of BMI. We found no significant association between AHI and any of the measures. We also tested the possibility of U-shaped relationships between the metabolic measures and AHI but found no significant associations. It is of interest that, in our study, SDB did not alter the relationship observed between short sleep duration and leptin. From our data, as expected, obesity has a strong and clear association with insulin resistance, the metabolic syndrome, and metabolic hormone levels (leptin and insulin). Any observed association between SDB and metabolic factors are therefore likely to be primarily driven by the association with BMI and, in particular, visceral obesity.

FUTURE DIRECTIONS

Excess weight clearly contributes to the incidence and progression of SDB. Based on current data, a considerable proportion of the future SDB burden would be eliminated by the prevention and reduction of overweight and obesity. To develop feasible strategies to address the current and growing burden, a better understanding is needed of what characteristics of body habitus are indeed significantly modifiable (i.e., beyond their genetic basis) besides weight. More information is needed on the natural history of physical fitness, as well as overweight and obesity with respect to SDB. For example, does childhood, adolescent, or lifelong obesity play a greater role in SDB pathogenesis than contemporary weight gain? Intervention studies are needed to determine the preventive role that exercise and improved physical fitness may play in coping with a possible epidemic of SDB in parallel with that of obesity. Although a causal role of excess weight in SDB is evident, the complex interactions of altered sleep, metabolic hormones, SDB, and obesity and their compound effect on morbidity are other important areas for future research.

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