Obstructive Sleep Apnea and Cardiovascular Disease in Blacks: A Call to Action from Association of Black Cardiologists

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Abstract

Obstructive sleep apnea (OSA) has emerged as a new and important risk factor for cardiovascular disease (CVD). Over the last decade, epidemiological and clinical research has consistently supported the association of OSA with increased CV morbidity and mortality. Such evidence prompted the American Heart Association to issue a Scientific Statement describing the need to recognize OSA as an important target for therapy in reducing CV risk. Emerging facts suggest that marked racial differences exist in the association of OSA with CVD. While both conditions are more prevalent in blacks, almost all NIH-funded research projects evaluating the relationship between OSA and CV risk have been conducted in predominantly non-black populations. There is an urgent need for research studies investigating the CV impact of OSA among high-risk minorities, especially blacks. This article first examines the evidence supporting the association between OSA and CVD and reviews the influence of ethnic/racial differences on this association. Public health implications of OSA and future directions, especially regarding minority populations, are discussed.

Keywords

Sleep apnea; Cardiovascular disease; Blacks
Introduction

Obstructive sleep apnea (OSA), the most common type of sleep disordered-breathing (SDB), is a major public health problem in the U.S., particularly among blacks. It is often characterized by loud snoring, breathing interruptions, awakenings, gasping or choking, and daytime sleepiness as a result of upper-airway collapse and intermittent impairment of ventilation during sleep. Although OSA was clinically recognized as a disease approximately three decades ago, awareness of the condition outside the specialized field of sleep medicine has been slow to develop, and the majority of those affected, particularly blacks, remain undiagnosed. In general, OSA is common in adults, with men, older individuals, and the obese being at higher risk.

Studies suggest that OSA is associated with hypertension, cardiac arrhythmia, coronary heart disease (CHD), heart failure (HF), pulmonary hypertension, stroke, traffic accidents, and increased mortality. Cardiovascular disease (CVD), despite recent decline, remains the leading cause of death in both blacks and whites in the U.S. However, the decline is less steep for blacks who carry a substantially higher cardiac mortality burden with a higher sudden cardiac death rate and significantly lower life expectancy. Convincing evidence has unequivocally demonstrated disproportional burden of CVD in blacks with a marked racial disparities in care and outcome by race in the U.S.

Despite these observations, large studies evaluating OSA and the CV connection have not focused on black participants. Moreover, inclusion of blacks in the majority of longitudinal sleep studies is limited or non-existent with the exception of the Jackson Heart Study. In this paper, we review findings supporting associations between OSA and CVD, and we examine the influence of ethnic/racial differences on these associations. The public health implications of CV risk attributed to OSA, especially as it applies to minority populations, are also discussed. Finally, proposals for future directions are offered.

Method

We searched MEDLINE using the index terms “sleep,” “sleep apnea,” “race,” “ethnicity,” “hypertension,” “coronary heart disease,” “heart failure,” cardiac arrhythmia,” stroke,” intermittent hypoxia,” sympathetic activity,” inflammation,” and “continuous positive airway pressure” for articles published between January 1980 and September 2012. Articles were examined and selected based on their relevance. Additional data were extracted from the bibliographies of selected articles. Priority was given to large prospective cohort studies, randomized controlled trials and experimental studies. This research was supported by funding from the NIH (R25HL105444, R01HL095799, and R01MD004113). The authors are solely responsible for the design, drafting, writing, and editing of this paper and its final contents.

Ethnic/racial differences in awareness and prevalence of OSA

The prevalence of OSA appears to vary with the severity of the disease. Using the Apnea-Hypopnea Index (AHI), AHI (5–15 per hour) indicates mild disease and AHI (16–30 per

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In the general middle-aged population with daytime sleepiness as a complaint, 2–4% have at least mild SDB, with higher incidence occurring in the older group of this segment. These estimates appear to be similar among North Americans, European whites, and Asians, with rates between 2% and 7%. However, some studies have suggested that approximately 20% of adults have at least mild OSA and that 6.6% of adults have at least moderate OSA. Blacks, in contrast, have a higher prevalence of OSA after controlling for confounding variables. Specifically, blacks younger than 25 years and older than 65 years have a higher prevalence of OSA than those of other racial groups. In the Cleveland Family Study, blacks presented with OSA at a younger age than their white counterparts. In addition, Ancoli-Israel et al. found that blacks over age 65 were 2.5 times more likely than whites to have severe OSA. This finding is in accord with that of another population-based study of adult Americans ages 40–60 years, suggesting that OSA rates were much higher among members of minority groups compared to non-Hispanic whites. However, the multicenter Sleep Heart Health Study of over 6000 subjects failed to show a higher prevalence of OSA in blacks compared with whites after adjustment for age, sex, and BMI.

In 1995, Ancoli-Israel et al. found a higher prevalence of symptoms associated with OSA in blacks compared to whites (Figure 1). This is also supported by relatively newer evidence indicating that blacks have a higher rate of daytime sleepiness and snoring (predominant symptoms of OSA) compared to whites. In the Sleep Heart Health Study involving 77% white and only 5% black participants, black men and women had significantly higher Epworth Sleepiness Scores (reflecting greater daytime sleepiness) than their non-Hispanic white counterparts. A prospective study of 523 subjects (55% black) showed that 33% of blacks considered snoring to be normal, compared to 20% of whites. In that study, bed partners of individuals of the black race/ethnicity were more likely to accept loud snoring as being normal. Awareness of the predominant symptom of OSA and knowledge of its clinical significance appear to be low among blacks.

**Proposed mechanisms for the link between OSA and cardiovascular disease**

As depicted in Figure 2, the pathophysiological mechanisms linking OSA to CVD are complex, involving interactions among the respiratory, central nervous and cardiovascular systems. These mechanisms include increased sympathetic tone, changes in intrathoracic pressure, oxidative stress, and vascular inflammation resulting from the nocturnal hypoxia and reoxygenation cycles. Hypoxemia appears to drive most of these important pathophysiological pathways.

The repetitive desaturations cause activation of the sympathetic nervous system and produce sustained hypertension. A similar mechanism might explain the association between OSA and tachyarrhythmia. Intermittent hypoxemia and reoxygenation have also been implicated in the pathogenesis of systemic inflammation due to OSA. Animal and cellular experiments suggest that repetitive reoxygenation promotes oxidative stress through the formation of reactive oxygen species. This process has been implicated in the selective...
activation of inflammation-promoting NF-κB.\textsuperscript{41} Investigators have also shown that reactive oxygen species could activate the transcriptional activator, hypoxia-inducible factor 1 (HIF-1), which mediates the cellular effects of hypoxia, particularly during the reoxygenation period.\textsuperscript{42} These physiological pathways contribute to free-radical production, increased production of adhesion molecules, diminished vasodilator production, and endothelial injury.\textsuperscript{43}

Patients with OSA have characteristically higher levels of endothelin and lower levels of nitric oxide than healthy sleepers.\textsuperscript{38,44} This elevated endothelin concentration increases peripheral vascular resistance and, consequently, blood pressure (BP). Notably, levels of endothelin and circulating nitric oxide invariably return to normal following the treatment of OSA with Continuous Positive Airway Pressure (CPAP).\textsuperscript{44} In addition, this activation pathway also affects inflammatory and immune responses by promoting the activation of endothelial cells, leukocytes, and platelets.\textsuperscript{38} Once activated, these cells express adhesion molecules and proinflammatory cytokines that may lead to endothelial injury and dysfunction,\textsuperscript{38,43} which inevitably leads to development of atherosclerosis.

Observing this chain of events, investigators postulate that endothelial dysfunction\textsuperscript{43} starts soon after the onset of OSA, and may be the mechanism by which OSA mediates the genesis or worsening of hypertension, arrhythmia, CHD, stroke, and, ultimately, HF.

**Ethnic/racial differences in cardiovascular risk associated with OSA**

Several longitudinal studies such as the Sleep Heart Health Study, Wisconsin Sleep Cohort, Pennsylvania Sleep Cohort, Cleveland Family Study, and recently the Jackson Heart Study have demonstrated to some degree that OSA is an independent risk factor for adverse CV outcome.\textsuperscript{9,14,32,45}

**OSA and hypertension**

Epidemiological and clinical studies suggest that between 35\% and 91\% of patients with hypertension have OSA.\textsuperscript{15,46} Emerging evidence also indicates that the presence of OSA in hypertensive patients is associated with treatment resistance.\textsuperscript{16} In a cross-sectional analysis of the Sleep Heart Health Study, individuals with severe OSA (AHI > 30 per hour) had a higher risk of hypertension compared to those without OSA (AHI < 1.5 per hour).\textsuperscript{45} Among subjects who were followed for four years in the Wisconsin Sleep Cohort, the risk of hypertension increased with increasing baseline AHI.\textsuperscript{14} In the cohort with SDB followed for an average of approximately 7 years, a dose-response increase in the risks of incident nocturnal nondipping of systolic BP was observed.\textsuperscript{47}

A strong racial disparity exists in the prevalence\textsuperscript{48} and treatment\textsuperscript{49} of hypertension, and its relationship to OSA. Among hypertensive blacks, we previously reported a 91\% prevalence of SDB.\textsuperscript{15} It is notable that hypertensive blacks had higher baseline BP, a greater number of oxygen desaturations, and higher AHI than their white counterparts.\textsuperscript{15} OSA may, in fact, be partly responsible for the higher prevalence of hypertension and treatment resistance in this group. Whether this link is mediated fully or in part via the strong association of obesity with OSA remains unclear. Of note, analysis of data from 2,470 participants of prospective
cohort of Sleep Heart Health Study\textsuperscript{50} revealed that much of the relationship between AHI and risk of incident hypertension in people with SDB was accounted for by obesity. In that study, SDB was not an independent risk factor for hypertension after adjusting for the effect of body mass index.\textsuperscript{50} However, in a recent study, weight gain over a decade did not appear to diminish the protective effect of CPAP therapy against development of new-onset hypertension in OSA.\textsuperscript{51}

**OSA and coronary heart disease**

The evidence linking OSA to CHD is rapidly increasing. A high prevalence (30\%) of OSA was found among 223 patients with angiographically proven CHD.\textsuperscript{21} In addition, OSA of moderate severity (AHI > 20) was independently associated with myocardial infarction.\textsuperscript{21} Data from the Sleep Heart Health Study also revealed a higher risk of self-reported CHD for individuals with high AHI,\textsuperscript{10} but subsequent longitudinal analyses of the study data indicate that the risk of incident CHD occurred primarily in men younger than 70 years.\textsuperscript{22} Following percutaneous coronary intervention, the presence of OSA was associated with increased vessel remodeling and restenosis\textsuperscript{52} and increased incidence of major adverse cardiac events, such as revascularizations and cardiac mortality.\textsuperscript{53} Studies evaluating the impact of race on the association of CHD with OSA are lacking.

**OSA and arrhythmia**

A wide range of cardiac arrhythmias, including atrial fibrillation, non-sustained ventricular tachycardia, and complex ventricular ectopies, have been described in persons with SDB.\textsuperscript{17–19,54} In a study of patients with OSA, Guilleminault et al. found that 48\% had cardiac arrhythmias, including 2\% with ventricular tachycardia, 11\% with sinus arrest, 8\% with second-degree atrioventricular block, and 19\% with premature ventricular contractions.\textsuperscript{18} Subsequent tracheostomy in selected patients cured them of OSA and abolished their arrhythmias. Building on these earlier findings, Mehra et al\textsuperscript{19} reports that individuals with severe SDB have up to 4-fold higher odds of complex arrhythmias than those without SDB. Further detailing this SDB-arrhythmia risk, Monahan et al.\textsuperscript{54} recent study showed a nearly 18-fold increase in the risk of nocturnal arrhythmia after the occurrence of apneas and hypopneas.

Among patients referred to a general cardiology practice, OSA was found in 49\% of patients with atrial fibrillation, compared to 32\% of those without atrial fibrillation.\textsuperscript{20} The risk of incident atrial fibrillation was higher in younger patients (< 65 years) and those with severe nocturnal hypoxemia.\textsuperscript{17} A recent meta-analysis showed that patients with OSA have a 25\% greater risk of atrial fibrillation recurrence after catheter ablation than those without OSA.\textsuperscript{55} The inadequate inclusion of blacks in most of these studies limits the generalizability of the findings. Particularly worrisome is the lack of OSA-related arrhythmia evidence in blacks in light of their higher sudden cardiac death (SCD) rate and the possible operative role of the OSA-arrhythmia-SCD\textsuperscript{56} connection.

**OSA and stroke**

Stroke, one of the most debilitating diseases, especially in blacks, has a significant association with OSA.\textsuperscript{10,25,26} In patients with first-time strokes or transient ischemic attacks,
SDB was frequently observed. An analysis of prospective data from the Sleep Heart Health Study indicates that severe SDB is an independent risk factor for stroke only in men. Similar findings were reported in the Wisconsin Cohort Study, although the fully adjusted odds ratio failed to reach statistical significance, likely due to inadequate study power.

The impact of race/ethnicity on the association of OSA with stroke is largely unknown. Mortality resulting from stroke is greater in blacks compared to whites. This finding, along with the aforementioned relationship between OSA and stroke, provides further compelling evidence of the need for more research in this area among blacks.

**OSA and heart failure**

With regard to HF, a disease affecting almost 6 million people, report from the Sleep Heart Health Study revealed a two-fold increase in the risk of HF among subjects with OSA. A prospective study of patients with systolic HF revealed a high prevalence (49%) of OSA. Some studies evaluating the relationship between HF and SDB have focused on central sleep apnea (CSA) – a less common type of SDB characterized by intermittent sleep disruptions due to impaired control of breathing by the brain that is more commonly encountered in HF patients. Research has shown that CSA with Cheyne-Stokes respiration is associated with increased incidence of cardiac arrhythmia and higher mortality in HF patients. However, preliminary analyses of data from the Sleep Heart Health Study indicate that men have an increased risk of incident HF as a consequence of SDB, even after exclusion of subjects with CSA.

OSA is common among patients with CVD (Figure 3). Studies investigating the role of OSA on CVD in the minority population are limited, and there are no adequately powered specific studies on the interaction of race on the association of OSA with increased CV risk or adverse outcomes.

**OSA interventions and the CVD impact**

The association of CVD with OSA is further corroborated by evidence suggesting that treatment of OSA decreases CV morbidity and mortality. Buchner et al reported that treatment of OSA is associated with a 64% reduction in CV risk. In the study by Milleron et al., significantly lower combined endpoints of CV, acute coronary syndrome, hospitalization for HF, or a need for coronary revascularization were observed in persons treated for OSA compared to those with OSA who declined therapy (hazard ratio 0.24). Following corrective surgery and the use of mandibular adjustment devices in patients with OSA, a significant reduction in BP was observed. Similarly, some studies have demonstrated improved response to antihypertensive therapy with the use of CPAP in patients with daytime sleepiness. These reductions in systolic BP have been observed in the range of 2–5 mm Hg in a meta-analysis. A smaller study demonstrated even more impressive findings in both systolic and diastolic BP, with a decrease of 11.0 ± 4.4 mm Hg in 24-hour systolic BP after two months of CPAP therapy. Nocturnal diastolic BP was reduced by 7.8 ± 3.0 mm Hg.
Among patients with HF and OSA, both left ventricular ejection fraction (LVEF) and quality of life improve with CPAP therapy. However, the effectiveness of CPAP therapy in patients with CSA and HF remains unclear. In the Canadian Continuous Airway Pressure for Patients with Central Sleep Apnea and Heart Failure (CANPAP) Trial, CPAP therapy improved six-minute walk distance, nocturnal oxygenation, and LVEF, but not CSA. Whether advanced methods of applying airway pressure in HF patients will be more efficacious remains to be determined. Small clinical studies have indicated that both adaptive servo ventilation and bi-level positive airway pressure may provide some benefits to patients with HF and CSA.

The electrical instability and risk of arrhythmia in patients with OSA decrease with CPAP treatment. Also, the recurrence rate of atrial fibrillation in OSA patients after elective cardioversion was lower in those treated with CPAP therapy. Among 23 patients with moderate to severe OSA who were monitored for arrhythmia over a 14-month period using a subcutaneously implanted loop recorder, the occurrence of severe arrhythmia decreased significantly after CPAP therapy.

The treatment of OSA has also been shown to improve survival in patients with CHD and stroke. Following percutaneous coronary intervention, the treatment of OSA was associated with a reduction in the number of cardiac deaths. Although CPAP is not well-tolerated in post-stroke patients and compliance is low, long-term survival post-stroke appears to be improved among those patients who are compliant with CPAP therapy. Although, blacks are at greater risk of OSA-related morbidity, the existing literature does not provide any specific findings addressing possible race/ethnic-based differences in treatment response. Currently, there is no reason to suspect that blacks would be more or less responsive to treatment.

The public health implication of cardiovascular risk associated with OSA among blacks

Potential costs attributable to OSA have been estimated to be in the billions of dollars. Since the disorder has detrimental multi-organ consequences, substantial increase in medical costs can be anticipated. The annual cost of treating the medical consequences of OSA was estimated at $3.4 billion in the United States. Research has also shown an approximately two-fold increase in medical costs prior to intervention in patients with clinically suspected OSA relative to a matched control group. In 2000, OSA-related motor vehicle collisions were estimated to cost $15.9 billion. The amount of indirect nonmedical costs related to days off work and quality of life in patients with OSA remain unknown. However, Findley et al. suggested that treating 500 patients with OSA for three years would save over 1 million in property damage, medical expenses, and legal and administrative costs.

The economic impact of OSA is indeed enormous, and its treatment may prove beneficial in reducing the overall public health burden, especially among blacks, given the higher prevalence of OSA and increased CV risk among this racial group.
**Future directions**

Many difficult ethical questions loom as we design future randomized controlled interventional trials because of the encouraging treatment benefits previously observed. Nevertheless, a few large randomized clinical trials (RCT) have been started to further determine the impact of treating OSA on CV risk. The Continuous Positive Airway Pressure Treatment of Obstructive Sleep Apnea to Prevent Cardiovascular Disease (SAVE) is a planned multicenter international study slated to enroll 5,000 volunteers to investigate whether CPAP will reduce incident CVD. In the United States, the Heart Biomarker Evaluation in Apnea Treatment (HeartBEAT) study is an ongoing multicenter randomized controlled trial that is enrolling patients with OSA and CHD or CHD risk factors to employ CPAP, low-flow nocturnal oxygen, and health lifestyle instruction to determine whether CPAP or oxygen will change cardiac biomarkers. Also in the United States, the proposed ancillary study to the Multi-Ethnic Study of Atherosclerosis (MESA) is aimed to perform standardized in-home polysomnography and 7-day wrist actigraphy in 2,500 African American, Hispanic, Asian American and Caucasian individuals participating in MESA to derive indices of sleep apnea, quality, duration and timing. The study will address the role of sleep disturbances in the pathogenesis of cardiovascular disease across ethnic groups. In Europe, the Randomized Intervention of Patients with CPAP in CAD and OSA (RICCADSA) trial is aimed at evaluating the impact of CPAP treatment on a composite endpoint of new revascularization, myocardial infarction, stroke, and CV mortality over a three-year period in persons with CHD and OSA.

It is notable that most of these trials are being conducted in predominantly non-black communities. Furthermore, major longitudinal studies in the United States that have evaluated the association between OSA and CVD involved small number of blacks. Studies of HF often underrepresent women, minorities and the elderly. One exception is the Jackson Heart Study, a rare all-African American cohort of over 5,000 participants that recently found an association of prevalent hypertension and CVD with higher odds of SDB. However the sleep data from the Jackson Heart Study were based on subjective sleep symptoms rather than objective evaluation as in other major longitudinal studies. Nevertheless, data on blacks from such a large study cohort is encouraging.

Perhaps, there are ethical dilemmas in randomizing minority patients to placebo arms of studies if the active treatments have shown benefit in majority studies. We advocate a range of investigational techniques and approaches including RCT, as appropriate, databases and longitudinal registries. One of the Achilles’ heels of addressing OSA is the high rate, across race and ethnicity, of refusal of, or non-compliance with, recommended treatments. Observational studies such as that by Marin et al., utilizing the large population of patients who refuse treatment as the “placebo” arm have provided important information in OSA treatment trials. In addition, adequate recruitment of minorities, occasionally voiced as a hurdle to minority inclusion into clinical trials, can be successfully accomplished by culturally competent investigators and minority community-based programs.
There is need for enhanced social awareness, widespread community-anchored programs targeted at minority populations, and establishment of relationship with the community leaders and stakeholders as highlighted in Table 2. Professional societies such as the American College of Physicians, American College of Cardiology, American Heart Association, American Academy of Sleep Medicine and the Association of Black Cardiologists among others should collaborate to support these efforts. Although position statements, guidelines, seminars, community outreach are a few of the educational tools currently being utilized, the efforts are still short of what is required to have the desired public health impact.

**Conclusion**

Over the past 30 years, a large body of scientific data firmly established the link between OSA and CVD. Blacks have a higher prevalence of OSA and a higher burden of CVD and its risk factors. Despite these facts, blacks are poorly represented in OSA-related clinical trials. We call for a change in this status with heightened awareness and systematic studies addressing OSA and CV risk in blacks.

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**References**


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Figure 1.
Differences in the prevalence of obstructive severe apnea (OSA) and associated symptoms between blacks and whites. Based on the average number of naps per day; number of times per week of having difficulty falling asleep; sleep satisfaction ranked as 1=best and 4=worst; number of morning headaches per month; percentage of study sample with severe OSA.
Adapted from Ancoli-Israel et al.\textsuperscript{3}
Figure 2.
Diagrammatic representation of the pathophysiological link between obstructive sleep apnea and cardiovascular disease.
Figure 3.
Prevalence of obstructive sleep apnea in various cardiovascular diseases.
Table 1

Population sample of major longitudinal studies on obstructive sleep apnea in the U.S.

<table>
<thead>
<tr>
<th>Author</th>
<th>Study</th>
<th>Year of enrollment</th>
<th>Diagnostic technique for OSA</th>
<th>Cohort size</th>
<th>Population</th>
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<tr>
<td>Redline et al. 1997.2</td>
<td>Cleveland Family Study</td>
<td>1990</td>
<td>Home polysomnography</td>
<td>847</td>
<td>27% Black 73% Whites</td>
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<tr>
<td>O’Conor et al. 2003.35</td>
<td>Sleep Heart Health Study</td>
<td>1995</td>
<td>Home polysomnography</td>
<td>13,194</td>
<td>5% Black 77% White</td>
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<tr>
<td>Vgontzas et al. 2010.78</td>
<td>Penn State Sleep Cohort</td>
<td>1996</td>
<td>In-lab polysomnography</td>
<td>1,741</td>
<td>&lt;15% Black 85% White</td>
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<tr>
<td>Fülöp T et al. 2012.32</td>
<td>Jackson Heart Study</td>
<td>2000</td>
<td>None. Symptoms based</td>
<td>5301</td>
<td>All black</td>
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Table 2
Guidelines for implementing a community-based sleep apnea program in minority populations.

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<th>Guidelines for Implementing a Community-based Obstructive Sleep Apnea Program</th>
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