

Obstructive Sleep Apnea and Cardiovascular Disease: Role of the Metabolic Syndrome and Its Components

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Although obstructive sleep apnea and cardiovascular disease have common risk factors, epidemiologic studies show that sleep apnea increases risks for cardiovascular disease independently of individuals' demographic characteristics (i.e., age, sex, and race) or risk markers (i.e., smoking, alcohol, obesity, diabetes, dyslipidemia, atrial fibrillation, and hypertension). Individuals with severe sleep apnea are at increased risk for coronary artery disease, congestive heart failure, and stroke. The underlying mechanisms explaining associations between obstructive sleep apnea and cardiovascular disease are not entirely delineated. Several intermediary mechanisms might be involved including sustained sympathetic activation, intrathoracic pressure changes, and oxidative stress. Other abnormalities such as disorders in coagulation factors, endothelial damage, platelet activation, and increased inflammatory mediators might also play a role in the pathogenesis of cardiovascular disease. Linkage between obstructive sleep apnea and cardiovascular disease is corroborated by evidence

that treatment of sleep apnea with continuous positive airway pressure reduces systolic blood pressure, improves left ventricular systolic function, and diminishes platelet activation. Several systematic studies are necessary to explicate complex associations between sleep apnea and cardiovascular disease, which may be compounded by the involvement of diseases comprising the metabolic syndrome (i.e., central obesity, hypertension, diabetes, and dyslipidemia). Large-scale, population-based studies testing causal models linking among sleep apnea, cardiovascular morbidity, and metabolic syndrome are needed.

Keywords: Sleep apnea, cardiovascular disease, metabolic syndrome

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BACKGROUND

Decades of research have provided evidence supporting the associations between obstructive sleep apnea with cardiovascular morbidity and mortality. In the early 1980s, investigators demonstrated that subsequent to tracheostomy, patients with sleep apnea experienced substantial decrease in systemic blood pressure and diminution of cardiac arrhythmia.¹ With the presentation of many case-control studies, replicating similar findings, a concern arose that initial studies may have been confounded by factors such as age, sex, and body habitus.²⁻⁴

Adequate response to address this concern required the performance of several large-scale epidemiologic studies to assess

the influence of suspected confounders on the associations between sleep apnea and cardiovascular disease. Despite adequate methodological and statistical control for known covariates, relationships between these 2 conditions have persisted.⁵⁻⁸ Notwithstanding the significance of these findings, presently there is a growing concern that associations between sleep apnea and cardiovascular disease might be mediated by the metabolic syndrome. It is equally plausible that sleep apnea and metabolic syndrome might have synergistic health risks, since both conditions are predictive of cardiovascular morbidity and mortality.

In this paper, we review findings supporting the associations between obstructive sleep apnea and cardiovascular disease. We also present evidence supporting the potential mediating effects of the metabolic syndrome and respective intermediate mechanisms involved in proposed causal pathways. The role of each of the component disease entities of the metabolic syndrome is delineated, and pertinent clinical management issues are discussed.

Associations between Sleep Apnea and Cardiovascular Disease

Obstructive sleep apnea is a serious, potentially life-threatening condition. It is characterized by repeated cessation of breathing while sleeping, due mostly to complete or partial

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pharyngeal obstruction. Objectively, it is recognized by a combination of symptoms and laboratory results. These include repetitive apneas and hypopneas, which are accompanied by hypoxia, sleep arousals, and hemodynamic changes.⁹⁻¹² Moreover, activation of the sympathetic nervous system during respiratory events potentiates vasoconstriction and often triggers increases in blood pressure and heart rate.^{10,13} Obstructive sleep apnea is also associated with several cardiorespiratory problems (e.g., loud snoring, loud gasps, and daytime breathlessness).^{14,15}

Obstructive sleep apnea causes significant sleep disturbances, leading to excessive daytime sleepiness and fatigue, which in turn may cause vehicular and industrial accidents.^{16,17} When left untreated, sleep apnea gradually induces cognitive deficits and poor performance.¹⁸ According to a chart audit of 4 million beneficiaries of the Veterans Health Administration, numerous psychiatric comorbid diagnoses accompany sleep apnea including depression (21.8%), anxiety (16.7%), posttraumatic stress disorder (11.9%), psychosis (5.1), and bipolar disorders (3.3%).¹⁹

Obstructive sleep apnea is thought to be more prevalent than asthma and adult diabetes, possibly affecting more than 18 million Americans.^{20,21} Public health advocates think it may be as big a public health hazard as smoking.²² The National Commission on Sleep Disorders Research estimated that sleep apnea is probably responsible for 38,000 cardiovascular deaths yearly, with an associated 42 million dollars spent on related hospitalizations.²³ Obstructive sleep apnea increases the risk of heart failure by 140%, the risk of stroke by 60%, and the risk of coronary heart disease by 30%.⁶ Thus, sleep apnea is an important target for public health interventions aiming at reducing cardiovascular disease, the leading cause of death among adults in developed countries.²⁴

Clinical and Epidemiologic Evidence

About 3 decades ago, a concerted effort was made to study the relationships between obstructive sleep apnea and cardiovascular disease. Early studies were largely observational, but results had been very impressive. In 2 independent laboratories, investigators performed tracheostomy to alleviate comorbid conditions among patients with a diagnosis of sleep apnea. Subsequent to tracheostomy, investigators observed complete disappearance of severe atrial flutter and postoperative decrease in systemic blood pressure.^{25,26} Others observed normalization of blood pressure in 2 hypertensive children with severe sleep apnea within 24 hours after surgery.²⁷ Of note, a contemporaneous study demonstrated a 10% reduction in mortality over a 10-year period among patients with sleep apnea who underwent tracheostomy, compared with those favoring conservative treatment.¹

Importance of Confounding Factors

Early studies showing associations between obstructive sleep apnea and cardiovascular disease were questioned, as some could not account for the influence of confounding factors since samples were too small. Critics pointed out that obstructive sleep apnea and cardiovascular disease have common risk factors including, age, gender, race/ethnicity, and

obesity, which could confound the observed associations.²⁸ Studies also needed to take into account that patients with obstructive sleep apnea were generally unhealthy. One analysis indicated that the 10-year risk of coronary heart disease and stroke, for instance, was approximately 30% among patients with sleep apnea.²⁹

More recent large-scale epidemiologic studies have confirmed associations between obstructive sleep apnea and cardiovascular disease, with adequate statistical control for known confounding factors.⁵⁻⁸ In one of those studies, sleep apnea significantly increased the risk for stroke or death (hazard ratio = 1.97; 95% CI: 1.12- 3.48) independently of other risk factors (i.e., age, sex, race, smoking, alcohol consumption, body mass index, and the presence or absence of diabetes mellitus, dyslipidemia, atrial fibrillation, and hypertension).⁵ This finding is consistent with a cross-sectional study showing that patients with an apnea hypopnea index (AHI) ≥ 20 had significantly greater odds for stroke (adjusted OR = 4.33; 95% CI: 1.32-14.24) than individuals without sleep apnea (AHI < 5).⁸

Other researchers have studied patients with sleep apnea presenting without other known medical conditions in order to rule out the influence of confounding factors.^{30,31} Those studies showed that patients with sleep apnea were characterized by higher levels of sympathetic nervous system activity during wakefulness as well during sleep, relative to healthy controls.^{30,31} Accordingly, during apnea events, oxygen levels decreased and carbon dioxide levels increased commensurately, which activated the sympathetic nervous system. Higher level of sympathetic nervous system activity induced blood vessel constriction, with blood pressure rising to 250/150 mm Hg. Those patients also exhibited faster heart rates during wakefulness.

One of the largest epidemiologic studies conducted to date, the Sleep Heart Health Study sampling 6,424 community-dwelling individuals who underwent home polysomnography, documented increased risk of coronary artery disease, congestive heart failure, and stroke among patients with severe sleep apnea.⁶ Specific analysis of the Sleep Heart Health Study showed that individuals with obstructive sleep apnea had 4 times the odds for atrial fibrillation (adjusted OR = 4.02; 95% CI: 1.03-15.74).³² This is consistent with data from a prospective study of consecutive patients undergoing electrocardioversion for atrial fibrillation indicating that the adjusted odds ratio for atrial fibrillation among patients with obstructive sleep apnea was 2.19 (95% CI: 1.40-3.42).³³ Data from the Sleep Heart Health Study also revealed that odds for coronary heart disease (OR = 4.02; 95% CI: 1.03-15.74) and tachycardia (OR = 3.40; 95% CI: 1.03-11.20) were also significantly greater among individuals with sleep apnea.³²

Proposed Mechanisms Explaining Link between Sleep Apnea and Cardiovascular Disease

The underlying mechanisms explaining the associations between obstructive sleep apnea and cardiovascular disease are not entirely understood, although several intermediate mechanisms are proposed. They include sustained sympathetic activation,^{34,35} changes in intrathoracic pressure,³⁶ and oxidative stress, and consequently vascular inflammation resulting from the nocturnal hypoxia and reoxygenation cycles.^{37,38}

With regard to the role of sympathetic activation, investigators have posited that repetitive apneic/hypopneic events along with ensuing arterial desaturation and hypercapnia cause activation of the sympathetic nervous system (see Figure 1).^{34,35,38} This then results in increases in systolic blood pressure that might ultimately lead to hypertension or exacerbation of this condition. A similar mechanism might explain the link between obstructive sleep apnea and tachyarrhythmia;³³ whereas bradyarrhythmia, which is more common than tachyarrhythmia,^{3,4} might be the resulting effect of an increase in vagal tone due to stimulation of receptor sites in the upper airway.³⁹ Utilization of pacemakers permitting long-term monitoring of cardiac arrhythmias and ventilation parameters might offer data leading to more comprehensive explanations of those relationships.^{40,41}

Other abnormalities observed among patients with obstructive sleep apnea might also be involved in the pathogenesis of cardiovascular disease. These include disorders in coagulation factors, endothelial damage, platelet activation, and an increase in inflammatory mediators.^{38,42-45} Patients with obstructive sleep apnea have characteristically greater levels of endothelin and lower levels of nitric oxide than healthy sleepers.^{38,43} This elevated endothelin is believed to impair blood pressure regulation as well. Thus, patients with obstructive sleep apnea often experience greater blood vessel constriction. Notably, levels of endothelin and circulating nitric oxide invariably return to normal with continuous positive airway pressure (CPAP) treatment.⁴³

Recently, research interests have centered on the relative contribution of oxidative stress in explaining the associations between sleep apnea and cardiovascular morbidity.^{38,45,46} Investigators have proposed that hypoxia, which is commonly observed in sleep apnea, promotes the formation of reactive oxygen species, which could activate the transcriptional activator hypoxia-inducible factor 1 (HIF-1), particularly during the reoxygenation period.^{47,48} Reactive oxygen species, regulate the activation of critical transcription factors that are redox sensitive, resulting in increased expression of genes, which encode proteins promoting adaptation to hypoxia.⁴⁷ It has also been suggested that redox-sensitive transcription factors, which elicit inflammatory pathways are also activated, thereby affecting inflammatory and immune responses by promoting activation of endothelial cells, leukocytes, and platelets.³⁸ Once activated, those cells express adhesion molecules and proinflammatory cytokines that may lead to endothelial injury and dysfunction,³⁸ which inevitably lead to the development of cardiovascular morbidity.

Observing this chain of events, investigators surmise that atherogenesis apparently starts soon after the onset of sleep apnea.³⁸ It is likely that substantial atherosclerotic insults are incurred by the time a diagnosis is rendered, since symptoms often become apparent around the age of 45 years.^{38,46} To some extent, this might explain why many patients with sleep apnea present with cardiovascular morbidity in the clinic. It is unclear whether such atherogenic damages can be reversed, but treatment can retard their progress.⁴⁹ Using CPAP therapy, investigators have shown significant reductions in levels of C-reactive protein and interleukin-6,⁴⁹ and atherogenic plaque regression has been observed among patients with dyslipidemia.⁵⁰ Therefore, in order to prevent cardiovascular morbidity, sleep apnea diagnosis and treatment should be made as early as possible.

Sleep Loss and Cardiovascular Disease

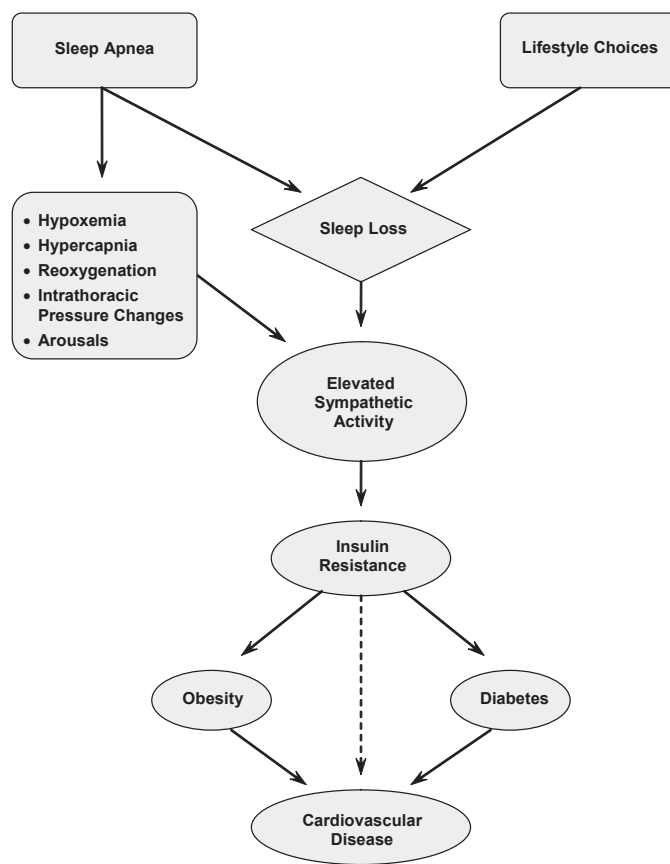


Figure 1—Proposed pathway linking sleep loss to cardiovascular disease. Of note, obesity triggers the onset of sleep apnea in a significant number of cases.

Evidence from CPAP Studies

The link between sleep apnea and cardiovascular disease has been further demonstrated through treatment studies of sleep apnea with nasal continuous positive airway pressure (CPAP).⁵¹⁻⁵³ Those studies have shown positive results, which include reduced diurnal and nocturnal blood pressure.^{51,52} Among patients with heart failure and congestive heart failure, for instance, treatment of coexisting sleep apnea with CPAP reduces systolic blood pressure, improves left ventricular systolic function, and increased ejection fraction.^{53,54} CPAP therapy has been found to eliminate apneic episodes and associated hemodynamic changes occurring during sleep.^{31,55} One implication of those findings is that adverse effects of obstructive sleep apnea on cardiac functions can be lessened with CPAP administration,⁵² although it is not certain whether it could delay mortality among patients with central sleep apnea and heart failure.⁵⁴

Sleep Apnea and Cardiovascular Disease: Role of the Metabolic Syndrome

The relationships between sleep apnea and cardiovascular disease are rather complex. Several systematic studies are necessary to explicate fully the nature of those relationships. These complexities are further compounded by findings suggesting that

Table 1— WHO and NCEP ATP III Definition of the Metabolic Syndrome

Characteristic	WHO	NCEP ATP III
Hypertension	Current antihypertensive therapy and/or BP > 140/90	Blood pressure medication or BP >130/85
Dyslipidemia	Plasma triglycerides > 1.7 mmol/L (150 mg/dL) and/or HDL < 0.9 mmol/L (35 mg/dL) in men and < 1.0 mmol/L (< 40 mg/dL) in women	Plasma triglycerides > 150 mg/dL, HDL cholesterol < 40 mg/dL in men and < 50 mg/dL in women.
Obesity	BMI > 30 and/or waist/hip ratio > 0.90 in men and > 0.85 in women	Waist circumference > 40 cm in men and > 50 cm in women
Diabetes	Type 2 diabetes or IGT	Fasting blood sugar > 110 mg/dL*
Other	Microalbuminuria = overnight urinary albumin excretion rate > 20 mcg/min (30 mg/g Cr)	
Requirements for Diagnosis	Type 2 diabetes or IGT and any 2 of the above criteria. If normal glucose tolerance is found, 3 other disorders must be present.	Any 3 of the above disorders

Information in the table was obtained from guidelines provided by the World Health Organization (WHO) and the National Cholesterol Education Program (NCEP). BMI denoted body mass index; BP, blood pressure; HDL, high-density lipoprotein; IGT, impaired glucose tolerance. *Fasting plasma glucose was recently updated to 100 mg/dL by the American Diabetes Association.

conditions comprising the metabolic syndrome might mediate effects of sleep apnea on cardiovascular disease (see Figure 2).

A direct link between the metabolic syndrome and sleep apnea has not been established, as previous research has considered linkage analysis only for individual components of the metabolic syndrome. Recent preliminary evidence from the Mayo Clinic suggests that the metabolic syndrome might be more prevalent among patients with obstructive sleep apnea than among individuals without OSA. Clinical data show that 60% of patients with sleep apnea had the metabolic syndrome, compared with 40% of patients without sleep apnea.⁵⁶ In the following sections, we consider the role of each component of the metabolic syndrome namely obesity, hypertension, diabetes, and dyslipidemia; but first, issues pertaining to definition and prevalence of the metabolic syndrome are presented.

The Metabolic Syndrome: Definition and Prevalence

Perhaps the first observation of the metabolic syndrome was made in 1923 when a cluster of co-occurring metabolic diseases namely hyperglycemia, hypertension, obesity, and hyperuricemia was first recorded.⁵⁷ This observation led to a growing area of clinical and basic research as well as one that has provided the impetus for new and innovative clinical care. In the sleep literature, the term *Syndrome Z* has been used to explain such interrelated diseases.⁵⁸ This incorporates the typical features of the metabolic syndrome (Syndrome X) namely central obesity, hypertension, diabetes, and dyslipidemia, with the addition of sleep apnea (see Figure 3).⁵⁸

The metabolic syndrome is an emerging public health concern.⁵⁹⁻⁶² It constitutes a collection of interrelated risk factors of metabolic origin that increase chances of developing heart disease, stroke, and diabetes. It increases the risk for coronary heart disease at any LDL-C level, and it is associated with prothrombotic and proinflammatory states, two common risk factors for coronary heart disease and diabetes mellitus.⁴⁵ The metabolic syndrome is now recognized as an important contributor to the development of atherosclerosis and cardiovascular disease. Individuals presenting with characteristics of the

metabolic syndrome are at increased risks of developing type 2 diabetes,^{62,63} and those with diabetes are at increased risks of developing cardiovascular disease.⁶⁴

Individuals with metabolic syndrome have several co-occurring disorders of the body’s metabolism: obesity, hypertension, dyslipidemia, and hypercholesterolemia. The causes of this condition are complex, and empirical data are in the beginning stages in shedding light on these complexities. To date, the most consistent observation has been that most patients who meet criteria for the metabolic syndrome are older and obese; they also tend to exhibit insulin resistance.^{65,66} However, it remains unclear whether obesity or insulin resistance is the cause of metabolic syndrome or a byproduct of a more extensive metabolic disorder. One theory postulates that insulin resistance might be the principal determinant of the metabolic syndrome.⁶⁵⁻⁶⁷ This explains in part why recent research has focused on the role of insulin resistance and glucose intolerance.

According to the third National Health and Nutrition Examination Survey (1988-1994) of 8814 adults (ages ≥ 20 years),

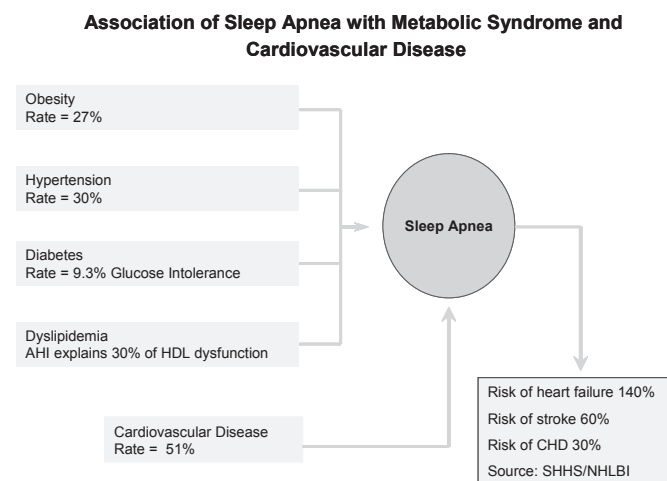


Figure 2—Prevalence of metabolic syndrome components and cardiovascular disease among patients with a diagnosis of sleep apnea; risks of cardiovascular disease for patients with sleep apnea are also indicated.

Table 2—Trends in Obesity by Ethnicity

Ethnicity	1991	1995	1998	1999	2000	2001
Black	19.3	22.6	26.9	27.3	29.3	31.1
White	11.3	14.5	16.6	17.7	18.5	19.6

Data originated from the Center for Disease Control; values represent percent of cases

In addition to the importance attributed to the impact of metabolic diseases in assessing cardiovascular risks, there is also considerable interest in understanding the contribution of circadian rhythms in cardiovascular events, which might indicate an interplay among sleep cycles, arousal mechanisms, and acute thrombosis.⁷² Recent evidence led to the belief that peripheral cells, including those of the cardiovascular system, contain a circadian clock functioning in a manner similar to the one found in the suprachiasmatic nuclei.⁷³ Varying facets of cardiovascular physiology are subject to diurnal variation.⁷² Indeed, cardiovascular events including stroke, myocardial infarction, and sudden cardiac death tend to occur during specific phases of the circadian cycle.^{72,74} Blood pressure patterns also have a circadian component, often used to categorize individuals as *dippers* and *nondippers*.⁷⁵ Preliminary evidence shows that the temporal distribution of blood pressure could be used to predict vascular events.⁷⁵ Accordingly, abnormal patterns of blood pressure variation correlate with advanced target organ damage and poor cardiovascular prognosis.⁷⁵⁻⁷⁷ Important work is underway to elucidate the contribution of circadian patterns of tumor necrosis factor- α (TNF- α) and interleukin-6 (IL-6) in blood pressure variations among sleep apnea patients.⁷⁸⁻⁸⁰ **AHA/NHLBI Scientific Statement**

Sleep Apnea and Cardiovascular Disease: Role of Obesity

According to data from the National Center for Health Statistics, about two-thirds of American adults are either overweight (BMI > 25; 33%) or obese (BMI > 30; 31%).⁸¹ The age-adjusted prevalence of overweight/obesity in ethnic minorities, especially minority women, is higher than in whites in the United States, reaching a critical level of greater than two-thirds of the female minority population.⁸² Blacks are at greater risks because they are disproportionately more obese than whites (see Table 2).

It has long been recognized that obesity plays a pivotal role in the development of obstructive sleep apnea. It may be the most significant predictor of sleep apnea.^{83,84} A recent study of obese men (BMI = 30 kg/m²) without major medical illnesses indicated that 60% of them met criteria for sleep-disordered breathing and 27% had obstructive sleep apnea.⁸⁵ It is estimated that 60% to 90% of patients with sleep apnea are obese (defined as BMI > 28 kg/m²), and that a BMI of 28 kg/m² has a sensitivity of 93% and a specificity of 74% for sleep apnea.⁸⁴ The risk of having moderate to severe sleep apnea over a 4-year period increases 6-fold among persons gaining 10% excess weight.⁸⁶ Thus, it has been assumed that the high incidence of cardiovascular morbidity among patients with sleep apnea is explained by the presence of obesity.^{87,88}

Most of the initial reports wrestled with the idea that associations of sleep apnea with cardiovascular morbidity were confounded by underlying obesity. Since both sleep apnea and car-

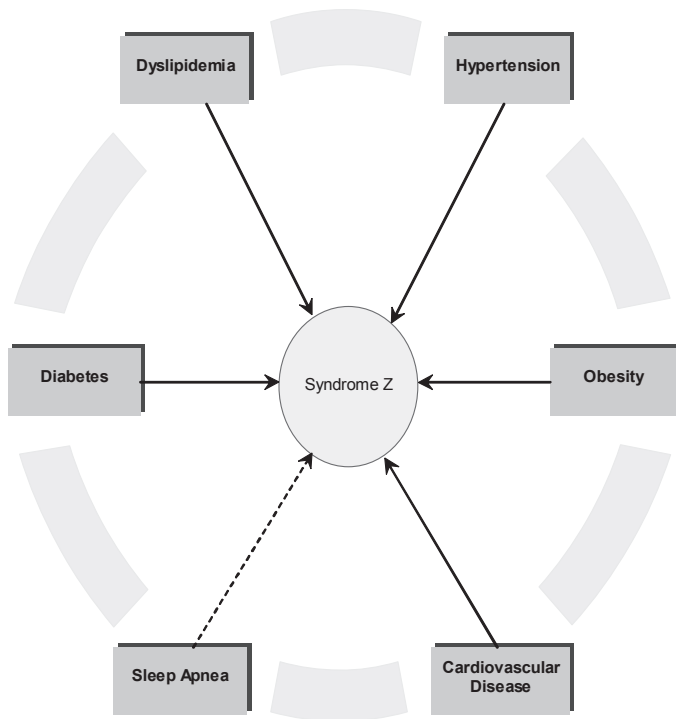


Figure 3—Interrelationships between metabolic diseases comprising the metabolic syndrome and sleep apnea. Together, these diseases are referred to as *Syndrome Z* in the field of sleep medicine. Available epidemiologic and clinical evidence suggests that all of these conditions interact with each other through complex, yet undifferentiated pathophysiological pathways, thereby increasing risks for cardiovascular disease.⁵⁸

the age-adjusted prevalence of the metabolic syndrome was 23.7%.⁶⁸ Analysis of data from the National Health and Nutrition Examination Survey (1999-2002; n = 3,601) using new definition from the National Cholesterol Education Program showed that the unadjusted prevalence of the metabolic syndrome among men and women (ages ≥ 20 years) was 33.7% and 35.4%, respectively.⁶⁹ Of note, the prevalence of metabolic syndrome in black women was 57% higher than in black men.⁶⁸

Since the first observation of the cluster of metabolic diseases, referred to as the metabolic syndrome, many definitions have been used. As the metabolic syndrome is now recognized as a worldwide health concern, a more formal definition has been proposed by several organizations including the World Health Organization, the National Cholesterol Education Program, and the American Association of Clinical Endocrinologists. In Table 1, we compare criteria provided by the World Health Organization and the National Cholesterol Education Program. These have been set forth to allow consensus agreement in recognizing the components of the metabolic syndrome as well as in identifying high-risk individuals.^{60,65,70} It should be noted that other criteria have been proposed by the American Heart Association/National Heart, Lung, and Blood Institute and the European Group for Study of Insulin Resistance (see AHA/NHLBI Scientific Statement).⁷¹ In sum, they all share similar definitional criteria, although they differ somewhat regarding etiology of the metabolic syndrome and degree of importance assigned to each of its components.

diovascular morbidity are linked to obesity, some investigators have conjectured a viable hypothesis, which suggested that both conditions are caused by a defect in a common pathway potentially resulting from central (visceral) obesity. Plausibly, with the onset of sleep apnea individuals develop leptin resistance, which in turn contributes to further weight gain. Leptin is an adipocyte-derived hormone that regulates weight by controlling appetite and energy expenditure.⁸⁹ We should also consider that inflammatory cytokines TNF- α and IL-6, which are associated with daytime sleepiness, might also be involved in the causal pathway, as they are elevated among obese patients with sleep apnea.⁸⁰ With new empirical evidence, the debate has recently evolved, and currently the comorbid relationship between sleep apnea and cardiovascular disease is seen as a manifestation of the metabolic syndrome.

Whether, in fact, obesity is the final common pathway remains to be determined. The preponderance of evidence indicates that obesity is associated with important metabolic diseases linked to cardiovascular disease (see Figure 5), and African Americans seem particularly vulnerable. Within the context of ethnicity and sleep apnea research, disparities favoring greater rates of sleep apnea for blacks might be a function of greater odds of being overweight or obese (see Table 1). Older blacks experienced severe sleep apnea with a relative risk twice that of their white counterparts.⁹⁰ This is consistent with case-control family study of sleep apnea comparing blacks and whites, ages 2 to 86 years, which has shown that 31% of blacks and 10% of whites had respiratory disturbance index greater than 10.⁹¹ Also important in that study was the observation that young blacks (≤ 25 years) may be at increased risk for sleep apnea. These findings led to research suggesting that genetic factors might underlie the susceptibility to sleep apnea among blacks.⁹²

Sleep Apnea and Cardiovascular Disease: Role of Hypertension

One of the complexities permeating relations between sleep apnea and cardiovascular disease relates to the fact that both conditions are potentially characterized by similar pathogenetic mechanisms. In effect, both sleep apnea and cardiovascular disease are linked to hypertension.⁹³⁻⁹⁶ Results of several multivariate analytical models have indicated that sleep apnea represents an independent risk factor for hypertension,^{93,97,98} and hypertension constitutes a significant predictor of cardiopulmonary deaths among patients with sleep apnea.⁹⁷

Regarding the link between sleep apnea and hypertension, there are data suggesting that approximately 40% of patients with sleep apnea suffer from hypertension, whereas 30% of hypertensive patients have occult sleep apnea.⁹⁴ Data from the Wisconsin Sleep Cohort Study, sampling 1060 women and men ages 30 to 60 years, showed that for individuals with a BMI of 30 kg/m² an AHI of 15 was associated with blood pressure increases of 3.6 mm Hg for systolic (95% CI: 1.3- 6.0) and 1.8 mm Hg for diastolic (95% CI: 0.3-3.3). Further analyses indicated a dose-response relationship between sleep apnea and blood pressure, independent of confounding factors,⁹³ which is consistent with other independent analyses.^{97,98}

Data from the Wisconsin Sleep Cohort Study exploring relationships between sleep apnea and hypertension indicated that the severity of sleep apnea based on initial sleep studies could

predict the development of new hypertension during the subsequent 4 years. Even with control for known confounders, analyses suggested the odds ratios for the presence of hypertension at follow-up were 1.42 (95% CI: 1.13-1.78) with an AHI of 0.1 to 4.9 at baseline relative to none, 2.03 (95% CI: 1.29-3.17) with an AHI of 5.0 to 14.9, and 2.89 (95% CI: 1.46-5.64) with an AHI of 15.0 or more.^{86,99} These data are consistent with findings of the Sleep Heart Health Study, showing that mean systolic and diastolic blood pressure and prevalence of hypertension increased significantly with increasing severity of sleep apnea.⁷ Reduction of sleep apnea severity through CPAP therapy results in a diminution of daytime systemic blood pressure,⁹⁵ although it has not been conclusively demonstrated that CPAP treatment lowers blood pressure on a long-term basis.

Sleep Apnea and Cardiovascular Disease: Role of Diabetes

The obesity pandemic over the last decade has accompanied a rise in the prevalence of type 2 diabetes mellitus. One of the characteristic features of diabetes mellitus is the inability to regulate serum glucose levels, resulting in impaired glucose tolerance affecting 11% to 15.6% of the U.S. population.¹⁰⁰ Both type 1 and type 2 diabetes are associated with insulin deficiency, but type 2 diabetes is further complicated by cellular resistance to insulin action.¹⁰¹ According to data from the Third National Health and Nutrition Examination Survey, 5.1% of U.S. adults have an existing diagnosis for diabetes; an additional 2.7% met criteria for the diagnosis, but have yet to receive one.¹⁰⁰ Analysis from the same research group indicated that 15.6% of American adults exhibit glucose intolerance (140 mg/dL) and 6.9% showed impaired fasting glucose levels (≥ 110 mg/dL).¹⁰⁰

On a parallel tract, there is a growing body of evidence suggesting that obstructive sleep apnea is involved in the pathogenesis of altered glucose metabolism. A number of epidemiologic and experimental studies have shown that patients with sleep apnea have increased glucose levels and increased insulin resistance,^{85,102-104} which might predispose afflicted individuals to developing type 2 diabetes mellitus. Cross-sectional data suggest that associations of sleep apnea with greater glucose levels and increased insulin resistance might be independent of the presence of obesity.^{80,85,102,105} It is known that both obese and non-obese patients with sleep apnea are insulin resistant, whereas not all apnea patients are obese. Specifically, investigators have proposed the following likely scenario. Sleep apnea causes an increase in sympathetic activity,⁵⁵ and increased sympathetic activity impairs glucose homeostasis by enhancing glycogen breakdown and gluconeogenesis.¹⁰⁶ Hence, recurrent hypoxemia along with abnormal sympathetic activity, commonly observed among patients with sleep apnea, might mediate the relationships between insulin resistance and sleep apnea (see Figure 1).

Data from the Sleep Heart Health Study indicated that the prevalence of 2-hour glucose tolerance values increased from 9.3% among patients with an AHI less than 5 to 15% among those with an AHI > 15 .¹⁰³ Among patients with an AHI ≥ 15 , the odds of having an abnormal glucose tolerance was 1.44. Results of the study also indicated that insulin resistance was also greatest among the latter group. This study provided evidence that apnea-induced hypoxemia is associated with glucose intolerance and insulin resistance.¹⁰³ Moreover, data from the

Nurse's Health Study suggest that curtailed sleep duration resulting from sleep fragmentation induced by sleep apnea may also lead to the development or exacerbation of type 2 diabetes mellitus.^{107,108} This is corroborated by analysis of data from the Sleep Heart Health Study.¹⁰⁹ Compared with Individuals sleeping 7 to 8 h/night, individuals sleeping ≤ 5 h or < 6 h/night had adjusted OR for diabetes of 2.51 (95% CI: 1.57-4.02) and 1.66 (95% CI: 1.15-2.39), respectively. On balance, there are data suggesting that the associations between sleep apnea and diabetes might be mediated through obesity, a common risk factor,¹¹⁰ although the prevalence of periodic breathing itself remained significantly higher among diabetic individuals, even after control for covariates. Thus, more definitive explanation of these relationships awaits further empirical studies.

Given the potential effects of reduced sleep on glucose metabolism, one wonders about the overall, long-term health impact of curtailed sleep time on American adults. Converging data indicate that the U.S. population has been sleeping less and less.^{21,111,112} Interestingly, although sleep duration is a strong predictor of morbidity and mortality, among American adults we found that the quality of one's well-being hinged on the quality, rather than on the quantity of one's sleep.¹¹³ Based on the most recent report by investigators from the University of California, San Diego who studied over 1 million men and women ages 30 to 102 years, the greatest longevity was observed among individuals sleeping 7 h/night. Those who slept ≥ 8 h experienced significantly increased mortality risks, as did participants who reported sleeping ≤ 6 h. The increased risk of mortality exceeded 15% for individuals who reportedly slept > 8.5 h or < 3.5 or 4.5 h.^{114,115} It would be interesting to examine whether excess mortality was associated with impaired glucose tolerance/insulin resistance or type 2 diabetes mellitus in that study. Controlled studies seem necessary to answer the question as to the correct sleep time for optimal survival and satisfying life.

If it can be demonstrated that there is an independent association of sleep apnea to impaired glucose metabolism, this might offer another mechanism to explain increased cardiovascular morbidity. Evidently, this will require better delineation of the contribution of cytokines and leptin. In support of such hypotheses, investigators have pointed out that CPAP studies produced significant improvement in insulin sensitivity and left ventricular function with a corresponding decrease in blood pressure.¹¹⁶ CPAP therapy can also normalize leptin levels, thereby reducing central obesity. On balance, there is evidence suggesting that CPAP treatment does not always lead to significant improvement in metabolic disorders.¹¹⁷ Failure to demonstrate positive CPAP effects often result from limited treatment compliance, inadequate duration of treatment, and lack of statistical power. In light of such evidence, therapeutic approaches might integrate methods to increase sleep time, both via reduction of sleep apnea severity and through lifestyle modifications. Synergistically, these would confer significant benefits in the management of cardiovascular complications resulting from uncontrolled diabetes and/or untreated sleep apnea.

Sleep Apnea and Cardiovascular Disease: Role of Dyslipidemia

Dyslipidemia is yet another condition characterizing the metabolic syndrome. It is primarily a disorder of lipoprotein

metabolism, usually caused by excessively high cholesterol levels. It is a known risk factor in the development of coronary artery disease,¹¹⁸ and it is highly prevalent among hypertensive adults. Data from the Multi-Ethnic Study of Atherosclerosis, a multicenter study of 6814 persons ages 45 to 84 years, indicated that 29.3% met criteria for dyslipidemia.¹¹⁹ In that study, the prevalence of dyslipidemia was similar among ethnic groups, although a disproportionate number of blacks and Hispanics, relative to whites, did not receive treatment to control their dyslipidemia.¹¹⁹ These findings were inconsistent with data obtained from the GENOA study, indicating that the prevalence of dyslipidemia was significantly greater among white than among blacks. Among women, rates were 64.7% and 49.5%, respectively; whereas for men, rates were 78.4% and 56.7%, respectively.¹²⁰ Patterns of treatment were nonetheless similar, favoring better treatment for whites.

Both factors involved in developing dyslipidemia (i.e., high triglyceride levels and low high-density lipoprotein) are affected by obesity, a common predictor of sleep apnea and cardiovascular morbidity. With increased adiposity, a commensurate increase in triglyceride levels is observed, whereas high-density lipoprotein levels decrease.^{88,121,122} Given that most of the available evidence comes from cross-sectional data, it remains a daunting task to establish directional causality. In that regard, it cannot be said that dyslipidemia causes sleep apnea or that sleep apnea causes dyslipidemia, although the two conditions tend to aggregate among patients with increased adiposity. It would certainly help to view these associations in the context of data pointing to a direct correlation between lipid profile and cortical arousals, as often observed among patients with sleep apnea. Patients with sleep apnea exhibit greater HDL dysfunction and oxidized LDL levels compared to matched control persons.¹²³ Of note, AHI explained 30% of the variance in HDL dysfunction in sleep apnea.¹²³

Moreover, clinical evidence indicates that patients with abnormal serum lipid/lipoprotein levels improved significantly with CPAP or bilevel PAP therapy.¹²⁴ In that follow-up (6 months) treatment study, investigators observed that the mean HDL-C serum level increased significantly by 5.8%. Such therapeutic interventions are consistent with the Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP III).¹²⁵ Accordingly, reduction of dyslipidemia is a potential secondary target of risk-reduction therapy, which could improve management of the metabolic syndrome.

Conclusions

The aforementioned associations do not seem to be fortuitous, judging from the consistency across studies. The epidemiologic and clinical evidence summarized in this paper constitutes a growing body of literature demonstrating relationships between sleep apnea and diverse systemic abnormalities. The epidemiologic evidence is abundant, but data explaining causal pathways are lacking. It may be that associations among those metabolic disorders point to a maladaptive autonomic response of chemoreceptors, reacting to hypoxia, hypercapnia, and acidosis commonly found in sleep apnea.¹²⁶ Activation of the sympathetic nervous system through hypoxia and hypercapnia triggers an inflammatory response cascading in several down-

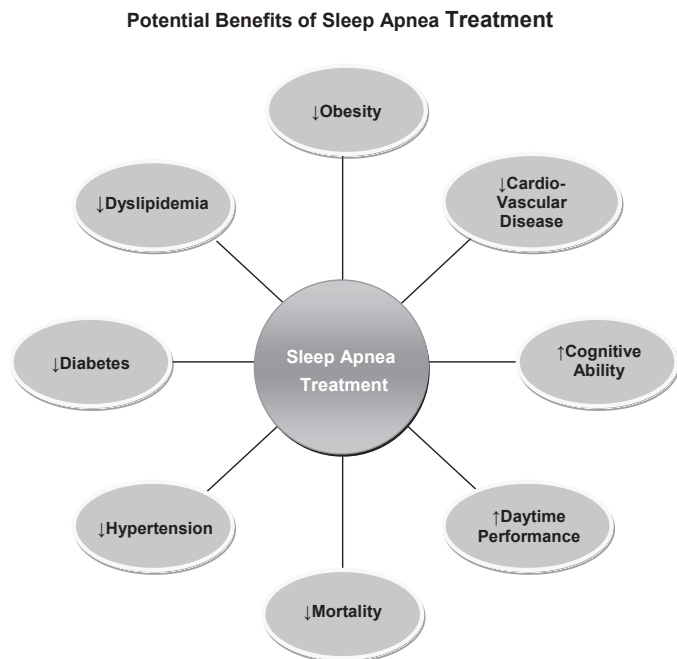


Figure 4—Benefits of sleep apnea treatment, which may include CPAP/bilevel PAP therapy (sometimes used in combination with behavior modification), use of oral-dental devices, or surgical procedures (e.g., UPPP and LAUP).

stream consequences including hypertension, diabetes, and dyslipidemia,³⁴ all of which represent significant risk factors for cardiovascular morbidity. It seems prudent, therefore, that patients with a suspicion of sleep apnea and meeting criteria for metabolic syndrome be properly evaluated and treated.

Clinical trials involving the use of CPAP or bilevel PAP therapy have delineated its positive benefits (see Figure 4). This therapeutic modality is very effective in improving left ventricular ejection fraction and quality of life, lowers blood pressure and sympathetic activity, and reduces mortality among patients with congestive heart failure.^{52,54,127} Among patients with coronary artery disease, CPAP treatment significantly reduces risks of cardiovascular death, acute coronary syndrome, and hospitalization for heart failure.¹²⁸ Moreover, CPAP therapy has significant effects on lipid levels.¹²⁴ CPAP studies show significant improvement in insulin sensitivity and left ventricular function with a corresponding decrease in blood pressure.¹¹⁶

The Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP III) identifies the metabolic syndrome as a potential secondary target of risk-reduction therapy.¹²⁵ It is recommended that patients meeting criteria for the syndrome receive adequate, tailored treatment aimed at reducing obesity through lifestyle modifications including increased physical activity and improved dietary habits.¹²⁹ Evidence from randomized controlled trials suggests that weight loss among overweight and obese individuals reduces blood pressure, improves lipid profiles, and improves blood glucose levels.^{130,131} Pharmacotherapy is recommended only for individuals who do not respond positively to behavioral therapies. As gradual sleep loss in the population (be it a sequela of sleep apnea or behaviorally determined) is a strong determinant of insulin resistance,¹⁰⁷⁻¹⁰⁹ individuals at risk for developing cardiovascular disease should be encouraged not to curtail their sleep time.

Prevalence of Metabolic Disease and Ethnicity

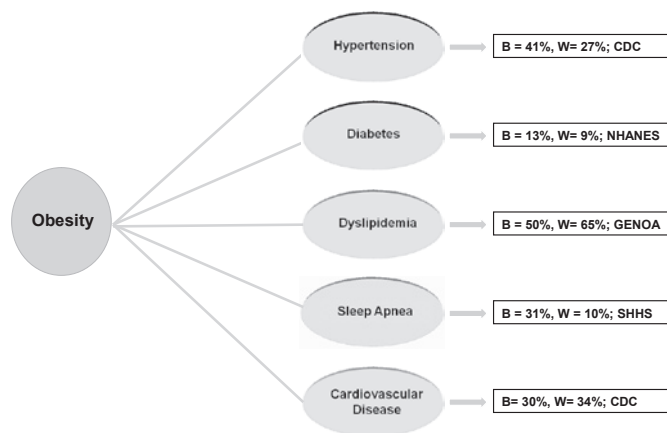


Figure 5—Prevalence of metabolic diseases linked to obesity based on ethnicity: black (B) vs. white (W). Data were retrieved from the Center for Disease Control (CDC), National Health and Nutrition Examination Survey (NHANES), the Genetic Epidemiology Network of Arteriopathy (GENOA) and the Sleep Heart Health Study (SHHS).

Future Directions and Clinical Implications

The epidemiologic and clinical studies summarized in this paper provide a framework for future research in the underpinnings of the metabolic syndrome and related morbidities. Current studies have raised many important issues that require empirical testing, although initial questions regarding relationships between obstructive sleep apnea and cardiovascular morbidity or between obstructive sleep apnea and the metabolic syndrome have been addressed to some extent. Whether the metabolic syndrome represents a mediating factor in the link between obstructive sleep apnea and cardiovascular disease remains to be determined. Alternatively, the metabolic syndrome itself might potentiate the effects of obstructive sleep apnea on cardiovascular disease.

Future research is necessary to rank individuals with regard to their risk of sudden cardiac death and target them for educational and medical intervention. Research is also needed to establish noninvasive markers with adequate sensitivity and specificity in predicting which patients are at greater risk. For example, patients with sleep apnea showing depressed LV function should be considered at greater risk for ventricular arrhythmias and other cardiovascular events.¹³² Identification and treatment of patients with overlapping syndromes (e.g., CHF and COPD with sleep apnea) is paramount in the fight to reduce cardiovascular morbidity.

While awaiting answers to those important questions, many interventions can be envisaged to improve the management of existing metabolic disorders. First, as sleep apnea is highly prevalent among patients with diabetes, hypertension, and dyslipidemia, it seems prudent to administer a sleep apnea screening questionnaire to those at-risk patients. Likewise, such questionnaires should be given to patients with increased adiposity in the neck area and/or who present with abdominal (visceral) obesity. Second, patients meeting criteria for sleep apnea should be referred to a sleep clinic for a detailed laboratory study. Third, tailored behavioral interventions should be

developed to ensure adherence to CPAP or bilevel PAP treatment recommendations. Fourth, individually tailored weight management programs should be designed to assist overweight/obese patients, as weight reduction helps diminish the severity of sleep apnea, thereby improving overall health, daytime performance, cognitive ability, and well-being.

It is evident that the recent rise in metabolic disorders comprising the metabolic syndrome affects persons of differing age groups, of both genders, and across geographic regions. However, public health advocates have been particularly concerned about individuals living in at-risk, underserved communities that are traditionally underrepresented in the health care industry. In black communities, for instance, cardiovascular risk factors are disproportionately high (see Figure 5). In the public health literature, many have argued in favor of greater access to health care,^{133,134} reasoning that with greater access there will be a commensurate decline in morbidity and mortality. Unfortunately, even when blacks have adequate insurance coverage, they are not as likely as their white counterparts to utilize available services.¹³⁵ This suggests that physicians practicing in those communities may have to develop novel strategies to encourage participation of black patients in healthcare practices, as they often endorse a disproportionate disease burden.^{68,90,91,136,137}

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