SNORING AND CARDIOVASCULAR DISEASE RISK IN MIDLIFE WOMEN: A MECHANISTIC MODEL OF SNORING-RELATED ATHEROGENESIS AND ASSOCIATIONS WITH C-REACTIVE PROTEIN

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SNORING AND CARDIOVASCULAR DISEASE RISK IN MIDLIFE WOMEN:
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Simple snoring is highly prevalent and should be considered a phenomenon distinct from sleep disordered breathing (SDB). Snoring is associated with cardiovascular disease (CVD) morbidity and mortality. Midlife women are at increased risk for snoring and cardiovascular disease, yet little is known about the relationships between these factors in this population. We propose and test a mechanistic model of snoring-related atherogenesis to explain these associations. This is the first study to examine the relationship in midlife women between objective and subjective snoring and C-reactive protein (CRP), a CVD biomarker, and the first study to characterize the correlates of snoring in midlife women. The full multi-ethnic sample included 300 women (52.07 ± 2.13 years, 44% African American) from the SWAN Sleep Study, ancillary to the Study of Women's Health Across the Nation (SWAN). Objective snoring and apnea-hypopnea index (AHI) were measured in a subset of 241 participants on one night of in-home polysomnography. CRP was measured at the core SWAN visit temporally closest to the sleep study. Linear regression models examined the relationships between objectively-derived snoring index, a ratio of snore epochs to sleep epochs, and CRP in both the full sample and in postmenopausal women only. Objective and subjective snoring group differences in mean CRP were tested using ANCOVA. Frequency of objective snoring was associated with higher CRP in postmenopausal

women only. Snoring was not significantly associated with CRP in the full sample. The relationship between snoring and CRP was not moderated by AHI or race. There were no group differences in CRP between objective or subjective snoring groups after adjusting for all covariates. Characterization of the sample revealed that simple snorers are distinct from women with SDB. Simple snorers also differed from absent snorers on key CVD risk factors, including higher BMI, systolic blood pressure, and number of metabolic syndrome criteria. There was little agreement between objective snoring frequency and subjective snoring self-report. These findings show that simple snoring should be considered a distinct construct from SDB and measured objectively alongside AHI in future studies. Snoring represents a unique and understudied risk factor for CVD, particularly in postmenopausal women.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1.0 INTRODUCTION

Simple snoring occurs separately from sleep disordered breathing (SDB) disorders. This form of snoring does not co-occur with the hypoxia, severe flow limitation, and apnea/hypopnea events that characterize SDB. While snoring is anecdotally linked to men, rates of self-reported snoring in adult women are moderate and increase substantially in midlife (e.g. Young et al., 1993; Lugaresi et al., 1980; National Sleep Foundation, 2007). However, the reasons for increased snoring in midlife women remain understudied and unclear. The downstream consequences of snoring to cardiovascular risk suggest that midlife women are an important and high-risk population for snoring and cardiovascular disease researchers.

Snoring may be an important component of the mechanistic pathways to atherogenesis and subsequent CVD mortality. Studies spanning the past four decades have found associations between both self-reported and objective snoring and cardiovascular and cardiometabolic risk factors, including carotid atherosclerosis (Lee et al., 2008) and the metabolic syndrome (Troxel et al., 2010). In the current study, we propose an inflammation-endothelial dysfunction model of snoring-related atherogenesis to explain these associations. We first provide the rationale for examining this model in midlife women and outline the prevalence of snoring in women, including age and race differences, and changes in CVD risk accompanying the menopausal transition. Next, we define snoring and SDB and review the currently understood associations between snoring and disease risk. We then review evidence linking snoring vibrations to inflammation and endothelial dysfunction. Finally, we discuss the role of the current study in testing and refining the proposed snoring-related atherogenesis model in midlife women.

1.1 RATIONALE FOR EXAMINING SNORING AND CVD RISK FACTORS IN MIDLIFE WOMEN

1.1.1 Prevalence of Self-Reported Snoring: Age and Race Differences

Simple snoring is a common disorder, with prevalence of habitual snoring in middle-aged adults ranging from 19% to 59% (Lugaresi et al., 1980; Hiestand et al., 2006; Fitzpatrick et al., 1993). While snoring is often considered a male phenomenon, it has an estimated lifetime habitual prevalence of 28% in adult women (Young et al., 1993). The prevalence of snoring in women is age-dependent and increases dramatically during midlife. The 2007 National Sleep Foundation's *Sleep in America* poll of women found that the prevalence of self-reported snoring increased from 33% in women aged 18-24 to 59% in women aged 45-54. A 2006 population-based study of 6,817 women in Sweden found that snoring was strongly age-dependent, with the highest prevalence of self-reported habitual snoring in women aged 50-59 years (Svensson et al., 2006). Earlier cross-sectional studies reported that habitual snoring increased from 5% in women under 30 to roughly 25% in women over 45 (Lugaresi et al., 1980). Increased snoring prevalence may be related to hormonal or morphological changes associated with the menopausal transition, indicating that midlife women may be uniquely predisposed to the risk factors associated with snoring.

In addition to these age differences, some race differences have also been observed in subjective snoring rates. Self-reported snoring and sleep disordered breathing prevalence are significantly increased in African American women compared to non-Hispanic white women (O'Connor et al., 2003; Redline et al., 1997; Scharf et al., 2004; Ram et al., 2010).

Cephalometric analysis suggests that differences in craniofacial morphology may underlie these differences (Lee, Ramirez, & Will, 1997; Redline et al., 1997). However, it is currently unknown whether objective measures of snoring differ on the basis of race.

1.1.2 CVD Risk and the Menopausal Transition

Previous research has demonstrated that postmenopausal women are at greater risk for cardiovascular events and coronary artery disease than premenopausal women (Kannel et al., 1976; Gohlke-Barwolf, 2000; Miller et al., 2003), although the mechanisms of menopause on disease risk remain unclear. One study found that postmenopausal women exhibit significantly higher prevalence of carotid atherosclerosis (54%) than premenopausal women (25%; Sutton-Tyrrell, 1998). A similar study found that postmenopausal women had a 1.84-fold increased risk of carotid atherosclerotic lesions compared to premenopausal women, despite lower mean rates of smoking in the postmenopausal group (Bonithon-Kopp et al., 1989). In the Study of Women's Health Across the Nation, increased low-density lipoprotein (LDL) cholesterol, total cholesterol, and apolipoprotein B were observed in conjunction with the menopausal transition (Matthews et al., 2009). Other risk factors identified in postmenopausal women have included smoking, obesity, hypertension, and sedentary lifestyle (Gohlke-Barwolf, 2000; Miller et al., 2003). Given the increased prevalence of self-reported snoring during and after the menopausal transition, it is conceivable that snoring represents an additional risk factor for CHD in postmenopausal women.

1.2 DEFINITIONS OF SNORING AND OBSTRUCTIVE SLEEP APNEA

Snoring is a dynamic event resulting from a decrease in the sagittal diameter of the oropharynx, followed by high frequency oscillations of the soft palate, pharyngeal walls, epiglottis, and tongue (Ayappa & Rapoport, 2003; Liistro et al., 1991, Figure 1).

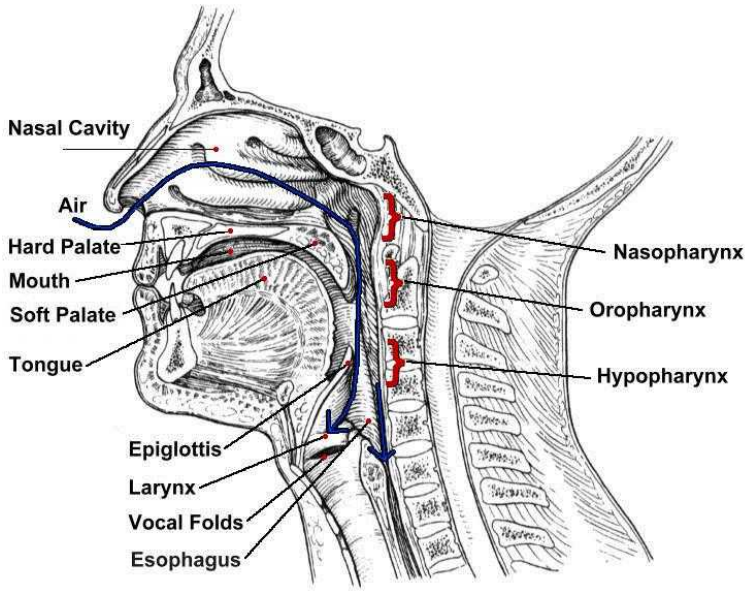


Figure 1. Anatomical Diagram of the Structures Involved in Snoring.

Decreased general muscle tone associated with sleep appears to cause some airflow limitation in snorers and non-snorers alike. However, snorers demonstrate an additional decrease in upper airway tone past a critical cross-sectional threshold, which then induces the soft palate oscillations of snoring (Liistro et al., 1991). Factors correlated with snoring include increased age, obesity, neck adiposity, supine sleeping position, alcohol-related decreased muscle tone,

inflammation of nasal and pharyngeal passageways due to active or passive smoke exposure, and upper airway infection (Schmidt-Nowara et al., 1990; Gohlke-Barwolf, 2000; Miller et al., 2003).

Despite the high prevalence of simple snoring, respiratory sleep research has largely focused on SDB, particularly obstructive sleep apnea/hypopnea syndrome (OSAHS, also called OSA). OSAHS is a sleep disorder wherein extreme sleep-related pharyngeal collapsibility leads to partial or full occlusion or obstruction of the upper airway, resulting in hypoxemia, reduced inspiratory airflow, intra-thoracic pressure swings, and surges of systemic blood pressure and sleep fragmentation resulting from autonomic arousal (Kirkness, Krishnan, Patil, & Schneider, 2006; Mbata & Chukwuka, 2011). In contrast, individuals with simple snoring may exhibit adequate compensatory neural responses to upper airway collapsibility, preventing the brief full occlusion of the oropharynx that is a hallmark of the apneic episode (Liistro et al., 1991; Ayappa & Rapoport, 2003). Beyond differences in mechanical respiratory characteristics observed during inspiration in simple snorers and OSA patients, researchers have also found differences in respiratory flow patterns between the groups. Supraglottic pressure and airflow rate relationships differ between nonapneic heavy snorers and OSA patients (Liistro et al., 1991). In the OSA pattern, the inspiratory flow rate plateaus at very low levels during the failed inspiratory efforts associated with apneic obstruction. This triggers a compensatory autonomic surge, causing the pharyngeal airway to open with a concurrent snore. Conversely, snoring in non-apneic heavy snorers is preceded by a decrease in pharyngeal airway diameter, resulting in a snore accompanying the next inspiration.

1.3 SNORING AND DISEASE RISK

Research suggests associations among habitual snoring and cardiovascular and cerebrovascular disturbances. In cross-sectional epidemiological surveys, snoring in women has been associated with increased prevalence of systemic hypertension (Lugaresi, Cirignotta, Coccagna, & Piana, 1975; Norton & Dunn, 1985) and heart disease (Norton & Dunn, 1985). Prospective studies have found that greater frequency of snoring conferred greater risk for coronary heart disease and stroke in women (Hu et al., 2000). Case-control studies have demonstrated that habitual snoring is also associated with greater risk for myocardial infarction (D'Alessandro et al., 1990) and ischemic cerebral infarction (Partinen & Palomaki, 1985; Palomaki, 1991; Neau et al., 1995). A survey of subjective snoring frequency in 1,222 Hispanic-American adults found that snoring was associated with myocardial infarction (odds ratio, 1.8) even after adjusting for confounding physiological factors (Schmidt-Nowara et al., 1990). More recently, loud snoring has been shown to independently predict the development of the metabolic syndrome, a cluster of risk factors linked with incident CV events (Troxel et al., 2010).

These studies have significant limitations. Few studies accounted for either clinical diagnosis or clinically-significant symptoms of sleep apnea. The studies did adjust for body mass index (BMI), which is often considered a proxy for SDB due to the positive correlation between BMI and apnea-hypopnea index (AHI). However, a sizable percentage of individuals diagnosed with sleep apnea are within normal BMI range, suggesting that BMI alone does not fully represent sleep apnea diagnosis or symptomatology. In addition, much of the snoring data from these studies was provided through self-report, often in the form of a single question assessing the weekly frequency of habitual snoring. While it is possible that individuals with bed partners

may be able to provide more accurate information, self-reported snoring frequency in all of the aforementioned studies was uncorroborated by bed partners.

Recently, Lee and colleagues (2008) recruited a sample of 110 male and female non-snorers and snorers, with a mean age of 58.2 ± 7.9 years, in order to investigate the cross-sectional association between objectively-assessed snoring and carotid atherosclerosis plaque. None of the participants were hypoxic for more than 1% of their total sleep time, indicating that this sample was relatively free of SDB. All of the participants underwent a polysomnographically-recorded sleep night where snoring data was captured using a unidirectional microphone and quantified in visually scored "snore epochs" across the night. Atherosclerotic plaque (absence or presence) in both the carotid and femoral artery was detected by ultrasound. Heavy snoring was significantly associated with the presence of carotid atherosclerotic plaque, independently of nocturnal hypoxia and AHI, and was not found to be associated with femoral plaque. This was the first study to use ultrasound methodology to investigate whether the presence of carotid plaque was associated with objectively-scored snoring.

1.4 THE INFLAMMATION-ENDOTHELIAL DYSFUNCTION MODEL OF SNORING-RELATED ATHEROGENESIS

If one separates simple snoring from the OSA literature, removing the potent effects of hypoxia and sleep fragmentation on physiological variables, it becomes necessary to propose a model that can account for the relationship between independent snoring-induced vibration and atherosclerosis. We argue that snoring represents an independent risk factor due to repeated

mechanical injury to pharyngeal and nearby structures. Drawing together disparate findings in the snoring literature, we proposed the inflammation-endothelial dysfunction model of snoring-related atherogenesis (Figure 2).

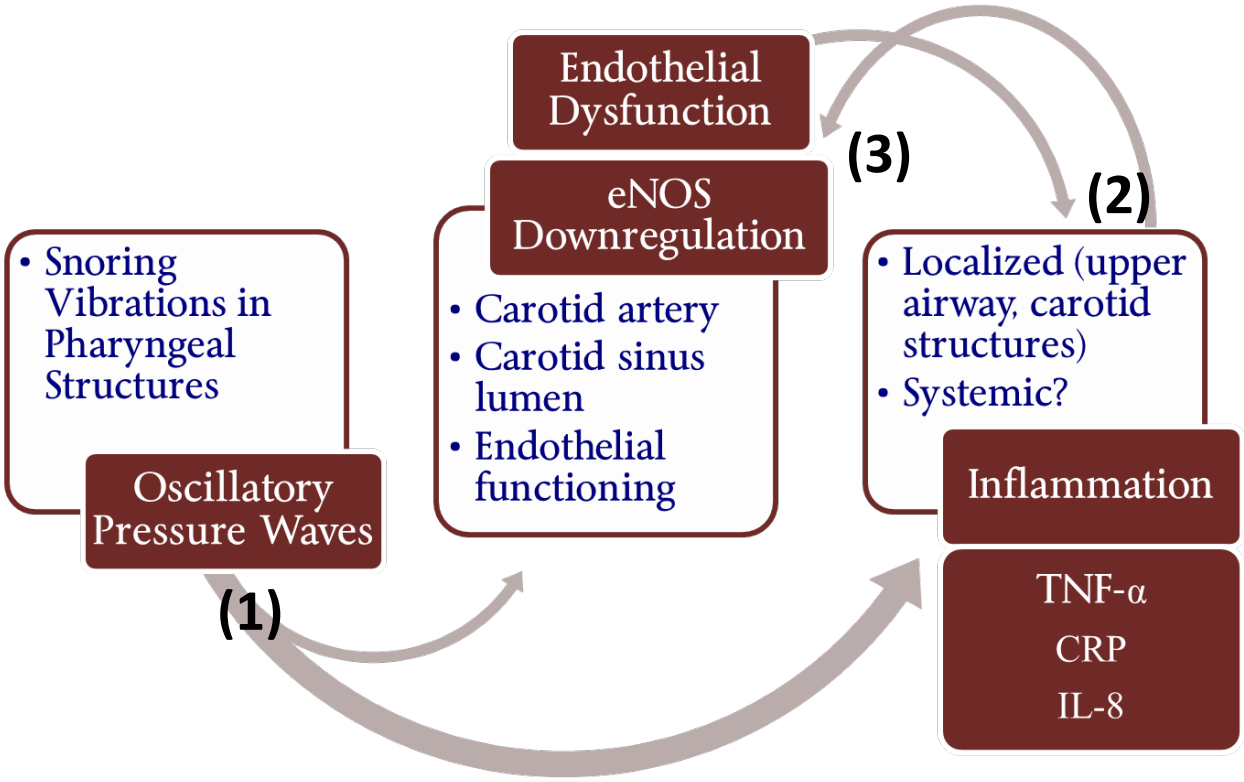


Figure 2. Inflammation-Endothelial Dysfunction Model of Snoring-Related Atherogenesis.

Snoring-induced vibrations result in oscillatory pressure waves (Hedner et al., 1994), which travel through the nearby carotid artery bifurcation, triggering both arterial endothelial damage and an inflammatory response (cf. Almendros et al., 2007; Curry et al., 2002; Cho et al., 2011; Amatoury et al., 2006). The bidirectional feed-forward relationship between inflammation and endothelial dysfunction may be maintained by habitual nocturnal snoring, contributing to carotid atherogenesis. Increased inflammation from the snoring vibrations results in higher levels of localized pro-inflammatory cytokines, which modulate the production of endothelial nitric oxide synthase (eNOS). eNOS produces nitric oxide (NO), the primary endothelium-released vasodilator and antithrombotic factor associated with maintaining vascular tone and endothelial functioning (Verma & Anderson, 2002; Yan et al., 2008). Down-regulated NO production or release results in increased vasoconstriction and decreased vasodilation, leading to endothelial dysfunction and an increase in the production of cytokines and other inflammatory factors, such as CRP. This cycle may be perpetuated by chronic snoring, eventually leading to the development and maintenance of atherosclerosis and potential plaque rupture. Further, this cycle may be independent of SDB, suggesting that simple snoring is an independent risk factor for CVD.

1.4.1 Vibration and Endothelial Dysfunction

As stated earlier, snoring occurs in the upper airway as pharyngeal constrictions result in vibrations of the soft palate, pharyngeal walls, epiglottis, and tongue (Ayappa & Rapoport, 2003; Liistro et al., 1991). Twenty years ago, Hedner and colleagues (1994) proposed that oscillatory pressure waves generated by snoring vibrations can be transmitted through the cellular medium to surrounding tissues, including the carotid artery. The bifurcation of the carotid artery lies

proximal to the hypopharynx, just below the oropharynx where the snoring pressure waves originate (Figure 3).

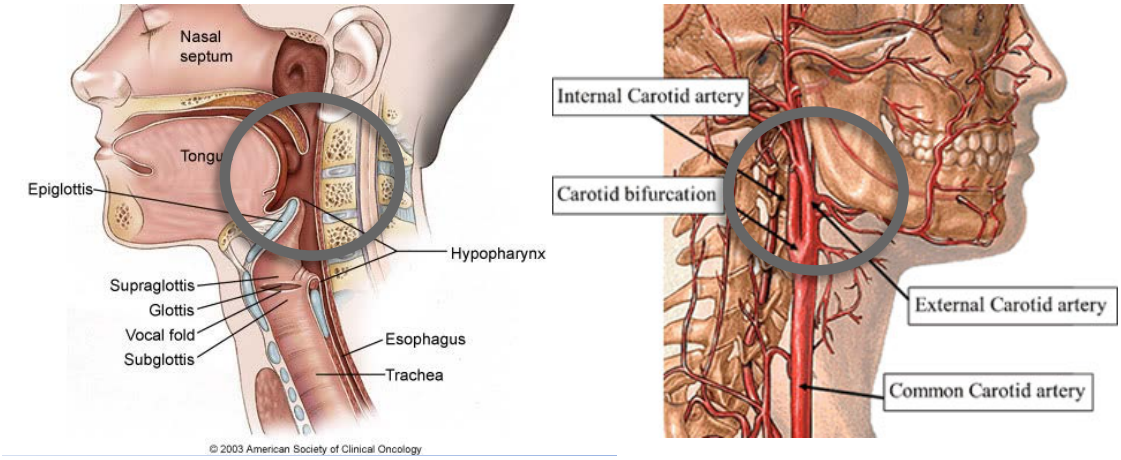


Figure 3. Location of the Human Hypopharynx Proximal to the Carotid Artery Bifurcation.

Recent studies in rabbit models have demonstrated that induced snoring in the pharyngeal region increases the tissue pressure not only at the carotid artery bifurcation, but also within the carotid sinus lumen, indicating that energy is successfully transmitted from the pharyngeal tissues across the carotid artery wall (Amatoury et al., 2006). In a similar study of induced snoring in rabbits, both frequency and amplitude of the oscillatory pressure wave generated in the pharyngeal structures resulted in detectable pressure oscillations in the carotid artery bifurcation and sinus lumen (Howitt et al., 2007). These data support the proposal that snoring induces oscillatory pressure waves that are transmitted to nearby vascular structures. Further, they provide support for a pathway between the objective snoring and atherosclerosis relationship reported by Lee and colleagues (2008).

Outside of the limited published snoring literature, other studies of vibration in humans and animals have been associated with endothelial dysfunction. For example, vibration-induced Raynaud's phenomenon (VRP) is associated with long-term exposure to hand-transmitted vibration at work, and is characterized by digital ischemic attacks and motor and neural symptoms in the hands and arms (Stoyneva, Lyapina, Tzvetkov, & Vodenicharov, 2003). Endothelial damage and dysregulation have been detected in individuals with VRP, supported by elevated plasma levels of thrombomodulin and endothelin-1, the latter of which inhibits the effects of NO (Bourque, Davidge, & Adams, 2011). Endothelin-1 and NO are counterparts in maintaining vascular function, and imbalance in these factors is implicated in the progression of vascular disease (Khimji & Rockey, 2010). Workers with VRP also exhibit deficient peripheral circulation resulting from vasoconstriction, a conceptual analogue to coronary arterial vasoconstriction resulting from chronic snore-induced vibration (Herrick, 2005).

Mechanistically, vibration injury in a rat tail model has shown that endothelial cells showed signs of damage after a single 4-hour bout of vibration, and vibration for 9 days at a level of 60 Hz for four hours a day resulted in thinning and death of endothelial cells (Curry et al., 2002). Vibration-induced vacuoles following one day of vibration are morphologically similar to those formed under norepinephrine application, suggesting that vibration induces vasoconstriction. Cho et al. (2011) have demonstrated that vibrated carotid arteries in rabbits show signs of endothelial dysfunction as measured by decreased vasorelaxation to acetylcholine. In order to isolate primary snoring-induced vibration as the sole independent variable, the authors utilized a rigorous method to prevent features associated with sleep apnea, including hypoxemia, large intra-pleural variation, and blood pressure changes. The results of these studies

cumulatively support the theory that vibration alone can cause endothelial damage, resulting in endothelial dysfunction.

1.4.2 Vibration and Inflammation

Vibration has been demonstrated to trigger inflammation and overexpression of pro-inflammatory cytokines. A sample of annulated rats was subjected to 3 hours of a 1-second upper airway vibration followed by 3-second no vibration pattern, which the authors conceptualized as analogous to the human snoring pattern of heavy snorers (Almendros et al., 2007). Gene expression analysis found mRNA overexpression of tumor necrosis factor-α (TNF-α) and macrophage inflammatory protein-2 (MIP-2) in the soft palates of the rats subjected to vibration compared to control cannulated rats who did not receive the vibration. A cell model of snoring-induced airway inflammation found that human bronchial epithelial cell cultures subjected to vibration for 12 to 24 hours exhibited significantly increased concentrations of the chemokine interleukin-8 (IL-8; Puig et al., 2005). It is currently unknown whether vibration results in the overexpression of other inflammatory markers.

1.4.3 Bidirectional Relationship between Inflammation and Endothelial Dysfunction

The results of these vibration studies provide support for the inflammation-endothelial dysfunction model of atherogenesis. TNF- α and IL-8 are both implicated in the maintenance of endothelial functioning, and elevations in both are associated with adverse cardiovascular outcomes. The primary function of IL-8, a chemokine synthesized by macrophages and endothelial cells, is to recruit and activate neutrophils at the site of inflammation (Hammond et

al., 1995). In a prospective case-control population study, individuals in whom coronary artery disease developed had elevated baseline IL-8 concentrations, and participants in the highest IL-8 quartile were at the greatest risk for future CAD (Boekholdt et al., 2004). Similarly, TNF-α has been shown to be related to endothelial functioning. TNF-α downregulates the expression of endothelial nitric oxide synthase (eNOS; Yan et al., 2008). eNOS produces nitric oxide, which regulates vascular function and maintains endothelial functioning. Increases in TNF-α are, therefore, associated with impaired endothelial functioning. Importantly, TNF-α-mediated inhibition of eNOS has been associated with atherosclerosis and heart failure (Picchi et al., 2006; Agnoletti et al., 1999). TNF-α also stimulates the production of IL-8 (Azevedo et al., 2013), suggesting that vibration-induced overexpression of these two factors contributes to a feed-forward inflammatory response that results in endothelial dysfunction.

1.4.4 Role of C-reactive Protein in Inflammation, Endothelial Dysfunction, and CVD

The production of IL-8 and TNF-α can be further stimulated by C-reactive protein (CRP) (Galve-de Rochemonteix et al., 1993; Xie et al., 2005). CRP is an inflammatory agent involved in the induction of pro-coagulant activity in the endothelium and in recruiting inflammatory cells into atherosclerotic plaques (Apostolopoulus, Davenport, & Tipping, 1996). Plasma CRP has been shown to be relatively stable in a given individual over 24 hours (Libby, 2002). To date, no study has directly tested whether vibration results in increased production of CRP, although this is a plausible mechanism. The observed associations between vibration and increased IL-8 and TNF-α may be mediated by increased levels of CRP, which further contributes to the formation of atherosclerotic plaques. In turn, macrophages from atherosclerotic plaques demonstrate an enhanced capacity to produce IL-8 (Apostolopoulus, Davenport, & Tipping, 1996). The

inflammation-endothelial dysfunction model of atherogenesis is therefore a feed-forward bidirectional relationship driven by vibration.

Studies in animal and human models have suggested a pro-atherogenic role of C-reactive protein (CRP) via the inflammation and endothelial dysfunction pathways. Exposure of the endothelium to CRP induces pro-coagulant activity and the expression of cell surface adhesion molecules, which impair vascular relaxation. An *in vivo* mouse model found that human CRP transgene expression resulted in accelerated aortic atherosclerosis (Paul et al., 2004). In humans, elevated CRP levels have been associated with blunted systemic endothelial vasodilator function, implicating CRP in endothelial dysfunction and long-term coronary artery disease (Fichtlscherer et al., 2000). One human study using an invasive measure of endothelial functioning found that chronic low-grade inflammation, characterized by elevated CRP levels, was significantly related to decreased endothelial NO synthesis, providing convincing support for the role of CRP in the development of hypertension and atherogenesis (Cleland et al., 2000).

In the human literature, CRP has been shown to be a remarkably robust biomarker for CVD risk. A meta-analysis of 7 prospective studies found that a 1.4 mg/L increase in circulating CRP above the upper limit clinical threshold of 1.0 mg/L (or 2.4 mg/L total) was associated with a combined risk ratio of developing CHD of 1.7 (95% CI=1.4-2.1; Danesh et al., 1998). CRP levels around the upper clinical limit of 1.0 mg/L have variously been associated with a 2- to 3-fold increased risk of adverse cardiovascular outcomes, including myocardial infarction and ischemic stroke (Ridker et al., 1998), peripheral vascular disease (Ridker, 1998), and coronary heart disease (Kuller et al., 1996; Koenig et al., 1999). Due to CRP's demonstrated role in both inflammation and endothelial functioning, it represents an opportune biomarker for investigation in the present study.

2.0 STUDY AIMS

While each of the aforementioned studies addresses a component of the proposed simple snoring-induced atherogenesis model, research is needed to draw together these disparate findings in order to test and refine the conceptual physiological model. As a first step, research is needed in humans to investigate how snoring vibration affects inflammatory markers. We have chosen to look at CRP on the basis of its predictive value for CVD risk in humans and its role in endothelial dysfunction, as established in the animal and cell model literature.

This is the first study to investigate the relationship between objective snoring and a cardiovascular disease biomarker in midlife women. The overall purpose of this study was to investigate whether snoring, as measured objectively by vibrations at the surface of human pharyngeal structures, is associated with elevations in circulating levels CRP. Specifically, the study aimed to investigate whether snoring and CRP were associated in a positive dose-response manner and whether this relationship was specifically observed in simple snorers, defined by the absence of sleep apnea (AHI $\geq$ 5). Further, given the hypothesized role of snoring-induced atherogenesis in postmenopausal women, we sought to investigate whether the snoring and CRP relationship differed as a function of menopausal status. Objective snoring data were derived and scored from existing polysomnographic (PSG) sleep studies, which included a microphone designed to detect snoring. Subjective snoring data were derived from participants' report of frequency of loud snoring across the week. Circulating CRP levels were derived from blood

samples assayed using a high sensitivity C-reactive protein (CRP) assay at two blood draw time-points temporally closest to the sleep recording night (Ockene et al., 2001). We hypothesized that simple snorers and individuals with sleep disordered breathing would have higher levels of CRP compared to non-snorers. Given that postmenopausal women are at the greatest risk for CVD morbidity and mortality, we further predicted that the association between objective snoring and CRP would be strongest in our group of postmenopausal women.

Because little is known about the correlates of snoring in midlife women, we further sought to characterize our sample on the basis of their objective and subjective snoring values. Post hoc characterization based on the presence or absence of both sleep disordered breathing and objective snoring enabled us to create three groups of women: absent or mild snorers (AHI<5), simple snorers (AHI<5), and sleep disordered breathers (AHI≥5). Based on known associations between OSA, obesity, and CVD risk, we predicted that women in the sleep disordered breathing group would have the poorest health profiles and greatest number of CVD risk factors, such as high blood pressure and BMI. Our conceptual model suggests that simple snorers would also display poor health profiles and greater CVD risk than absent or mild snorers. On the basis of previous research showing that loud snoring is associated with increased metabolic risk (Troxel et al., 2010), we further predicted that simple snorers would have poorer metabolic profiles. Finally, given established differences in self-reported snoring prevalence between Caucasian and African American women and craniofacial differences in morphology (Lee, Ramirez, & Will, 1997; Redline et al., 1997), we predicted subjective and objective snoring would be more prevalent in African American compared to Caucasian participants.

3.0 METHODS

3.1 PARTICIPANTS

The SWAN Sleep Study is a cross-sectional study of sleep in a multi-ethnic cohort of midlife women. It is an ancillary study of the Study of Women's Health Across the Nation (SWAN), a longitudinal, multi-site study of the psychological, behavioral, social, and physiological correlates and consequences of the menopausal transition. The SWAN Sleep Study cohort included 368 Caucasian, African American, and Chinese participants studied at four sites: Pittsburgh, PA; Chicago, IL; Detroit, MI; and Oakland, CA. Each site recruited Caucasian participants as well as one minority group: African American participants were recruited from the Pittsburgh, Chicago, and Detroit sites, and all Chinese participants were recruited from the Oakland site. To maintain sufficient power to examine racial differences, our study included only African American and Caucasian participants whose closest SWAN Core follow-up visit occurred within a window of 365 days either before or after the SWAN Sleep Study date (Caucasians: n=140, mean age = 51.29 ± 2.10 years; African Americans: n=116, mean age = 50.94 ± 2.13 years).

Participants were excluded from participation in the SWAN Sleep Study for: current menopausal hormone replacement therapy (HRT) use; current oral corticosteroid use; current chemotherapy or radiation; regular shiftwork; and noncompliance with core SWAN procedures. Participants with missing snore channel data or who reported the use of interventions to modify

or reduce snoring [e.g. continuous positive airway pressure (cPAP)] were excluded from analyses. Informed consent was obtained at each participating institution. Participants were compensated for their participation. For the purposes of the present study, each participant's CRP data were drawn from the closest annual SWAN Core assessment that fell within one year of their SWAN Sleep Study visit date (range: 362 days prior to sleep night to 364 days post-sleep night). For those women whose two closest annual SWAN Core assessments fell within one year on either side of their sleep study visit date (n=138), an average of both CRP values were used to improve measure reliability (Ockene et al., 2001). This measure appears fairly stable, given the high degree of correlation between the two CRP values for these participants (r=0.517, p=.001).

3.2 DEMOGRAPHIC MEASURES

Sociodemographics were assessed through participant self-report at the SWAN Core baseline assessment and included age, racial/ethnic identification (Black or African American, non-Hispanic White, or Chinese or Chinese American), highest educational attainment, total family income, and employment status. Menstrual bleeding patterns were used to characterize menopausal status (premenopause/early perimenopause, late perimenopause, and postmenopause/surgical menopause) according to World Health Organization criteria (World Health Organization, 1996).

3.3 PHYSIOLOGICAL MEASURES

Given the established relationship between adiposity and tissue mass and both snoring and SDB, key anthropometric data were collected (Kaditis et al., 2008; Nieto et al., 2000; Olson et al., 1995). Neck circumference was measured in centimeters at the cricothyroid cartilage. The measurement was taken by the sleep study technician on the first night of in-home PSG. Waist-hip ratio was calculated from measurements taken at the closest preceding SWAN Core visit. Waist circumference was measured at the natural waist or narrowest part of the torso, and hip circumference was measured at the widest part of the hip. Body mass index (BMI) was measured as weight in kilograms divided by height in meters squared, and measurements were taken at the baseline SWAN Sleep study assessment using calibrated scales.

Blood and vascular physiological data were collected at the closest SWAN Core visit preceding the SWAN Sleep study. Blood pressure readings were measured according to a standardized protocol, with readings taken on the right arm and with the participant seated with feet flat on the floor for at least 5 minutes before measurement. Participants had not smoked or consumed caffeine within 30 minutes of measurement. Two sequential blood pressure readings were averaged for systolic and diastolic blood pressure. Phlebotomy was scheduled to coincide with the early follicular phase (days 2-7) of the participant's menstrual cycle (in 87.6% of women) and was performed on the morning following an overnight fast (in 96.2% of women). Total cholesterol and triglyceride levels were analyzed using previously described enzymatic methods (Steiner et al., 1981) on a Hitachi 747 analyzer (Boehringer Mannheim Diagnostics, Indianapolis, Indiana). High-density lipoprotein cholesterol (HDL-C) was isolated using heparin-2M manganese chloride (Warnick & Albers, 1978). Glucose levels were measured using a

hexokinase-coupled reaction (Boehringer Mannheim Diagnostics, Indianapolis, Indiana). Insulin level was measured using solid-phase radioimmunoassay (DPC Coat-A-Count Insulin RIA; Diagnostic Products, Los Angeles, CA).

Overall health and physician-reported medical diagnoses were assessed at the SWAN Core baseline interview. Participants provided dichotomous (yes/no) responses to medical diagnosis of anemia, Type II diabetes, high blood pressure, high cholesterol, migraine, stroke, osteoarthritis, over- or under-active thyroid, heart attack, angina, osteoporosis, or cancer. All positive responses were summed for each participant to create a sum of physician-diagnosed health conditions.

3.4 HEALTH BEHAVIOR MEASURES

Mean daily cigarette, caffeine, and alcohol consumption were drawn from the participants' responses on the Pittsburgh Sleep Diary (Monk, 1994), which was administered concurrently with the PSG-assessed sleep nights. Sleep medication usage, exercise, and vasomotor symptoms were calculated as the percent any was reported on the Pittsburgh Sleep Diary across all study days. Passive smoke exposure category was derived from total person hours of exposure to passive smoke in the home, at work, or other in one week, as previously described (Coghlin, Hammond, & Gann, 1989).

3.5 PSYCHOLOGICAL MEASURES

A number of psychological variables were assessed in the study. Bodily pain (SF-36 Pain Index) and quality of life (0=worst to 10=best) were assessed at the SWAN Core baseline interview. Social support (0=least to 16=most) and financial strain (0=not hard at all, 1=somewhat/very hard) were assessed by interview at the closest SWAN Core visit preceding the SWAN Sleep study. Scores on the 16-item Inventory of Depressive Symptomatology (IDS), the 4-item Perceived Stress Scale (PSS), and the 10-item Spielberger State-Trait Anxiety Inventory (STAI) were averaged across administrations during the SWAN Sleep Study.

3.6 PSG-ASSESSED AND SELF-REPORTED SLEEP MEASURES

Polysomnographic studies were conducted over three consecutive nights using Vitaport-3 (TEMEC VP3) ambulatory monitors. Sleep study staff visited the participant's home on the evening of each sleep study night to apply electrodes and calibrate the channels. Upon arising in the morning, participants turned off the recorders and removed their equipment. Quality assurance assessments, processing, and scoring of all sleep records were performed at the University of Pittsburgh Neuroscience-Clinical and Translational Research Center (N-CTRC). The raw snore channel was archived for later scoring.

Polysomnography signals included bilateral central referential EEG channels (C_3 and C_4, referenced to A_1 tied to A_2), electrooculogram (EOG), submentalis electromyogram (EMG), and electrocardiogram (EKG), nasal pressure cannula, oral-nasal thermistors, fingertip oximeter, and abdominal and thoracic respiratory effort, as measured by inductance plethysmography. Nasal

pressure was used to measure airflow for scoring apneas and hypopneas, and the apnea/hypopnea index (AHI) was scored according to standard guidelines (ASDA, 1992).

Two measures of self-reported sleep were assessed in the study. The 8-item Epworth Sleepiness Scale (ESS) was administered on the last day of the SWAN Sleep Study. Scores on the Pittsburgh Sleep Quality Index (Buysse et al., 1989) were averaged across administrations on the 4th and last days of the study.

3.7 OBJECTIVE SNORING MEASURES

The snore signal was collected using a specialized microphone, which translated snoring-induced vibrations into an electrical signal that oscillated in proportion to air pressure variations. The raw signal, collected in millivolts (mV), captured both duration (length of snoring event) and amplitude (strength of vibration pressure). Previous studies have found no statistically significant change in AHI or SDB across PSG nights, indicating little night-to-night variability in breathing-related channels (Davidson, Gerhman, & Ferreyra, 2003; Stepnowsky, Orr, & Davidson, 2004; Chediak et al., 1996). These data suggest that one night of PSG-recorded sleep was sufficiently representative of snoring activity.

Snore events were visually scored following a scoring paradigm established *a priori* under the aegis of a respiratory sleep medicine expert, Dr. Tom Rice, and a PSG signal analyst expert, David Cashmere. The visual scoring paradigm included the following criteria, all of which had to be met for a positive snore event: 1) duration of ≥0.4 seconds; 2) ≥300% amplitude change from baseline mV signal; 3) occurring only once per breath, as established using

respiratory PSG signals; 4) occurring during inspiration and/or expiration; 5) not occurring during epochs scored as wake or at the juncture of a transition to or from wake.

3.7.1 Rationale for Snoring Scoring Paradigm

The scoring methodology was adapted from that used by Lee et al. (2008) for uncalibrated signals. The duration parameter represented a sufficient period for snoring accompanying inspiration or expiration and was deemed sufficiently long to eliminate artifacts of sleep, such as sighing, rustling, and snorts (T. B. Rice, personal communication, June, 2012). The amplitude parameter was established to eliminate non-snoring sleep artifacts, including labored breathing and non-snoring sounds, such as murmurs or mumbles. Because the snore channel was not calibrated to a standardized baseline voltage before recording, the baseline signal was established independently for each individual using the bio-calibrations performed at the beginning of the night's recording period. Since snoring occurs with either the inspiration or expiration phase, and occasionally throughout both phases, only events occurring in one of these phases were counted as snore events, pursuant to convention (e.g. Schwartz, Salome, Ingmundon, & Rugh, 1996; Hoffstein, Mateika, & Mateika, 1991). Snoring events occurring during both the inspiration and expiration phase were scored as a single event. Only NREM and REM sleep epochs were scored. Putative events occurring immediately on or before sleep-to-wake transitions were excluded as candidate events and not scored, as they may have been artifacts of wake. To ensure that these parameters were satisfied, the snore channel was visually compared to the corresponding respiration (thoracic, abdominal effort), oxymetry, submentalis EMG, and EEG (C4) channels.

3.7.2 Training and Reliability of Scorers

In addition to the paradigm developer, who was considered the Ground Truth scorer, we trained 5 raters on the snoring scoring paradigm. Twelve reliability files were used to evaluate the reliability of scorers. These records were identified *a priori* on the basis of four primary characteristics associated with snoring: race (African American or Caucasian), BMI (≥30 or <30), presence of sleep disordered breathing (AHI <5 or ≥5), and self-reported snoring (Never, Infrequent, or Frequent). Permutations of these characteristics were selected and may be seen in Table 1. These reliability files were selected to train scorers on varying degrees of PSG channel complexity and assess inter-rater reliability along a spectrum of scoring difficulty. One reliability file was excluded from scoring and reliability analysis due to technical complications.

Table 1. Participant Characteristics for Selected Reliability File Records.

	Race	BMI	AHI	Self-Reported Snoring Frequency
511070	White	Normal	Non-SDB	Never
511037	Black	Normal	SDB	Never
513052	Black	Overweight	Non-SDB	Never
511009	White	Overweight	SDB	Never
513031	Black	Normal	Non-SDB	Infrequent
517043	White	Normal	SDB	Infrequent
517072	White	Overweight	Non-SDB	Infrequent
511012	Black	Overweight	SDB	Infrequent
513079	Black	Normal	Non-SDB	Frequent
514061	White	Normal	SDB	Frequent
511061	Black	Overweight	Non-SDB	Frequent
513094	White	Overweight	SDB	Frequent
Totals	White = 6 Black = 6	Normal = 6 Overweight = 6	Non-SDB = 6 SDB = 6	Never = 4 Infrequent = 4 Frequent = 4

Notes: BMI categorization: Normal <30; Overweight ≥30. AHI categorization: Non-SDB <5; SDB ≥5. Subjective snoring categorization based on responses to PSSQ loud snoring question.

Training was done in two waves: three scorers were trained in January-February 2013 and two scorers were trained in September-October 2013. The training protocol lasted approximately 20-30 hours in total and followed a sequential process: a) group overview of the paradigm parameters and rationale for each parameter; b) group training in the use of Harmonie software (Stellate System, Montréal, Québec, Canada); c) group training in identification of snoring events per paradigm criteria; d) blind group identification of putative events, with rationale and discussion; and e) individual scoring of the reliability files and exportation of events to the Ground Truth scorer. All components of the training process were led by the paradigm developer.

Inter-rater reliability was calculated using the *F*-measure (Goutte & Gaussier, 2005). Each snore event was given a binary label l representing the correctness of that identification per the paradigm criteria. Each trained scorer assigned a binary label z indicating whether he or she believed the event to be a snore or not. The following table summarizes the possible outcomes:

		Snore Label (Ground Truth) l	
		+	-
Snore Assignment (Trainee) z	+	True Positive (TP)	False Positive (FP)
	-	False Negative (FN)	True Negative (TN)

From these counts, precision (*P*), recall (*R*), and *F*-score were calculated as follows:

$$P = \frac{TP}{TP + FP} \qquad R = \frac{TP}{TP + FN} \qquad F = \frac{2(P * R)}{(P + R)}$$

The *P*, *R*, and *F*-score statistics were calculated for each of the final reliability files (*n*=11). Table 2 shows that overall reliability was high, with an average *F*-score of .84. The observed low and non-existent (designated not a number, or "Nan") *F*-scores for 511070 and 513079, respectively,

are due to the small number of scored snoring events in these records (511070 had 2 events; 513079 had 0 events). Exclusion of these records yields an overall *F*-score of .89. Graphical representations of *F*-score comparisons for all reliability files where snoring was present (n=10) are included in Appendix A. For robustness, permutations of the F-measure were conducted using each trained scorer as the Ground Truth, for a total of 66 reliability calculations and overall *F*-scores of .80 (all records) and .89 (excluding non-snorers; see Appendix B). The results of these analyses suggest that inter-rater reliability was acceptable overall.

Table 2. Reliability File F-scores Compared to Gold-Standard Ground Truth.

	511037	513031	513052	511009	511006	511070	513079	513094	514061	517043	517072
Expert 1	.84	.93	.89	.88	.85	.36	Nan	.87	.90	.96	.94
Expert 2	.84	.95	.78	.90	.84	.40	Nan	.84	.87	.95	.93
Expert 4	.85	.96	.82	.89	.80	Nan	Nan	.85	.96	.96	.93
Expert 5	.80	.94	.76	.82	.92	.22	Nan	.92	.94	.94	.93
Expert 6	.83	.91	.78	.88	.88	.40	Nan	.92	.91	.94	.92

Notes: Nan = not a number.

3.7.3 Objective Snoring Group Classification

Each 20-second sleep epoch that contained 2 or more snore events was scored as a snore epoch (cf. Lee et al., 2008). The average respiratory rate in a healthy adult at rest is 12-18 breaths per minute (Tortora & Anagnostakos, 1990) or 4-6 breaths per 20-second epoch. Two or more snore events, each occurring with one breath, therefore represents one-third to one-half of the sleep

epoch and is of sufficient duration to denote a "snore epoch" (T. B. Rice, personal communication, June, 2012). The independent variable "snoring index" ("SI") was calculated as a continuous variable and represented the percentage of the total number of snoring epochs divided by the number of total sleep epochs.

Participants were categorized into three orthogonal objective snoring groups pursuant to criteria established by Lee et al. (2008): Individuals with a snoring index (SI) < 25% and AHI < 5 were classified as "Absent" (*n*=31); individuals with an SI ≥ 25% and AHI < 5 were classified as "Simple Snorers" (*n*=82); and individuals with an AHI ≥ 5 were classified as "Sleep Disordered Breathing" (*n*=128).

3.7.4 Subjective Snoring Group Classification

Four subjective snoring groups were established using participants' responses to the following question on the Pittsburgh Sleep Symptom Questionnaire (PSSQ): "During the past month, how many nights have you had, or been told you had, loud snoring?" Responses included "Never", "Do not know", "Rarely (less than once per week)", "Sometimes (1-2 times per week)", "Frequently (3-4 times per week)", and "Always (5-7 times per week)". We used the established criteria for detecting clinically significant sleep disturbances as defined by symptoms occurring 3 or more times per week (Okun et al., 2009). Participants who endorsed loud snoring "Rarely" or "Sometimes" were classified as "Infrequent" (*n*=54). Participants who endorsed loud snoring "Frequently" or "Always" were classified as "Frequent" (*n*=51). Respondents endorsing "Never" were classified as "Never" (*n*=119). Respondents endorsing not knowing their snoring frequency were classified as "Don't Know" (*n*=76).

3.8 HIGH SENSITIVITY C-REACTIVE PROTEIN

A fasting blood draw was collected annually during SWAN core visits. The majority of the blood draws were scheduled to coincide with the early follicular phase of the participant's menstrual cycle and prior to 10:00 a.m. CRP is robust to diurnal variation (Meier-Ewert, 2001), suggesting that any time-of-day variation may not have affected the CRP values in this sample. All samples were maintained at 4°C until separated, frozen at -80°C, and shipped on dry ice to the central laboratory (Medical Research Laboratories, Highland Heights, KY, USA). CRP was measured using an ultra-sensitive rate of immunonephelometry (Dade-Behring, Marburg, Germany). The CRP level taken at the SWAN core visits closest to the SWAN Sleep study date (within 365 days) was used as our outcome variable. For women with CRP measured at two time points within 365 days of their sleep study night (n=138), the average of these values was used. The rationale for this inclusion is that two time points would provide a more stable and reliable measure of CRP. Research suggests that CRP > 10 mg/L indicates acute inflammation (Ridker, 2003) and may not be representative of average baseline level of inflammation. Because of this, analyses were conducted with the full sample first, and sensitivity analyses were then conducted with individuals with CRP values > 10 mg/L (n=33) removed.

4.0 PRIMARY DATA ANALYSES

4.1 DESCRIPTIVE STATISTICS

Continuous predictor and dependent variables were tested for normality of distribution. CRP was normalized using natural log transformation, and AHI was normalized using square root transformation. Descriptive statistics [mean (s.d.) or n (%)] were first run on the full sample for the 7 variable classes identified in our measures: 1) demographic, 2) physiological, 3) health behavior, 4) psychological, 5) PSG-assessed sleep, 6) self-reported sleep, and 7) snoring variables.

4.2 CORRELATES OF OBJECTIVE AND SUBJECTIVE SNORING

Few studies have included both objective and subjective measures of snoring, so both measures were used to characterize our sample of midlife women. We examined snoring group for each of the 7 classes of variables. One-way analysis of variance (ANOVA) or chi-square tests were conducted to test for overall differences between the 3 objective snoring groups (Absent, Simple Snorers, SDB). Identical comparisons were conducted to test for overall differences between the 4 subjective snoring groups (Never, Don't Know, Infrequent, Frequent). For analyses with

significant omnibus F-statistics ($p<0.05$), post-hoc Tukey's least significant differences (LSD) tests were run to identify the nature of the group differences.

4.3 MAIN MODELS

Candidate covariates selected *a priori* for inclusion in analyses were age, race, absolute value of days between blood draw and sleep study night, use of medications that affect sleep, cigarette and alcohol use, BMI, and menopausal status. All covariates were selected on the basis of established associations with sleep disordered breathing, snoring, or CRP. While total average cigarettes was initially selected as the smoking covariate, it was not significantly correlated with either SI or CRP. However, passive smoking exposure was significantly associated with both variables, and was included as a covariate. All covariates were found to be significantly correlated with either snoring index (SI) or CRP in bivariate correlation analyses ($p<0.05$).

We used three main models to test associations in the full sample between CRP and a) snoring index (SI), b) objective snoring group, and c) subjective snoring group. To determine whether SI was associated with CRP and whether this relationship was dependent on AHI, we used multiple linear regression to test the main effects of SI and AHI as well as the interaction between SI and AHI on CRP. SI and AHI were both centered prior to creating the interaction term. Covariates were entered into the model first, SI and AHI were entered next, and the SI by AHI interaction variable was added third. To conduct the sensitivity analysis, we ommitted all participants with CRP>10 mg/L before running the multiple linear regression model again. To evaluate differences in CRP levels between the three objective snoring groups (Absent, SS, and

SDB) and between the four subjective snoring groups (Never, Don't Know, Infrequent, Frequent), analysis of covariance (ANCOVA) was used.

Two sub-analyses were conducted to test exploratory hypotheses. First, given the hypothesized particular significance of snoring in postmenopausal women, we used multiple linear regression to test the main effect of SI, main effect of AHI, and SI by AHI interaction on CRP in postmenopausal women only (n=41). Second, given the higher prevalence of self-reported snoring and SDB in African American women reported elsewhere (O'Connor et al., 2003; Redline et al., 1997; Scharf et al., 2004; Ram et al., 2010), we used multiple linear regression to test whether race moderated the relationship between SI and CRP. Race was dummy coded with the Caucasian group as the referent group and African American as the comparison group. Covariates were entered into the model first, followed by SI and dummy-coded race, then the SI by race interaction term. We then calculated and plotted simple regression equations for Caucasian and African American groups and tested whether the simple slopes were significantly different from zero and from each other.

5.0 RESULTS

5.1 CORRELATES OF OBJECTIVE SNORING

A total of 171 Caucasian and 138 African American women participated in the SWAN Sleep Study. Of these, 133 Caucasian and 108 African American participants (total: 241, mean age 51.95 ± 2.22 years) had usable apnea screening night PSG data and comprise the objective snoring sample used in analyses. Table 3 summarizes sample characteristics as a function of objective snoring group category.

Table 3. Characterization of Midlife Women by Objective Snoring Group Designation.

	Objective Snoring Group					
	Absent (A) (n=31)	***Simple Snorers (SS)*** (n=82)	***Sleep Disordered Breathing (SDB)*** (n=128)	***Total*** (n=241)	***Post-Hoc Group Differences***	***Overall p***
Demographic Variables	**Mean (S.D.) or n (%)**	**Mean (S.D.) or n (%)**	**Mean (S.D.) or n (%)**	**Mean (S.D.) or n (%)**		
Age (years)	51.49 (2.10)	51.61 (1.92)	52.28 (2.38)	51.95 (2.22)*	SS < SDB	0.045
Race						n.s.
Caucasian (%)	19 (14.3%)	43 (32.3%)	71 (53.4%)	133		
African American (%)	12 (11.1%)	39 (36.1%)	57 (52.8%)	108		
Menopausal Status						n.s.
Premenopause / Early peri-menopause (%)	21 (67.7%)	58 (71.6%)	75 (58.6%)	154 (64.2%)		
Late peri-menopause (%)	5 (16.1%)	16 (19.8%)	24 (18.8%)	45 (18.8%)		
Postmenopause (%)	5 (16.1%)	7 (8.6%)	29 (22.7%)	41 (17.1%)		
Hormone replacement therapy use (%)	4 (12.9%)	2 (2.5%)	7 (5.5%)	13 (5.4%)		n.s.
Employment status						n.s.
Not employed (%)	4 (12.9%)	19 (23.5%)	21 (16.4%)	44 (18.3%)		
Any employment (%)	27 (87.1%)	62 (76.5%)	107 (83.6%)	196 (81.7%)		
Education level						n.s.
HS degree/some college (%)	17 (54.8%)	40 (50.0%)	65 (52.0%)	122 (51.7%)		
College/postgraduate degree (%)	14 (45.2%)	40 (50.0%)	60 (48.0%)	114 (48.3%)		
Income						n.s.
< $10,000 (%)	0 (0%)	4 (4.9%)	6 (4.7%)	10 (4.2%)		
$10,000 - 19,999 (%)	2 (6.5%)	3 (3.7%)	9 (7%)	14 (5.8%)		
$20,000 - 34,999 (%)	3 (9.7%)	8 (9.9%)	15 (11.7%)	26 (10.8%)		
$35,000 - 49,999 (%)	6 (19.4%)	15 (18.5%)	15 (11.7%)	36 (15%)		
$50,000 - 74,999 (%)	3 (9.7%)	18 (22.2%)	31 (24.2%)	52 (21.7%)		

	Objective Snoring Group					
	Absent (A) (*n*=31)	***Simple Snorers (SS)*** (*n*=82)	***Sleep Disordered Breathing (SDB)*** (*n*=128)	***Total*** (*n*=241)	***Post-Hoc Group Differences***	***Overall p***
$75,000 - 99,999 (%)	5 (16.1%)	14 (17.3%)	20 (15.6%)	39 (16.2%)		
$100,000 - 149,999 (%)	4 (12.9%)	10 (12.3%)	18 (14.1%)	32 (13.3%)		
> $150,000 (%)	4 (12.9%)	2 (2.5%)	9 (7%)	15 (6.2%)		
Physiological Variables						
Body mass index (BMI) (kg/m2)	25.99 (3.25)	29.61 (5.93)	34.40 (8.51)	31.69 (7.82)**	A < SS < SDB	0.0001
Waist-to-hip ratio	0.795 (0.065)	0.828 (0.064)	0.849 (0.077)	0.835 (0.073)**	A < SS < SDB	0.001
Neck circumference (cm)	34.03 (2.48)	35.80 (2.71)	38.01 (4.08)	36.73 (3.76)**	A < SS < SDB	0.0001
Apnea-hypopnea index (AHI)	2.46 (1.31)	2.49 (1.51)	18.83 (1.55)	11.20 (15.21)**	A & SS < SDB	0.0001
Systolic blood pressure (mm/Hg)	111.97 (13.08)	119.70 (17.35)	123.70 (17.22)	120.83 (17.17)**	A < SS & SDB	0.002
Diastolic blood pressure (mm/Hg)	72.84 (8.11)	73.06 (9.71)	74.96 (11.31)	74.04 (10.43)		n.s.
Vasomotor symptoms$^{\Delta}$	39.63 (33.52)	29.70 (32.14)	33.65 (35.62)	33.10 (34.20)		n.s.
No. metabolic syndrome criteria met	0.77 (0.97)	1.56 (1.25)	2.11 (1.47)	1.76 (1.41)**	A < SS < SDB	0.0001
Meets criteria for metabolic syndrome diagnosis (%)	3 (11.5%)	20 (28.6%)	49 (45.0%)	72 (35.1%)**	A < SDB*	0.002
Biomarkers						
Average CRP values (mg/dL)	1.89 (1.65)	3.96 (5.20)	6.94 (8.08)	5.25 (6.87)**	A & SS < SDB	0.0001
Glucose (mg/dL)	84.13 (6.57)	88.56 (15.20)	98.60 (35.69)	93.30 (28.09)**	A & SS < SDB	0.006
Insulin (ulU/mL)	9.55 (3.62)	13.22 (12.86)	17.87 (14.71)	15.29 (13.52)**	A & SS < SDB	0.004
Physician-Reported Diagnosis						
Diabetes (%)	1 (3.2%)	3 (3.7%)	10 (7.8%)	14 (5.8%)		n.s.
High blood pressure (%)	6 (19.4%)	5 (6.2%)	36 (28.1%)	47 (19.6%)**	SS < SDB	0.001
High cholesterol (%)	9 (29.0%)	5 (6.3%)	25 (19.8%)	39 (16.5%)**	A > SS; SS < SDB	0.005
Stroke (%)	0 (0%)	0 (0%)	1 (0.8%)	1 (0.4%)		n.s.
Heart attack (%)	0 (0%)	2 (2.5%)	0 (0%)	2 (0.8%)		n.s.

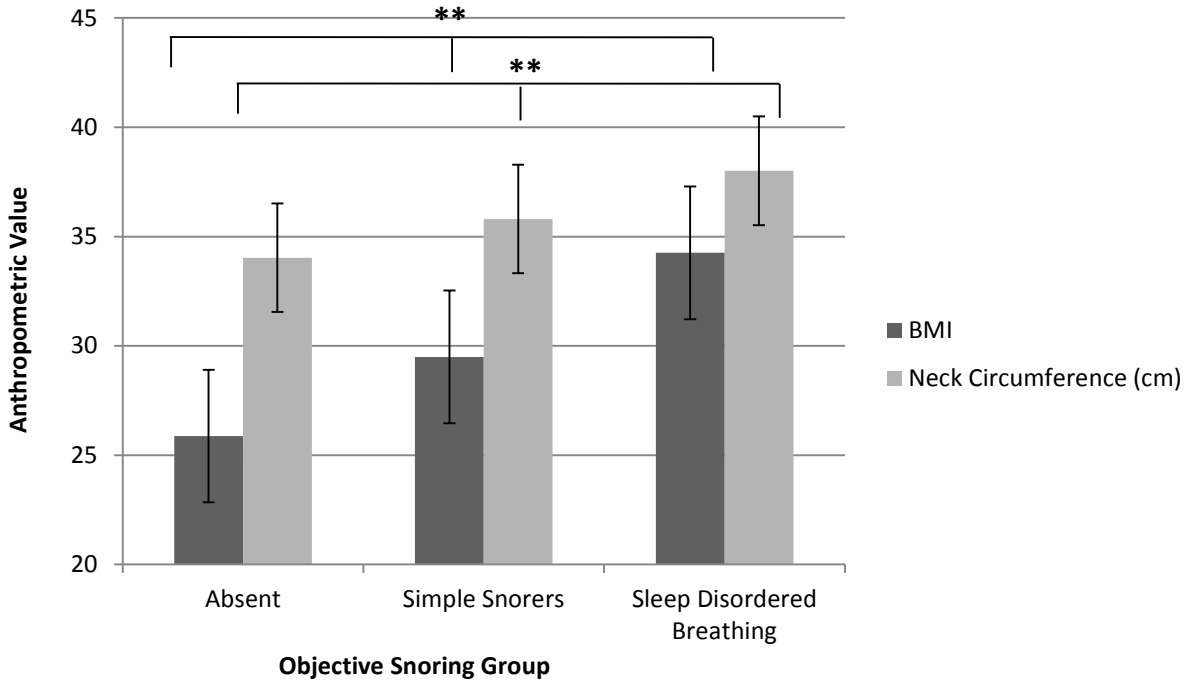
	Objective Snoring Group					
	Absent (A) (*n*=31)	***Simple Snorers (SS)*** (*n*=82)	***Sleep Disordered Breathing (SDB)*** (*n*=128)	***Total*** (*n*=241)	***Post-Hoc Group Differences***	***Overall p***
Sum of all physician-reported health diagnoses (scale 0-10)	0.807 (1.05)	0.482 (0.084)	0.930 (1.102)	0.763 (1.03)**	SS < SDB	0.008
General health						n.s.
Excellent/very good/good (%)	27 (87.1%)	73 (90.1%)	109 (85.2%)	209 (87.1%)		
Fair / poor (%)	4 (12.9%)	8 (9.9%)	19 (14.8%)	31 (12.9%)		
Health Behavior Variables						
Exercise$^{\Delta}$	53.43 (30.62)	55.98 (31.17)	49.26 (35.18)	52.09 (33.30)		n.s.
Caffeine‡	2.05 (1.60)	1.48 (1.35)	1.58 (1.29)	1.61 (1.36)		n.s.
Alcohol‡	0.49 (0.62)	0.38 (0.61)	0.22 (0.43)	0.31 (0.53)*	A & SS > SDB	0.016
Cigarettes‡	0.46 (1.72)	0.92 (2.88)	1.09 (3.18)	0.95 (2.92)		n.s.
Sleep medication usage$^{\Delta}$	39.26 (49.09)	23.51 (41.41)	23.05 (40.54)	25.32 (42.19)		n.s.
Passive smoking exposure						n.s.
0 person-hours (%)	64.50%	37.20%	48.00%	46.60%		
1-4 person-hours (%)	25.80%	33.30%	29.60%	30.30%		
>5 person-hours (%)	9.70%	29.50%	22.40%	23.10%		
Psychological Variables						
IDS	4.62 (2.58)	4.53 (2.74)	5.41 (3.17)	5.01 (2.98)		n.s.
IDS no sleep variables	2.52 (2.29)	2.54 (2.54)	3.32 (2.96)	2.96 (2.76)		n.s.
Perceived Stress Scale	3.66 (2.66)	3.64 (2.39)	4.20 (2.85)	3.94 (2.68)		n.s.
State/Trait Anxiety Inventory	15.70 (4.95)	14.81 (3.99)	15.94 (2.93)	15.53 (4.65)		n.s.
Social support scale (scale 0-16)	13.06 (2.95)	13.07 (3.17)	13.27 (2.81)	13.18 (2.94)		n.s.
Bodily pain scale	72.10 (17.54)	72.19 (19.68)	67.77 (22.12)	69.82 (20.81)		n.s.
Quality of life scale (scale 0-10)	7.74 (1.75)	7.68 (1.38)	7.66 (1.65)	7.68 (1.57)		n.s.
Difficulty paying for basics						n.s.
Not hard at all (%)	21 (67.7%)	53 (66.2%)	90 (70.3%)	164 (68.6%)		
Somewhat / very hard (%)	10 (32.3%)	27 (33.8%)	38 (29.7%)	75 (31.4%)		
PSG-assessed Sleep Variables						
Sleep latency (min.)	18.17 (12.60)	21.07 (19.87)	23.34 (21.16)	21.91 (19.83)		n.s.

	Objective Snoring Group					
	Absent (A) (n=31)	***Simple Snorers (SS)*** (n=82)	***Sleep Disordered Breathing (SDB)*** (n=128)	***Total*** (n=241)	***Post-Hoc Group Differences***	***Overall p***
Wake after sleep onset (min.)	47.76 (21.17)	57.23 (34.56)	60.51 (35.33)	57.76 (33.72)		n.s.
Total sleep time (min.)	389.24 (58.37)	372.71 (63.88)	366.30 (55.06)	371.43 (58.83)		n.s.
Sleep efficiency (%)	85.56 (5.38)	82.62 (9.09)	81.55 (8.22)	82.43 (8.30)	A < SDB	0.052
Stage 1 sleep (%)	6.04 (3.09)	7.34 (5.62)	8.12 (6.19)	7.59 (5.71)		n.s.
Stage 2 sleep (%)	66.85 (6.56)	64.99 (7.04)	64.44 (8.43)	64.94 (7.77)		n.s.
Delta sleep (%)	3.96 (4.30)	3.57 (4.28)	3.58 (4.52)	3.63 (4.40)		n.s.
REM sleep (%)	23.15 (5.02)	24.09 (4.60)	23.85 (4.71)	23.84 (4.70)		n.s.
No. of awakenings	19.86 (5.88)	20.35 (7.65)	19.74 (6.63)	19.96 (6.89)		n.s.
REM latency minus awake time (min.)	81.12 (39.80)	71.76 (28.45)	70.70 (37.49)	72.40 (35.05)		n.s.
Self-Reported Sleep Variables						
Pittsburgh Sleep Quality Index (PSQI)	5.74 (3.05)	5.11 (2.81)	6.18 (3.35)	5.76 (3.17)	SS < SDB	0.06
Epworth Sleepiness Scale (ESS)	7.86 (4.59)	6.91 (3.77)	8.09 (4.22)	7.66 (4.14)		n.s.
Snoring Variables						
Snoring index	0.036 (0.077)	0.668 (0.156)	0.658 (0.225)	0.581 (0.282)**	A < SS & SDB	0.0001
Snoring index – NREM	0.025 (0.092)	0.507 (0.259)	0.526 (0.273)	0.486 (0.288)**	A < SS & SDB	0.0001
Snoring index - REM	0.040 (0.080)	0.670 (0.192)	0.676 (0.231)	0.599 (0.289)**	A < SS & SDB	0.0001
Total snore count	10.23 (26.33)	719.82 (761.18)	1266.13 (1113.53)	918.7 (1017.97)**	A < SS < SDB	0.0001
Total snore count - NREM	7.61 (12.80)	608.57 (607.00)	1088.19 (954.94)	794.58 (863.27)**	A < SS < SDB	0.0001
Total snore count - REM	7.43 (21.79)	128.48 (220.26)	198.87 (216.30)	161.41 (216.33)**	A < SS < SDB	0.002
Self-reported snoring group						
Don't Know	6 (20.0%)	30 (38.0%)	26 (21.0%)	62 (26.6%)		0.0001
Never	19 (63.3%)	29 (36.7%)	40 (32.3%)	88 (37.8%)		
Infrequent (<3x/wk)	3 (10.0%)	14 (17.7%)	26 (21.0%)	43 (18.5%)		

	Objective Snoring Group					
	Absent (A) (n=31)	***Simple Snorers (SS)*** (n=82)	***Sleep Disordered Breathing (SDB)*** (n=128)	***Total*** (n=241)	***Post-Hoc Group Differences***	***Overall p***
Frequent (≥3x/wk)	2 (6.7%)	6 (7.6%)	32 (25.8%)	40 (17.2%)		

Notes: *p<0.05; **p<0.01; ǂmean daily consumption reported across days of study; ᐞpercent of days any reported across study

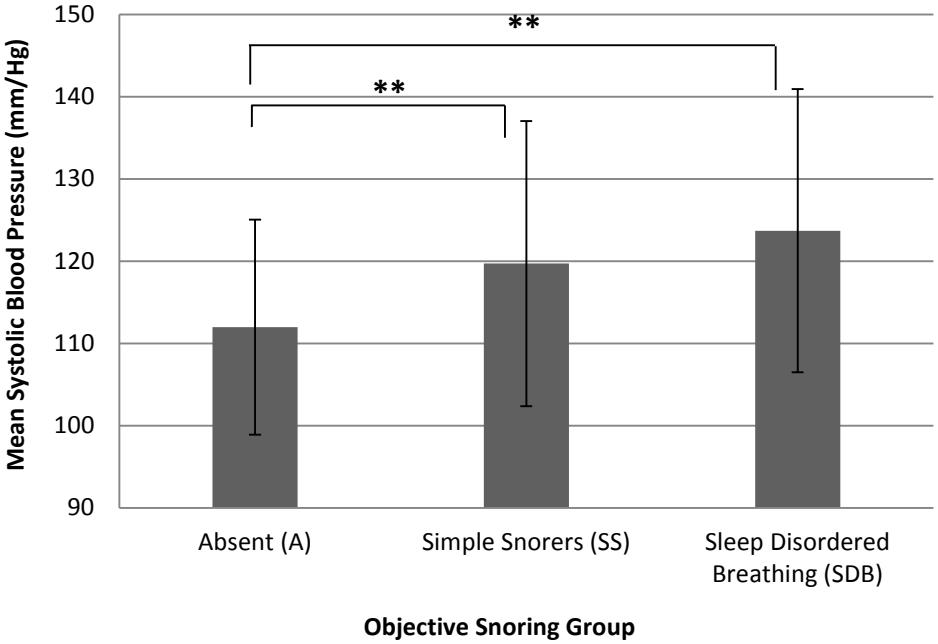
As expected, one-way ANOVAs revealed that the groups differed significantly on all anthropometric risk factors. Tukey's LSD post-hoc analyses confirmed that the groups differed in a stepwise fashion, such that the Absent group had the lowest mean values for BMI, waist-hip ratio, and neck circumference, followed by the Simple Snorers and then the SDB group (*p*'s<0.001, Figure 4).



Note: **p<0.01. All group means are significantly different from each other within each anthropometric measure.

Figure 4. Body Mass Index (BMI) and Neck Circumference (cm) by Objective Snoring Group.

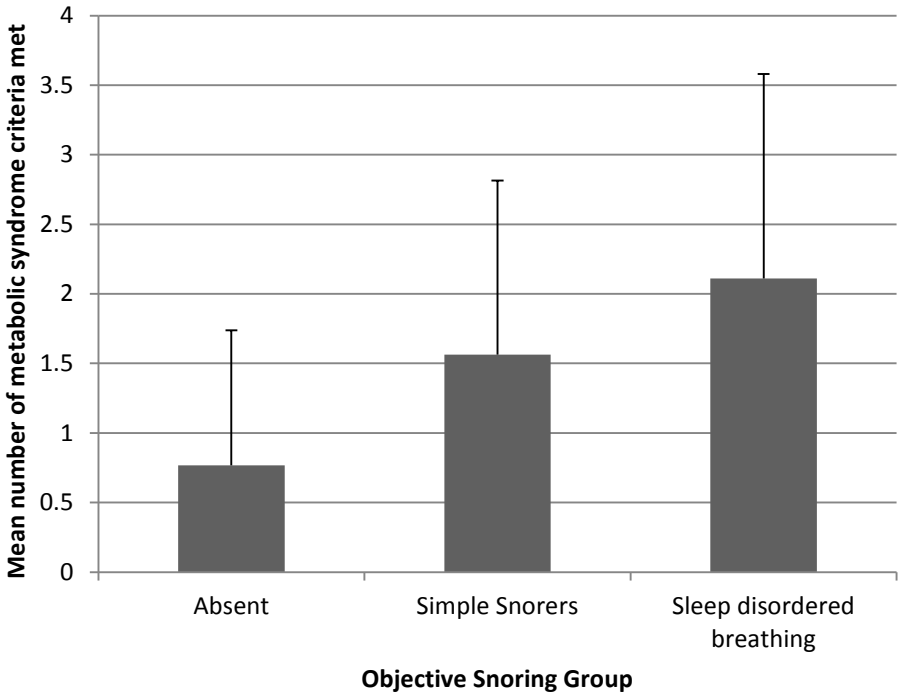
The groups also differed on systolic blood pressure (SBP; p=0.002). Post-hoc analysis showed that both the SS and SDB groups had significantly higher SBP than the Absent group (p's<0.01, Figure 5).



Note: **p<0.01.

Figure 5. Mean Systolic Blood Pressure (mm/Hg) by Objective Snoring Group.

Groups also differed on measures of metabolic risk, where the Absent group met significantly fewer criteria for the metabolic syndrome than either the SS or SDB groups (p<0.0001). Nearly one-third of the SS group (29%) and nearly one-half of the SDB group (45%) met criteria for metabolic syndrome diagnosis, significantly greater percentages than in the Absent group (p=0.002). The SS and SDB groups also met significantly greater number of metabolic syndrome criteria than the Absent group (p=0.0001, Figure 6).



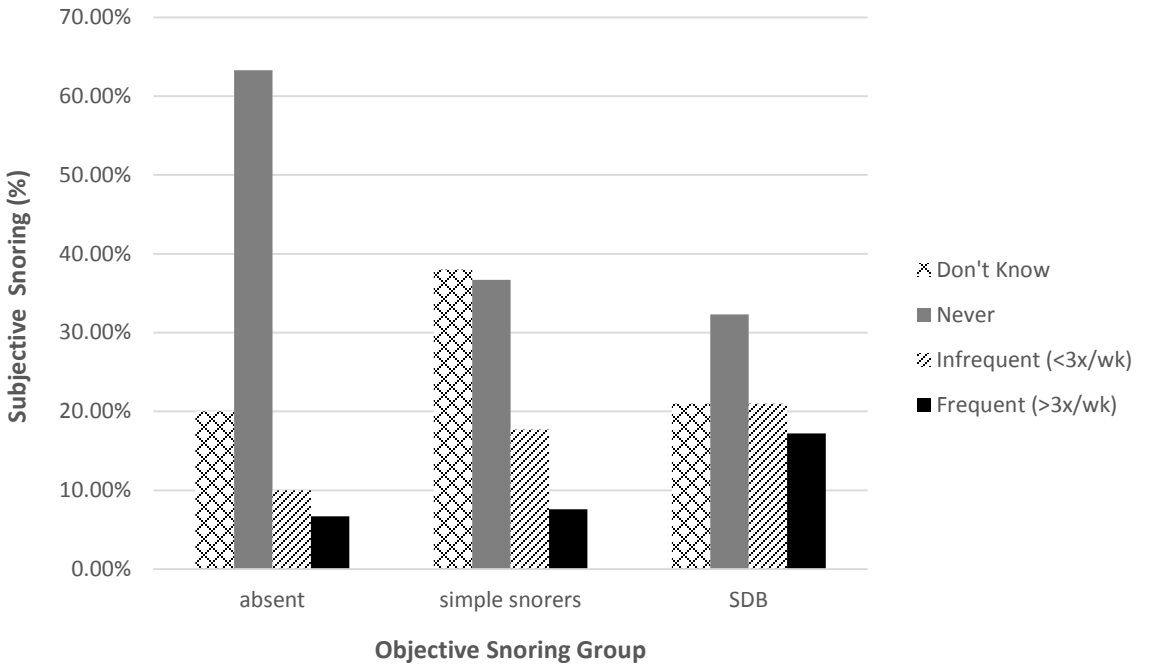
Note: **p<0.01.

Figure 6. Mean Number of Metabolic Syndrome Criteria Met by Objective Snoring Group.

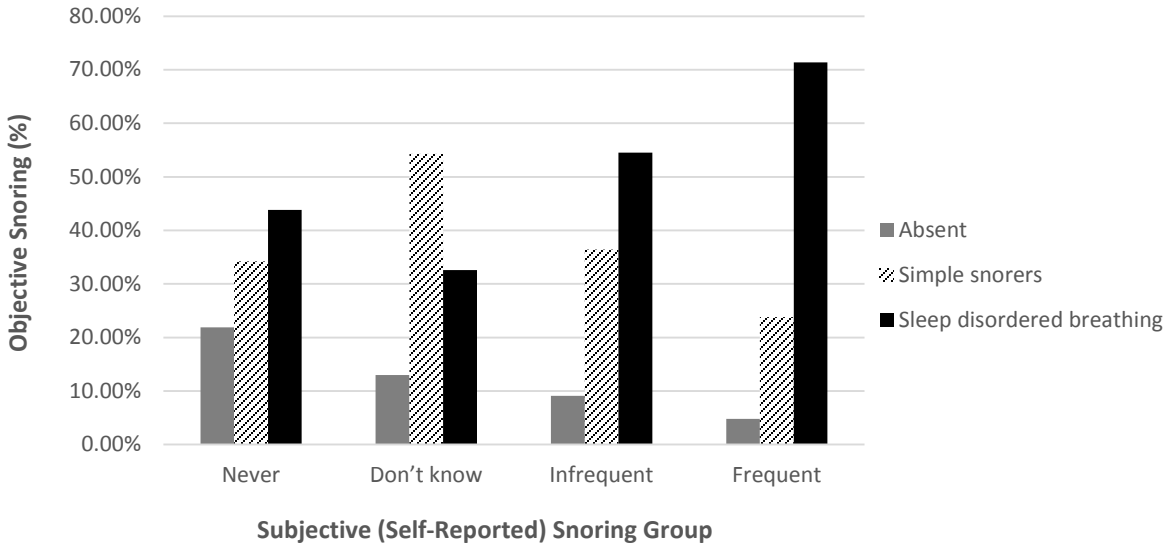
There were significant differences in key cardiovascular and cardiometabolic biomarker levels between the groups as well, with the SDB group showing the highest mean levels of CRP (p=0.0001), fasting glucose (p=0.006), and insulin (p=0.004). However, the Absent and SDB groups were more likely to have a physician-reported diagnosis of high blood pressure (p=0.001) or high cholesterol (p=0.005), compared to Simple Snorers.

There were few noteworthy differences among the groups for health behaviors, psychological variables, or PSG-assessed or self-reported sleep variables. The groups did not differ on menopausal status (X^2=7.26, p=0.12) or indices of socioeconomic status (p's>0.05). As expected, there were significant differences in the distribution of self-reported snoring frequency by objective snoring group designation (X^2=25.17, p<0.0001). Figure 7 shows that 53.3% of the

women who met criteria for SDB and almost 75% of simple snorers endorsed never snoring or not knowing that they snore. Only 7.6% of simple snorers endorsed clinically frequent snoring, despite the fact that these women snored 67% of their night on average, and had a mean of 720 (± 761) scored snoring events on one night of sleep.



(A)



(B)

Figure 7. (A) Objective Snoring Group by Subjective Snoring Group Percentage. (B) Subjective Snoring Group by Objective Snoring Group Percentage.

5.2 CORRELATES OF SUBJECTIVE SNORING

Of the 309 total Caucasian and African American women who participated in the SWAN Sleep Study, 300 of them had usable self-reported snoring data and were included in subjective snoring analyses (mean age 52.07 ± 2.13 years). The samples included in the objective and subjective snoring characterizations did not significantly differ from each other on key variables (*p*'s>0.05). Table 4 summarizes sample characteristics as a function of subjective snoring group category.

Table 4. Characterization of Midlife Women by Subjective Snoring Group Designation.

	Subjective Snoring Group						
	Never (N) (n=119)	***Don't Know (DK)*** (n=76)	***Infrequent (I)*** (n=54)	***Frequent (F)*** (n=51)	***Total*** (n=300)	***Post-Hoc Group Differences***	***Overall p***
Demographic Variables	Mean (S.D.) or n (%)	Mean (S.D.) or n (%)	Mean (S.D.) or n (%)	Mean (S.D.) or n (%)	Mean (S.D.) or n (%)		
Age (years)	52.11 (2.02)	51.82 (2.19)	52.25 (2.36)	52.15 (2.07)	52.07 (2.13)		n.s.
Race							0.04
Caucasian (%)	76 (45.2%)	36 (21.4%)	33 (19.6%)	23 (13.7%)	168 (56%)		
African American (%)*	43 (32.6%)	40 (30.3%)	21 (15.9%)	28 (21.2%)	132 (44%)		
Menopausal Status							n.s.
Premenopause / Early menopause	78 (66.1%)	47 (61.8%)	33 (61.1%)		184 (61.5%)		
Late peri-menopause (%)	20 (16.9%)	14 (18.4%)	12 (22.2%)		59 (19.7%)		
Postmenopause (%)	20 (16.9%)	15 (19.7%)	9 (16.7%)		56 (18.7%)		
Hormone replacement therapy use (%)	8 (6.8%)	4 (5.3%)	1 (1.9%)	2 (3.9%)	15 (5.0%)		n.s.
Employment status							n.s.
Not employed (%)	18 (15.3%)	18 (23.7%)	9 (16.7%)	10 (19.6%)	55 (18.4%)		
Any employment (%)	100 (84.7%)	58 (76.3%)	45 (83.3%)	41 (80.4%)	244 (81.6%)		
Education level							n.s.
HS degree/some college (%)	55 (47.0%)	45 (60.0%)	24 (45.3%)	24 (49.0%)	148 (50.3%)		
College/postgraduate degree (%)	62 (53.0%)	30 (40.0%)	29 (54.7%)	25 (51.0%)	146 (49.7%)		
Income							n.s.
< $10,000 (%)	10 (8.5%)	7 (9.2%)	3 (5.6%)	1 (2.0%)	21 (7.0%)		
$10,000 - 19,999 (%)	3 (2.5%)	4 (5.3%)	2 (2.7%)	1 (2.0%)	10 (3.3%)		
$20,000 - 34,999 (%)	3 (2.5%)	5 (6.6%)	4 (7.4%)	5 (9.8%)	17 (5.7%)		
$35,000 - 49,999 (%)	9 (7.6%)	11 (14.5%)	1 (1.9%)	9 (17.6%)	30 (10.0%)		
$50,000 - 74,999 (%)	17 (14.4%)	10 (13.2%)	11 (20.4%)	5 (9.8%)	43 (14.4%)		

	Subjective Snoring Group						
	Never (N) (*n*=119)	***Don't Know (DK)*** (*n*=76)	***Infrequent (I)*** (*n*=54)	***Frequent (F)*** (*n*=51)	***Total*** (*n*=300)	***Post-Hoc Group Differences***	***Overall p***
$75,000 - 99,999 (%)	26 (22.0%)	17 (22.4%)	9 (16.7%)	14 (27.5%)	66 (22.1%)		
$100,000 - 149,999 (%)	22 (18.6%)	12 (15.8%)	9 (16.7%)	6 (11.8%)	49 (16.4%)		
> $150,000 (%)	17 (14.4%)	6 (7.9%)	13 (24.1%)	8 (15.7%)	44 (14.7%)		
Physiological Variables							
Body mass index (kg/m2)**	29.11 (6.82)	30.29 (5.68)	33.17 (8.56)	36.13 (9.70)	31.34 (7.87)	N, DK < I, F I < F	0.0001
Waist-to-hip ratio**	0.82 (0.07)	0.83 (0.07)	0.84 (0.08)	0.86 (0.08)	0.83 (0.73)	N, DK < F	0.01
Neck circumference (cm)**	35.15 (3.34)	35.93 (2.72)	37.75 (4.00)	39.04 (4.30)	36.47 (3.79)	N, DK < I, F	0.0001
Apnea-hypopnea index (AHI)**	6.35 (6.48)	5.98 (5.84)	11.89 (12.09)	28.62 (29.13)	11.02 (16.12)	N, DK < I, F I < F	0.0001
Systolic blood pressure (mm/Hg)**	116.76 (15.98)	122.74 (18.50)	117.91 (16.39)	128.34 (17.96)	120.47 (17.52)	N < DK, F I < F	0.0001
Diastolic blood pressure (mm/Hg)	72.38 (9.58)	75.38 (11.48)	73.10 (8.68)	76.12 (10.84)	73.91 (10.23)		n.s.
Vasomotor symptoms$^{\Delta}$	29.01 (35.54)	38.46 (36.53)	33.74 (31.94)	38.42 (35.72)	33.81 (34.10)		n.s.
No. metabolic syndrome criteria met	0.72 (1.02)	0.83 (1.17)	1.00 (1.00)	0.50 (0.71)	0.76 (0.99)		n.s.
Meets criteria for metabolic syndrome diagnosis (%)	1 (16.7%)	2 (13.3%)	0 (0.0%)	0 (0.0%)	3 (12.0%)		n.s.
Biomarkers							
Average CRP (mg/dL)**	3.76 (5.18)	4.05 (4.63)	5.74 (6.70)	10.25 (10.31)	5.24 (6.81)	N,DK,I < F	0.0001
Glucose (mg/dL)**	87.23 (12.82)	88.70 (15.59)	92.26 (16.46)	109.46 (50.56)	92.30 (25.77)	N,DK,I < F	0.0001
Insulin (ulU/mL)**	11.63 (10.59)	13.35 (10.41)	18.32 (15.47)	22.51 (16.87)	15.18 (13.37)	N,DK < I,F	0.0001
Health Behavior Variables							
Exercise$^{\Delta}$	59.11 (31.80)	55.76 (32.57)	53.64 (31.51)	51.98 (35.25)	56.08 (32.48)		n.s.
Caffeine‡	1.76 (1.39)	1.52 (1.28)	1.56 (1.19)	1.56 (1.41)	1.63 (1.33)		n.s.
Alcohol‡	0.34 (0.51)	0.34 (0.63)	0.31 (0.50)	0.14 (0.30)	0.30 (0.52)		n.s.
Cigarettes‡	0.66 (2.43)	1.09 (3.38)	0.94 (2.44)	1.44 (4.03)	0.95 (3.00)		n.s.
Sleep medication usage$^{\Delta}$	23.55 (41.11)	32.40 (46.18)	21.38 (40.23)	29.66 (45.07)	26.43 (42.97)		n.s.

	Subjective Snoring Group						
	Never (N) (*n*=119)	***Don't Know (DK)*** (*n*=76)	***Infrequent (I)*** (*n*=54)	***Frequent (F)*** (*n*=51)	***Total*** (*n*=300)	***Post-Hoc Group Differences***	***Overall p***
Passive smoking exposure							n.s.
0 person-hours (%)	63 (54.8%)	29 (38.7%)	24 (45.3%)	18 (38.3%)	134 (46.2%)		
1-4 person-hours (%)	28 (24.3%)	25 (33.3%)	16 (30.2%)	19 (40.4%)	88 (30.3%)		
>5 person-hours (%)	24 (20.9%)	21 (28.0%)	13 (24.5%)	10 (21.3%)	68 (23.4%)		
Psychological Variables							
IDS**	4.33 (2.48)	4.89 (2.90)	4.98 (2.75)	5.93 (3.43)	4.86 (2.86)	N & DK < F	0.009
IDS—no sleep variables*	2.35 (2.65)	2.89 (2.66)	2.94 (2.45)	3.80 (3.28)	2.84 (2.63)	N < F	0.012
Perceived Stress Scale	3.55 (2.74)	4.23 (2.76)	3.63 (2.57)	4.31 (2.52)	3.87 (2.69)		n.s.
State/Trait Anxiety Inventory	15.04 (4.41)	15.71 (4.83)	15.36 (4.15)	16.11 (4.93)	15.45 (4.56)		n.s.
Social support scale (scale 0-16)	13.60 (2.79)	12.97 (2.89)	13.37 (2.64)	13.41 (2.84)	13.37 (2.80)		n.s.
Bodily pain scale	72.67 (18.12)	74.01 (19.60)	67.02 (22.12)	66.25 (22.69)	70.90 (20.23)		n.s.
Quality of life scale (scale 0-10)	7.64 (1.67)	7.67 (1.61)	8.06 (1.11)	7.57 (1.64)	7.71 (1.56)		n.s.
Difficulty paying for basics							n.s.
Not hard at all (%)	89 (75.4%)	49 (64.5%)	39 (73.6%)	35 (70.0%)	212 (71.4%)		
Somewhat / very hard (%)	29 (24.6%)	27 (35.5%)	14 (26.4%)	15 (30.0%)	85 (28.6%)		
PSG-assessed Sleep Variables							
Sleep latency (min.)	22.56 (22.20)	20.89 (15.40)	23.32 (26.06)	23.74 (21.24)	22.47 (21.23)		n.s.
Wake after sleep onset (min.)	52.41 (27.88)	63.07 (40.65)	54.40 (37.52)	55.60 (28.29)	56.02 (33.53)		n.s.
Total sleep time (min.)	373.09 (57.35)	376.35 (57.41)	362.94 (57.00)	372.04 (55.93)	371.91 (56.87)		n.s.
Sleep efficiency (%)	83.16 (8.72)	82.30 (7.49)	82.53 (9.04)	82.40 (7.53)	82.70 (8.26)		n.s.
Stage 1 sleep (%)	7.60 (5.72)	6.81 (3.71)	7.76 (7.24)	8.06 (5.79)	7.51 (5.61)		n.s.
Stage 2 sleep (%)	64.20 (7.37)	65.56 (6.69)	64.92 (7.43)	66.70 (7.44)	65.10 (7.24)		n.s.
Delta sleep (%)	3.63 (4.51)	3.67 (5.14)	3.70 (3.83)	2.95 (3.42)	3.54 (4.39)		n.s.
REM sleep (%)*	24.58 (4.61)	23.96 (5.26)	23.62 (4.50)	22.29 (4.55)	23.86 (4.80)	N > F	0.04
No. of awakenings	19.46 (6.44)	20.61 (7.47)	19.72 (7.66)	20.40 (6.66)	19.96 (6.96)		n.s.
REM latency minus awake time (min.)	68.56 (32.68)	77.60 (33.57)	72.98 (33.88)	78.20 (43.70)	73.30 (35.29)		n.s.

	Subjective Snoring Group						
	Never (N) (*n*=119)	***Don't Know (DK)*** (*n*=76)	***Infrequent (I)*** (*n*=54)	***Frequent (F)*** (*n*=51)	***Total*** (*n*=300)	***Post-Hoc Group Differences***	***Overall p***
Self-Reported Sleep Variables							
Pittsburgh Sleep Quality Index (PSQI)*	5.10 (2.97)	6.03 (3.22)	6.34 (3.39)	6.41 (3.17)	5.78 (3.18)	N < DK, I, F	0.024
Epworth Sleepiness Scale (ESS)**	6.76 (3.69)	6.87 (3.82)	7.61 (4.11)	9.69 (4.74)	7.44 (4.12)	N,DK,I < F	0.0001
Snoring Variables							
Snoring index**	0.53 (0.32)	0.53 (0.27)	0.65 (0.25)	0.69 (0.20)	0.58 (0.28)	N,DK < I,F	0.002
Snoring index - NREM**	0.55 (0.32)	0.54 (0.28)	0.67 (0.26)	0.71 (0.21)	0.60 (0.29)	N,DK < I,F	0.003
Snoring index – REM**	0.44 (0.30)	0.46 (0.31)	0.46 (0.24)	0.63 (0.22)	0.48 (0.29)	N, DK, I < F	0.008
Total snore count**	619.97 (764.5)	638.38 (813.25)	1223.91 (1101.6)	1581.62 (1254.96)	901.42 (1014.09)	N,DK < I,F	0.0001
Total snore count – NREM**	547.30 (633.61)	522.21 (656.32)	1092.49 (952.72)	1334.00 (1087.27)	781.04 (861.74)	N,DK < I,F	0.0001
Total snore count – REM**	113.08 (179.45)	145.94 (210.08)	144.90 (199.95)	288.89 (251.20)	159.48 (213.55)	N, DK, I < F	0.001
*Objective snoring group**						-	0.024
Absent	16 (21.9%)	6 (13.0%)	3 (9.1%)	1 (4.8%)	26 (15.0%)		
Simple snorers	25 (34.2%)	25 (54.3%)	12 (36.4%)	5 (23.8%)	67 (38.7%)		
Sleep disordered breathing	32 (43.8%)	15 (32.6%)	18 (54.5%)	15 (71.4%)	80 (46.2%)		

Notes: *$p<0.05$; **$p<0.01$; [ɨ]mean daily consumption reported across days of study; [Δ]percent of days any reported across study.

Compared to Caucasian participants, a smaller percentage of African American participants endorsed never snoring (X^2=8.32, p=0.04, Figure 8).

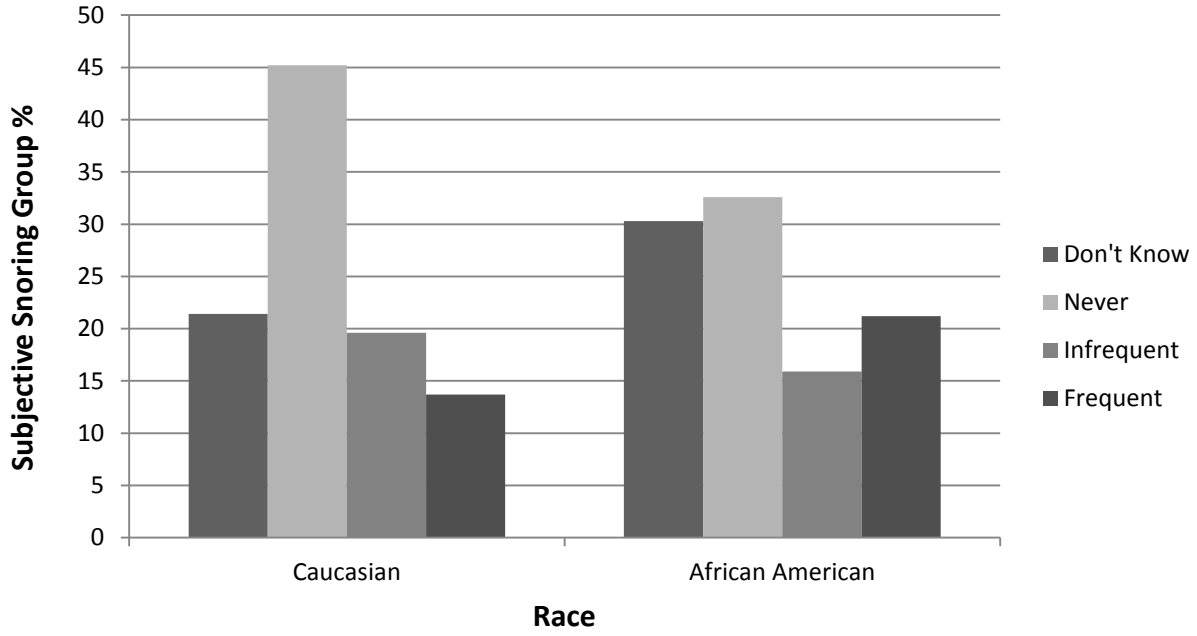


Figure 8. Race Differences in Self-Reported Snoring Frequency.

Using ANOVA, we observed the hypothesized results for anthropometric measures, which were similar to differences found between objective snoring groups. Any snoring was associated with higher BMI (p=0.0001), neck circumference (p=0.0001), and AHI (p=0.0001) compared to Never or Don't Know groups. Post-hoc tests of significant one-way ANOVAs revealed that only frequent snoring was correlated with higher SBP (p=0.0001), CRP (p=0.0001), and fasting glucose (p=0.0001). However, unlike objective snoring, self-reported snoring endorsement was not correlated with metabolic syndrome criteria. There was a trend for Frequent snorers to have a higher physician-reported rate of Type II diabetes (p=0.069).

Compared to the other groups, Frequent snorers also had a higher rate of fair or poor perceived general health (p=0.0001), endorsed more depressive symptoms (p=0.009), and reported greater daytime sleepiness (p=0.0001). REM sleep percentage was the only PSG-assessed sleep variable to differ as a function of subjective snoring group, with Frequent snorers showing significantly less REM sleep than Never snorers (p=0.04).

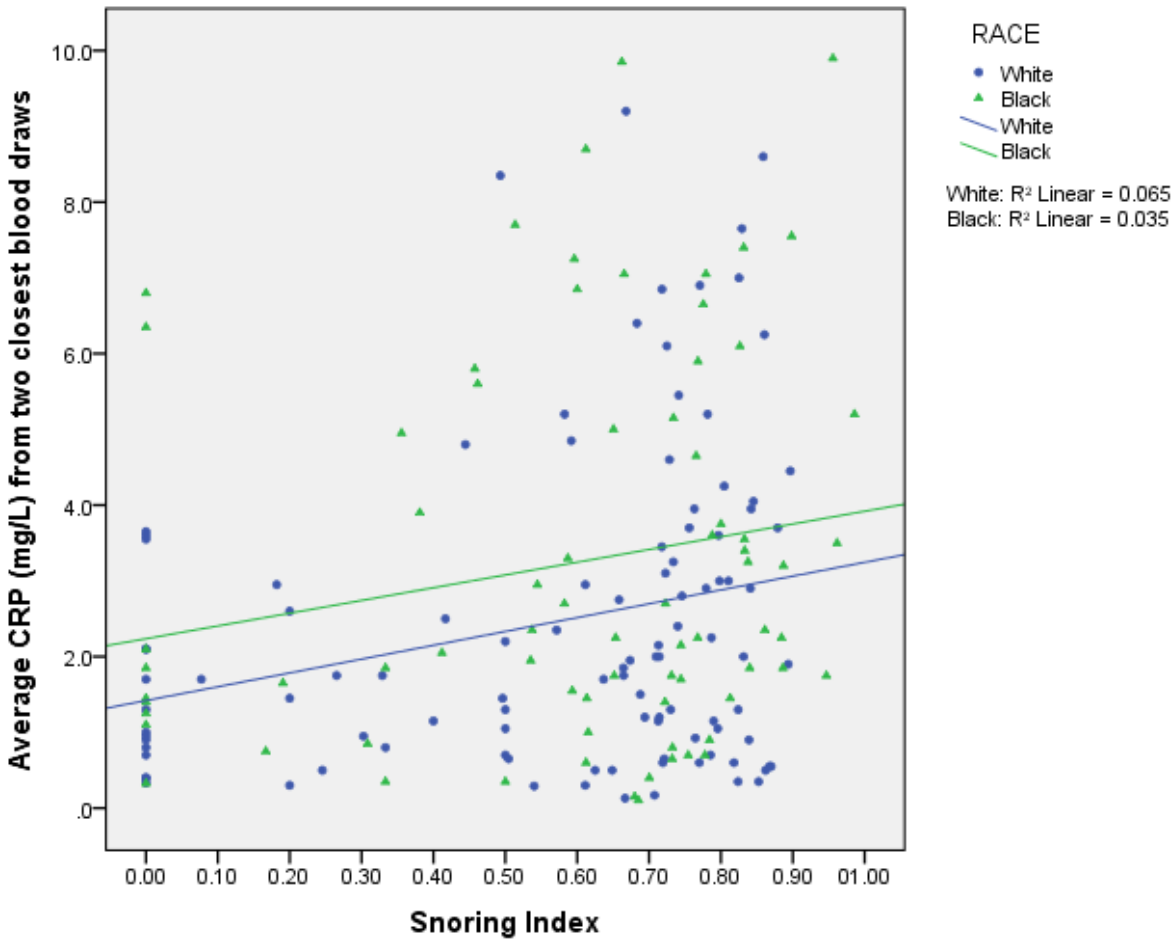
5.3 CRP

As shown in Table 5, the full regression model accounting for age, race, menopausal status, average number of days between CRP blood draws and sleep study dates, mean daily servings of alcohol, passive smoking exposure, percent of study days on which sleep-affecting medication was used, and BMI revealed no significant associations between snoring index, AHI, and CRP levels (p>0.05, Figure 9).

Table 5. Snoring Index and Apnea-Hypopnea Index are Not Associated with CRP in Midlife Women.

	B	**SE**	***p***
Step 1			
Race	0.095	0.153	0.53
Age	-0.016	0.035	0.65
Menopausal status	0.073	0.103	0.48
Average # days between CRP and sleep	-0.001	0.0001	0.17
Mean daily servings of alcohol across study	-0.075	0.147	0.61
Passive smoking exposure category	0.059	0.09	0.52
Percent of days in which sleep-affecting medication used	0.001	0.002	0.52
BMI	0.081**	0.011	0.0001
Step 2			
AHI	0.006	0.007	0.38
Snoring index (SI)	0.084	0.265	0.75
Step 3			
SI x AHI	-0.011	0.019	0.56

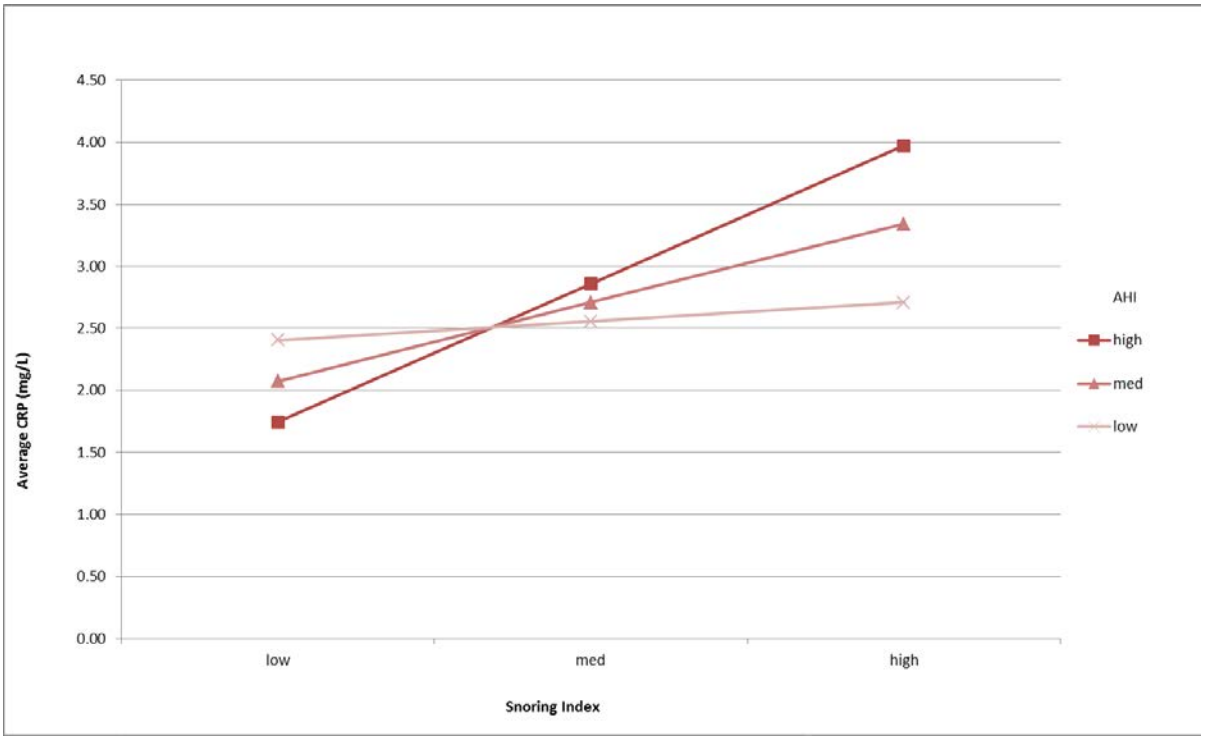
Note: **$p<0.01$.



Note: Average CRP ≥10 mg/L excluded from analyses.

Figure 9. Snoring Index and CRP by Race.

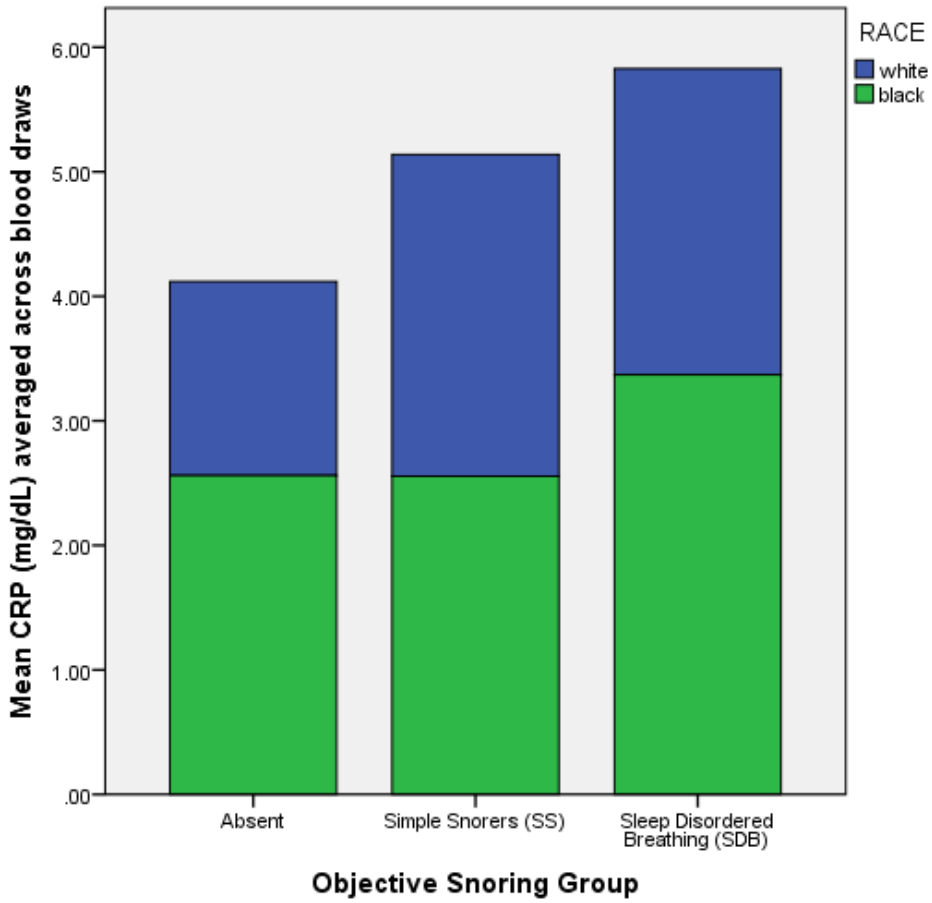
There was no significant interaction effect of SI x AHI on CRP (*p*'s>0.05, Figure 10). These results did not change when the sample was restricted to exclude participants with CRP>10 mg/L in sensitivity analyses (*p*'s>0.05).



Note: Average CRP ≥10 mg/L excluded from analyses.

Figure 10. Association Between Snoring Index and CRP is Not Moderated by AHI.

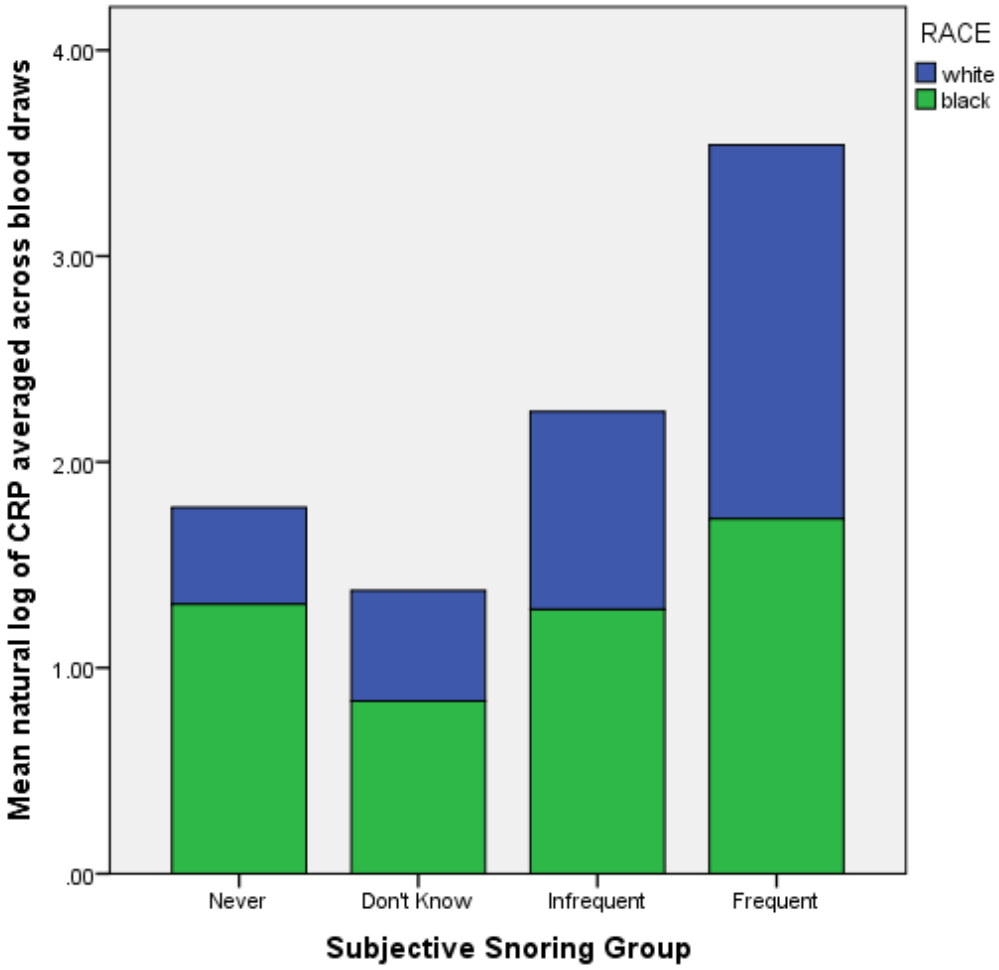
ANCOVA [between-subjects factor: objective snoring group (Absent, Simple Snorers, Sleep Disordered Breathing); covariates as listed above] revealed no main effects of objective snoring group on CRP, $F(2,173)=0.235$, $p=0.791$ (Figure 11). Again, BMI remained the only variable significantly associated with CRP level.



Note: Average CRP ≥10 mg/L excluded from analyses.

Figure 11. Objective Snoring Group and CRP by Race.

ANCOVA [between-subjects factor: subjective snoring group (Never, Don't Know, Infrequent, Frequent); covariates as listed above] revealed no main effects of self-reported (subjective) snoring group on CRP, $F(3,168)=1.259$, $p=0.29$ (Figure 12).



Note: Average CRP ≥10 mg/L excluded from analyses.

Figure 12. Subjective Snoring Group and CRP by Race.

5.4 EXPLORATORY ANALYSES

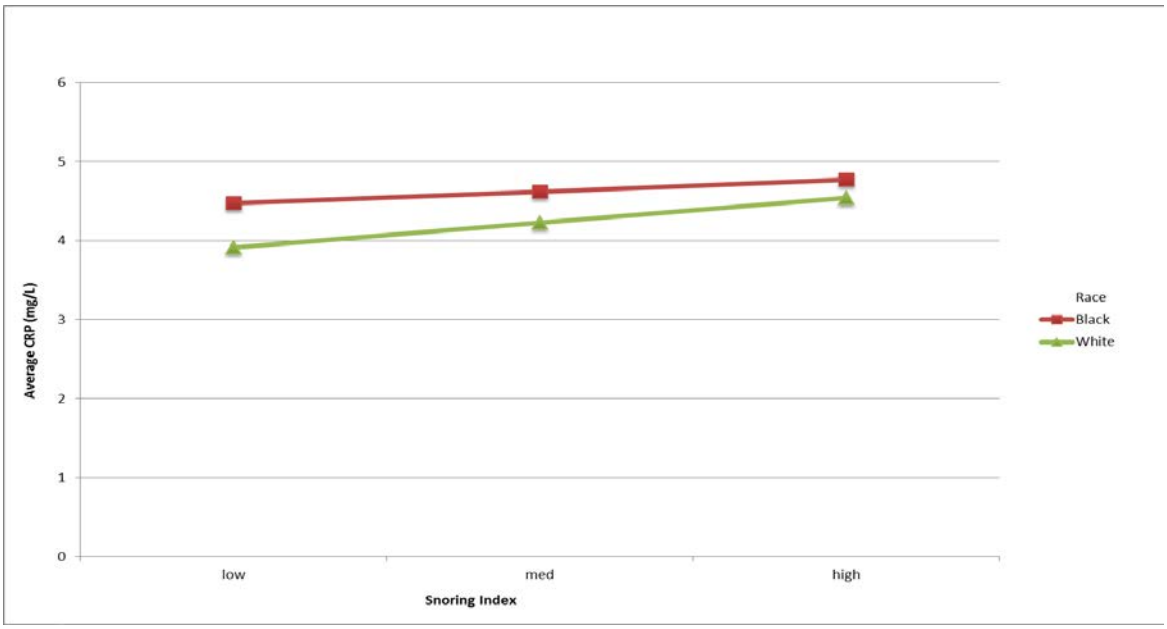
Since we had hypothesized that the relationship between snoring and CRP may be particularly important for postmenopausal women, we re-tested our SI model in the group of postmenopausal women only (*n*=41). As shown in Table 6, the full regression model accounting for age, race, average number of days between CRP blood draws and sleep study dates, mean daily servings of alcohol, passive smoking exposure, percent of study days on which sleep-affecting medication was used, and BMI revealed that snoring index (SI) was significantly associated with CRP (B=2.35, SE=0.97, *p*=0.025). Again, there was no main effect of AHI or SI by AHI interaction effect on CRP in the postmenopausal group.

Table 6. Snoring Index but Not Apnea-Hypopnea Index is Associated with CRP in Postmenopausal Women.

	B	**SE**	***p***
Step 1			
Race	-.347	.550	0.54
Age	.193	.128	0.15
Average # days between CRP and sleep	.0001	.001	0.81
Mean daily servings of alcohol across study	-1.634*	.612	0.015
Passive smoking exposure category	.501	.320	0.13
Percent of days in which sleep-affecting medication used	.006	.006	0.36
BMI	.005	.038	0.90
Step 2			
AHI	.019	.031	0.55
Snoring index (SI)	2.276*	1.017	0.037
Step 3			
SI x AHI	-.037	.103	0.73

Note: *$p<0.05$.

We had hypothesized that race may moderate the relationship between SI and CRP. However, moderation analyses revealed no main effects of snoring index or race and no significant SI by race interaction effect on CRP. Secondary analysis of simple slopes revealed no significant differences in simple slopes between Caucasians and African Americans (B_{diff} = 0.191, t=0.464, p=0.64), suggesting that race is not a statistically significant moderator of snoring index and CRP (Figure 13).



Note: Fully adjusted model (covariates: age, menopausal status, average number of days between blood draws and sleep study night, mean daily alcohol consumption, passive smoking exposure, BMI). Average CRP ≥10 mg/L excluded from analyses.

Figure 13. Associations Between Snoring Index and CRP are Not Significant and Not Moderated by Race.

6.0 DISCUSSION

The present study evaluated associations among snoring and C-reactive protein in a multi-ethnic cohort of midlife women. We found no significant associations between snoring index and CRP in fully adjusted models. In the full sample, only BMI was significantly associated with CRP levels. However, in the group of postmenopausal women, we did find that snoring index was positively associated with CRP, supporting our hypothesis that snoring may be related to cardiovascular changes observed following the menopausal transition.

We proposed a conceptual physiological model of snoring-induced atherogenesis that may putatively underlie previously established associations among snoring and cardiovascular disease. Our model suggests that two components—a heightened inflammatory response and endothelial dysfunction—are associated in a bidirectional manner and maintained by nightly recurrence of snoring-induced oscillatory pressure waves. Ongoing inflammatory responses and dysfunction of the endothelium play important roles in atherogenesis (Libby, 2002; De Caterina et al., 1995; Smith et al., 1995; Rajavashisth et al., 1999) and are therefore possible pathways linking snoring and cardiovascular disease (CVD). We chose to investigate C-reactive protein because circulating levels are fairly stable within individuals across 24 hours, and it is an established nonspecific marker of inflammation (Visser et al., 1999; Libby, 2002). In a meta-analysis of 7 prospective studies, moderately elevated CRP levels of 2.4 mg/L have been shown to predict future risk of coronary heart disease (Danesh et al., 1998). Even modest increases of

CRP, within the upper clinical limit of 1 mg/L, have been associated with a 2- to 3-fold increased risk of adverse cardiovascular outcomes (Kuller et al., 1996; Ridker et al., 1998; Koenig et al., 1999). On average, the women in our sample had a mean CRP level of 5.25 ± 6.87 mg/L, suggesting a disproportionate rate of heightened or even acute inflammation. While we feel that CRP remains an important inflammatory marker and worthy of investigation, it is plausible that any downstream effects of snoring-induced oscillatory pressure waves on inflammatory processes may be localized to the carotid artery, and therefore they may not be captured by a more global measure of inflammation like circulating CRP.

Additionally, the relationship between BMI and CRP is well-substantiated, with CRP a marker of elevated adiposity (Timpson et al., 2011). Our null findings in the overall sample may, therefore, largely be explained by BMI, given the mean BMI in our study of 31.69 ± 7.82, above the World Health Organization clinical cutoff for obesity of 30 (WHO, 1995). Obese women have a 4.76-fold increased risk of clinically raised CRP levels (95% CI=3.42-6.61; Visser et al., 1999). In addition, larger individuals may simply display more snoring due to increased collapsibility of pharyngeal structures from adipose tissue weight. It is therefore plausible that the overwhelming associations between BMI and CRP in the present study may have obscured whatever associations may exist between objective snoring and CRP levels. Given these findings, future studies investigating the role of snoring and inflammation may benefit from including only normal weight women (BMI < 30), where a possible signal is less likely to be obscured by adiposity.

Our finding that snoring index is significantly associated with CRP in postmenopausal women is striking for two reasons. One, these women had a mean BMI even higher than the overall BMI in the full sample (postmenopausal: 32.91± 8.74). This suggests that the snoring

index signal was strongest in these women, despite their increased adiposity. Two, the addition of AHI into the model did not attenuate this relationship, despite the high mean level of AHI in this group (14.02 ± 13.06). Together, these findings suggest that the snoring phenomenon contributes something to our understanding of cardiovascular risk in postmenopausal women above and beyond the well-established risk factors of obesity and sleep apnea. While only 17.1% of the postmenopausal group were Simple Snorers, our findings suggest that snoring may represent an important and understudied risk factor for postmenopausal women outside of traditional risk factors, such as smoking, SDB, low socioeconomic status, depression, or anxiety. In support of this, we found few significant differences between snoring groups on these risk factors, yet snoring was still associated with increased cardiovascular risk factors, particularly in the postmenopausal women.

It is of interest to note that AHI was not significantly associated with CRP in our study. Previous research has established that obstructive sleep apnea syndrome (OSAS) is an independent risk factor for cardiovascular disease (CVD) morbidity and mortality (Peker et al., 1999; Leung et al., 2001; Kokturk et al., 2005; Lattimore et al., 2003). Given the mechanistic role of inflammatory processes in both OSAS and CVD, inflammatory markers have been a well-studied pathway linking apnea to CVD pathogenesis. Circulating CRP levels have been shown to be elevated in individuals with OSAS and CVD (Kokturk et al., 2005; Shamsuzzaman et al., 2002). One study found that median circulating CRP levels of OSA patients were 3.30 mg/L, less than half of the sleep disordered breathing group mean CRP level of 6.94 ± 8.08 mg/L present in our study. Despite these elevated levels, and the fairly high mean AHI across our entire sample (11.20 ± 15.21), we did not find the expected association between AHI and CRP. Once again, it is plausible that the strength of BMI-related adiposity in our full sample fully

attenuated any weaker relationships. In support of this explanation, researchers in Delhi recently found that obesity, and not OSA, was responsible for increased serum hsCRP levels in sleep disordered breathing patients (Sharma et al., 2008).

Despite the mixed results of our primary aims, we believe that our characterizations of the correlates of objective and subjective snoring are of merit and advance our understanding of what snoring looks like in midlife women. As we predicted, women who met clinical criteria for sleep disordered breathing did have the poorest physiological profiles, providing convergent support with the extant literature. However, our study is the first to identify characteristics of midlife women who are simple snorers. We found that these women had elevated systolic blood pressure and increased BMI, both established risk factors for CVD. Additionally, simple snorers met significantly more metabolic syndrome criteria than non-snorers and were more likely to meet criteria for the metabolic syndrome, findings that converge with Troxel and colleague's (2010) reported association between loud snoring and the metabolic syndrome.

Simple Snorers did not differ from Absent snorers on conventional risk factors for snoring, such as cigarette smoking, passive smoking exposure, sleep medication usage, or exercise. Most importantly, Simple Snorers did not differ from Absent snorers on AHI (2.49±1.51 versus 2.46±1.31) but had significantly higher levels of snoring (719.82 ± 761.18 versus 10.23 ± 26.33 total snore events), supporting the argument that simple snoring should be considered its own construct and separate from SDB.

Research on racial differences in prevalence has focused almost exclusively on sleep-disordered breathing. To our knowledge, our study is the first to examine racial differences in objective snoring. Our study failed to replicate the differences in self-reported snoring and SDB between African Americans and Caucasians observed elsewhere (O'Connor et al., 2003; Redline

et al., 1997; Scharf et al., 2004; Ram et al., 2010). The absence of racial differences in our sample may be interpreted as further support that simple snoring may be a separate construct from SDB. Because race may play a more important role in SDB than simple snoring, it is possible that craniofacial morphology is not the primary determinant of racial differences in SDB. Instead, factors such as BMI and socioeconomic status may largely be driving the higher rates of SDB in African Americans (Scharf et al., 2004).

6.1 LIMITATIONS

This study is the first to examine a possible pathway of snoring-induced inflammation that links objectively-scored snoring frequency to cardiovascular disease risk in midlife women. However, several limitations exist. Because snoring data were collected on one night of PSG recording, objective snoring variable could not be tested for inter-night reliability. In addition, the snore channel was not calibrated ahead of time to a standardized and consistent baseline voltage across participants, necessitating an individualized approach to establish a baseline for each participant. As a result, only relative changes in amplitude from baseline values were ascertained; absolute values of snore events could not be analyzed to determine whether greater vibration intensity was predictive of greater inflammation. However, no gold standard currently exists for snore channel scoring, whether calibrated or not, making it difficult to determine how much of a limitation this actually posed to this study.

Additionally, our overall null findings could suggest that injury resulting from snoring-induced vibrations, if any, may be localized to the pharyngeal structures, and circulating measures might not capture any effects. Our study was limited in outcome measures available,

and future studies should include multiple indices of cardiovascular risk. Alternatively, snoring-induced vibrations may not be of sufficient amplitude or duration to induce endothelial injury in humans, despite the promising findings of the animal and cell models. Instead, a third factor related independently to both simple snoring and atherosclerosis may be at play. It is also possible that a single night of quantified objective snoring is not sufficiently representative of habitual snoring frequency. Prospective longitudinal studies of habitual snoring using objective methods are needed to address these research questions. To date, little is known about whether a single night of objectively scored snoring is representative of habitual snoring.

In addition, this study is a secondary data analysis of data collected during the SWAN Sleep Study and the temporally related Core SWAN Study. The participants were not screened for factors shown to be related to snoring and sleep disordered breathing, such as adenotonsillectomy, adenoidectomy, and tonsillectomy history, current upper airway or bronchial infection or inflammation, and facial, sinus, throat, and nasal surgery. Despite the fairly large sample size of women for whom objective snoring data were available (n=241), this study may have been underpowered to explore the relationship between primary snoring, independent of sleep apnea, and inflammation.

6.2 IMPLICATIONS AND FUTURE DIRECTIONS

Future studies should examine whether objectively scored snoring is associated with objective cardiovascular risk factors, such as carotid intramedial thickness (cIMT) and atherosclerotic plaque in the carotid artery. In particular, additional research examining the association between snoring and endothelial dysfunction is necessary to investigate whether the bidirectional

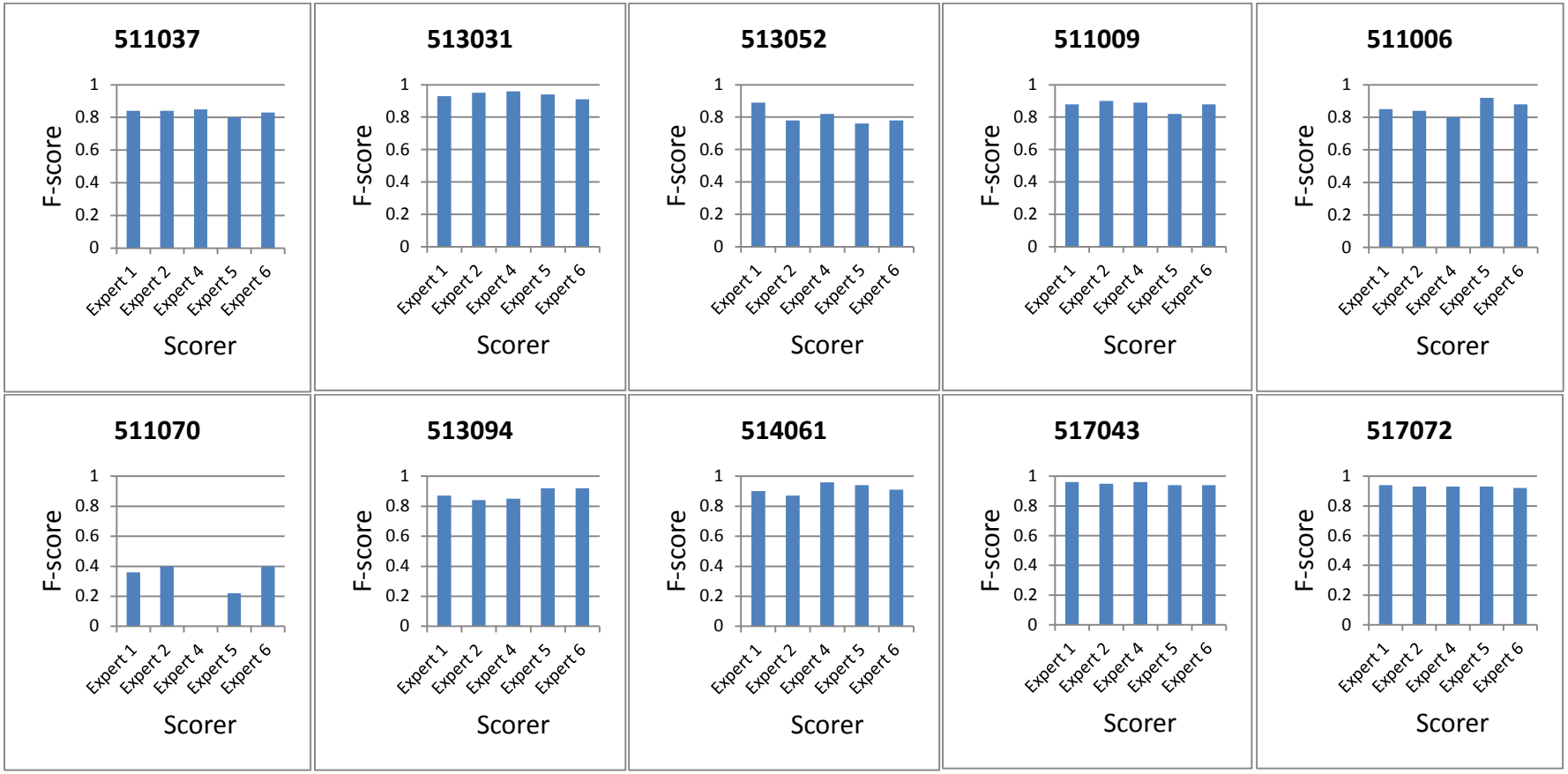
inflammation-endothelial dysfunction model proposed in this study is supported. Such studies would do well to utilize objective measures of endothelial functioning, such as cIMT or coronary angiography, as well as additional measures of inflammation previously shown to be related to snoring and atherosclerosis, including TNF-∝ and IL-8.

Our comparisons of objective and subjective snoring groups provide evidence that self-reported snoring is a poor measure of true snoring frequency, and our findings suggest that midlife women may not know the true extent of either their sleep disordered breathing or snoring. The substantial discrepancies between objective and self-reported snoring frequencies in this sample illustrate the need to measure snoring objectively in future studies.

To our knowledge, this study was the first to propose a possible mechanistic pathway of snoring vibration-induced atherogenesis and the first to investigate the relationship between objective snoring and a CVD risk inflammatory biomarker in midlife women. Women during the menopausal transition have been shown to be at increased risk for hypertension, coronary heart disease, and stroke (Lugaresi, Cirignotta, Coccagna, & Piana, 1975; Norton & Dunn, 1985; Hu et al., 2000). Concurrently, the prevalence of nocturnal snoring increases as women transition through midlife and the menopause (National Sleep Foundation, 2007). While we did not find the expected associations between nighttime percentage of snoring and CRP in our entire sample of midlife women, we did find the hypothesized relationship in postmenopausal women. Overall, our findings suggest that snoring may represent a unique and understudied variable linking nocturnal physiology to increased CVD risk and atherosclerosis in postmenopausal women.

APPENDIX A

F-SCORE VALUES FOR TRAINEE SCORERS COMPARED TO GOLD-TRUTH SCORER



Note: *P* = Precision, *R* = Recall, *F* = *F*-score. Nan = not a number.

Figure 14. F-score Values for Trainee Scorers Compared to Gold-Standard Ground Truth Scorer.

APPENDIX B

PRECISION, RECALL, AND F-SCORE VALUES FOR RELIABILITY FILES

Table 7. Table of Precision, Recall, and F-score Values for Six Scorers Across 11 Reliability Files.

		511037			513031			513052			511009			511006			511070			513079			513094			514061			517043			517072		
		P	*R*	*F*	*P*	*R*	*F*	*P*	*R*	*F*	*P*	*R*	*F*	*P*	*R*	*F*	*P*	*R*	*F*	*P*	*R*	*F*	*P*	*R*	*F*	*P*	*R*	*F*	*P*	*R*	*F*	*P*	*R*	*F*
Ground truth 1	Expert 2	.85	.91	.88	.95	.93	.94	.91	.66	.77	.97	.82	.89	.89	.89	.89	.33	.25	.28	0	0	Nan	.87	.90	.88	.94	.91	.93	.97	.94	.96	.95	.93	.94
	Expert 3	.83	.86	.84	.95	.92	.93	.94	.84	.89	.97	.81	.88	.78	.93	.85	.28	.50	.36	Nan	0	Nan	.78	.98	.87	.82	.99	.90	.95	.96	.95	.93	.95	.94
	Expert 4	.90	.87	.88	.97	.97	.97	.83	.93	.88	.95	.90	.92	.85	.92	.88	Nan	0	Nan	0	0	Nan	.86	.92	.89	.92	.97	.94	.97	.98	.98	.90	.96	.93
	Expert 5	.86	.87	.86	.97	.96	.97	.80	.89	.84	.87	.94	.90	.72	.99	.83	0	0	Nan	.25	1	.40	.78	.97	.87	.81	.99	.89	.94	.98	.96	.88	.99	.93
	Expert 6	.93	.79	.85	.92	.97	.94	.74	.96	.83	.90	.96	.93	.77	.95	.85	.50	.50	.66	0	0	Nan	.79	.97	.87	.63	.84	.72	.95	.97	.96	.84	.99	.91
Ground truth 2	Expert 1	.91	.85	.88	.93	.95	.94	.66	.91	.77	.82	.97	.89	.89	.89	.89	.25	.33	.28	0	0	Nan	.90	.87	.88	.91	.94	.93	.97	.94	.96	.93	.95	.94
	Expert 3	.85	.83	.84	.95	.95	.95	.71	.87	.78	.90	.90	.90	.77	.92	.84	.28	.66	.40	Nan	0	Nan	.78	.93	.84	.79	.98	.87	.95	.96	.95	.91	.96	.93
	Expert 4	.95	.85	.90	.94	.92	.93	.63	.96	.76	.86	.98	.92	.82	.88	.85	Nan	0	Nan	.50	1	.66	.89	.92	.90	.88	.97	.92	.97	.98	.98	.89	.98	.93
	Expert 5	.88	.84	.86	.95	.93	.94	.58	.89	.70	.76	.97	.85	.72	.99	.83	0	0	Nan	.25	1	.40	.79	.95	.86	.77	.98	.86	.94	.98	.96	.86	.99	.92
	Expert 6	.92	.73	.81	.87	.93	.90	.52	.92	.67	.78	1	.88	.73	.99	.84	.33	.33	.33	.25	1	.40	.78	.91	.84	.62	.83	.71	.95	.97	.96	.82	.99	.90
Ground truth 3	Expert 1	.86	.83	.84	.92	.95	.93	.84	.94	.89	.81	.97	.88	.93	.78	.85	.50	.28	.36	0	Nan	Nan	.98	.78	.87	.99	.82	.90	.94	.97	.96	.95	.93	.94
	Expert 2	.83	.85	.84	.95	.95	.95	.87	.71	.78	.90	.90	.90	.92	.77	.84	.66	.28	.40	0	Nan	Nan	.93	.78	.84	.98	.79	.87	.94	.97	.95	.96	.91	.93
	Expert 4	.88	.81	.85	.95	.97	.96	.74	.92	.82	.84	.96	.89	.84	.76	.80	Nan	0	Nan	0	Nan	Nan	.91	.79	.85	.98	.87	.96	.95	.98	.96	.91	.95	.93
	Expert 5	.80	.79	.80	.92	.95	.94	.68	.85	.76	.73	.94	.82	.86	.99	.92	.50	.14	.22	0	Nan	Nan	.92	.92	.92	.91	.93	.94	.91	.98	.94	.89	.98	.93
	Expert 6	.93	.76	.83	.88	.95	.91	.66	.95	.78	.76	.98	.86	.83	.95	.88	.66	.28	.40	0	Nan	Nan	.93	.91	.92	.67	.92	.91	.92	.97	.94	.86	.99	.92
Ground truth 4	Expert 1	.87	.90	.88	.97	.97	.97	.93	.83	.88	.90	.95	.92	.92	.85	.88	0	Nan	Nan	0	0	Nan	.92	.86	.89	.97	.92	.94	.98	.97	.98	.96	.90	.93
	Expert 2	.85	.95	.90	.92	.94	.93	.96	.63	.76	.98	.86	.92	.88	.82	.85	0	Nan	Nan	1	.50	.66	.92	.89	.90	.97	.88	.92	.98	.95	.96	.98	.89	.93
	Expert 3	.81	.88	.85	.97	.95	.96	.92	.74	.82	.96	.84	.89	.76	.84	.80	0	Nan	Nan	Nan	0	Nan	.79	.91	.85	.87	.98	.92	.96	.96	.96	.95	.91	.93
	Expert 5	.82	.87	.84	.89	.90	.90	.89	.89	.89	.85	.97	.90	.75	.95	.84	0	Nan	Nan	.25	.50	.33	.81	.93	.86	.85	.98	.91	.85	.98	.96	.93	.98	.96
	Expert 6	.93	.82	.87	.91	.96	.93	.84	.97	.90	.87	.98	.92	.80	.98	.88	0	Nan	Nan	.25	.50	.33	.82	.92	.87	.65	.86	.74	.96	.97	.96	.89	.99	.94
Ground truth 5	Expert 1	.87	.86	.86	.96	.97	.97	.89	.80	.84	.94	.87	.90	.99	.77	.85	0	0	Nan	1	.25	.40	.97	.78	.87	.99	.81	.89	.98	.94	.96	.99	.88	.93
	Expert 2	.84	.88	.86	.93	.95	.94	.89	.58	.70	.97	.76	.85	.99	.73	.84	0	0	Nan	1	.25	.40	.95	.79	.86	.98	.77	.86	.98	.91	.94	.99	.86	.92
	Expert 3	.79	.80	.80	.95	.92	.94	.85	.68	.76	.94	.73	.82	.99	.83	.88	.14	.50	.22	Nan	0	Nan	.92	.92	.92	.93	.91	.92	.93	.90	.91	.98	.89	.93
	Expert 4	.87	.82	.84	.90	.89	.90	.89	.89	.89	.97	.85	.90	.95	.80	.88	Nan	0	Nan	.50	.25	.33	.93	.81	.86	.98	.85	.91	.98	.95	.96	.98	.93	.96
	Expert 6	.93	.78	.85	.92	.97	.95	.83	.96	.89	.93	.92	.92	.93	.93	.93	.33	.50	.40	.50	.50	.50	.94	.92	.93	.67	.94	.78	.98	.95	.96	.94	.98	.96
Ground truth 6	Expert 1	.79	.93	.85	.97	.92	.94	.96	.74	.83	.96	.90	.93	.95	.77	.85	.50	.66	.57	0	0	Nan	.97	.79	.87	.84	.63	.72	.97	.95	.96	.99	.84	.91
	Expert 2	.73	.92	.81	.93	.87	.90	.92	.52	.67	1	.78	.88	.99	.73	.84	.33	.33	.33	1	.25	.40	.91	.78	.84	.83	.62	.71	.97	.92	.94	.99	.82	.90
	Expert 3	.76	.93	.83	.95	.88	.91	.95	.66	.78	.98	.76	.86	.95	.83	.88	.28	.66	.40	Nan	0	Nan	.91	.93	.92	.92	.67	.78	.96	.94	.95	.99	.86	.92
	Expert 4	.82	.93	.87	.96	.91	.93	.97	.84	.90	.98	.87	.92	.98	.80	.88	Nan	0	Nan	.50	.25	.33	.92	.82	.87	.86	.65	.74	.97	.96	.96	.99	.89	.94
	Expert 5	.78	.93	.85	.97	.92	.95	.96	.83	.89	.92	.93	.92	.93	.93	.93	.50	.33	.40	.50	.50	.50	.92	.94	.93	.94	.67	.78	.95	.98	.96	.98	.94	.96

Note: *P*=Precision, *R*=Recall, *F*=F-score, Nan=not a number.

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