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Racial differences in heart rate variability during sleep in women: The SWAN Sleep Study

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Abstract

Background—Heart rate variability (HRV) differs markedly by race, yet few studies have evaluated these relationships in women. Moreover, none have evaluated HRV during sleep, despite sleep's importance to cardiovascular health.

Methods—We addressed these gaps by examining HRV during sleep in African American, Chinese and white women (mean age 51.2 ± 2.2). Sleep and HRV during sleep (sHRV) were measured concurrently.

Results—Heart rate variability during stage 2 non-rapid eye movement (NREM) and rapid eye movement (REM) sleep differed significantly by race after adjusting for possible confounders. Normalized high frequency HRV was significantly lower in white compared to African American and Chinese participants (white NREM=0.35 ±.01, REM=0.23 ± .01; African American NREM=0.43 ± 0.02, REM=0.29 ± 0.02; Chinese NREM=0.47 ± 0.03, REM=0.33 ± 0.02; p's<.001). The inverse was seen for low frequency power, with higher values in white compared to African American and Chinese participants (white NREM=0.66 ± .01, REM=0.77 ± .01; African American=NREM 0.58 ± 0.02, REM=0.71 ± 0.02; Chinese=0.53 ± 0.03, REM=0.68 ± 0.02; p's<.010). Whites also exhibited higher low-to-high frequency HRV ratios during sleep compared to African American and Chinese women (white NREM=2.42 ± 1.07, REM=5.05 ± 1.07; African American NREM=1.69 ± 1.09, REM=3.51 ± 1.09; Chinese NREM=.35 ± 1.07, REM=2.88 ± 1.13; p's<.001).

Conclusions—Race was robustly related to HRV during sleep. Compared to African American and Chinese women, whites exhibited decreased vagally-mediated control of the heart during sleep. Rresearch is needed to evaluate whether sHRV, including race differences, is prospectively associated with cardiovascular disease.

Keywords

heart rate variability; sleep; race; cardiovasular disease; autonomic tone; women

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INTRODUCTION

Mounting evidence suggests that heart rate variability (HRV) is a robust predictor of cardiovascular morbidity and mortality (1). Identification of key correlates of HRV is critical to primary prevention efforts in vulnerable populations, as well as to our understanding of the mechanisms through which HRV influences cardiovascular health. Race is one of the most consistent correlates of HRV. Paradoxically, many studies have reported higher indices of cardiac vagal control in African Americans compared to whites (2–8), although others have found contradictory results (9, 10). The overall direction of these effects is somewhat surprising in light of marked disparities in cardiovascular morbidity and mortality among African Americans relative to Cuacasians (11). Significantly, the majority of studies that have examined racial/ethnic differences in HRV have been conducted in men; few have included appreciable numbers of females. This is an important oversight given that cardiovascular disease is the leading cause of death for women in the United States (12).

A second oversight in the extant literature is a near universal focus on HRV assessed during wakefulness, primarily based on brief electrocardiogram (EKG) recordings. Without exception, studies examining racial differences in HRV have used data gathered during short, controlled laboratory protocols or during 24-hour Holter monitoring. None of these studies, including the Holter monitoring studies, specifically examined HRV during sleep, despite mounting evidence that sleep and sleep disruptions play a key role in cardiovascular health (13). Among patients with sleep apnea, for example, disruptions in nocturnal physiology are associated with cardiovascular morbidity, including incident hypertension and stroke (14). Although it has been long recognized that daytime blood pressure is a strong predictor of future mortality and cardiovascular events, a recent meta-analysis found that nighttime blood pressure was a stronger predictor of mortality in both individuals with hypertension and the population at large (15).

Assessment of HRV during sleep (sHRV) offers several advantages over brief waking or 24-hour Holter recordings. First, sHRV can be measured continuously and non-invasively throughout the night in relation to specific stages of sleep (16, 17). Second, assessment of sHRV limits the amount of random error attributable to differences in physical activity and postural changes that occur during 24-hour Holter recordings. This is particularly important in a multi-racial/ethnic context, given known racial differences in work and social environments (18). A third advantage of sHRV is that these data may be especially important to understanding circadian variation in the timing of cardiovascular disease (CVD) events which are more likely to occur during the early morning hours (19). Finally, assessment of sHRV provides a quantitative measure of autonomic tone during a consolidated period of physiologic restoration critical to the maintenance of cardiovascular health (13, 20, 21).

The present study examined racial/ethnic differences in HRV during throughout sleep in a community sample of African American, white, and Chinese women from the Study of Women across the Nation (SWAN) ancillary Sleep Study. Critically, these data address the “biological mechanism” evidence gap cited in the 10Q Report on cardiovascular disease in women by seeking to evaluate interrelationships among race and HRV in midlife women (22).

METHODS

The SWAN Sleep Study is an observational study of sleep in a multi-racial/ethnic sample of midlife women conducted over a 5-year period starting in the fall of 2002. A total of 368 white, African American, and Chinese participants were enrolled from four study sites: Chicago, IL; Detroit area, MI; Oakland, CA; and Pittsburgh, PA. Race was assessed by self-identification. Exclusions for the Sleep Study were: current menopausal hormone replacement therapy or oral corticosteroid use; current chemotherapy or radiation treatment; self-reported diagnosis of sleep apnea; regular nocturnal shiftwork; regular consumption of more than 4 alcoholic drinks per day; and noncompliance with Core SWAN procedures. Informed consent was obtained in accordance with approved protocols and guidelines of the Institutional Review board at each participating institution. Participants were paid for their participation.

Participants underwent 3 consecutive nights of in-home polysomnography (PSG) as previously described (23). Self-report data, including daily sleep diaries, were collected concurrently with sleep studies. For the present report, analyses were restricted to SWAN Sleep Study participants in whom HRV was available and of sufficient quality for analysis (n=332), as described below. SWAN Sleep Study participants excluded from the present analyses had a higher body mass index (BMI), on average, compared to women included in the analyses. Average BMI for the present sample was 29.70 (±7.45) compared to 32.36 (±8.88) for participants in whom sufficient HRV data were not available. Other sample characteristics, including race, did not differ as a function of availability of HRV data.

Measures

Vitaport-3 (TEMEC VP3) ambulatory monitors were used to collect sleep, breathing, and leg movement signals throughout the sleep period as previously described (23). Quality assurance assessments, scoring, and processing of all sleep study records was performed by trained PSG technologists with established reliability at the University of Pittsburgh Neuroscience - Clinical and Translational Research Center. Visual sleep stage scoring was based on Rechtschaffen and Kales criteria and scored in 20-second epochs,(24) as data were collected prior to the updated American Academy of Sleep Medicine manual. Sleep staging was used to characterize the sample and to identify specific HRV epochs for analysis, as described below.

A modified 2-lead electrode placement was used to collect the EKG signal continuously throughout sleep at a sampling rate of 1024 Hz. Commercially-available software was used to identify successive R waves and suspected artifacts (Mindware Heart Rate Variability Scoring Module, Mindware Technologies Ltd., Gahanna, OH). Artifact editing was accomplished using an automated artifact detection algorithm and visual inspection and inter-beat intervals were then calculated for each successive pair of R waves. The time series of successive R-R intervals was used to quantify the variability between R waves, or heart rate variability. Specifically, the Fast Fourier Transform was used to derive HRV power spectral estimates for each 2-minute epoch during sleep.

Power was integrated in the low-frequency (LF-HRV: 0.04 to 0.15 Hz) and the high-frequency (HF-HRV; 0.15 to 4.0 Hz) bands over a total power spectrum of 0.04 to 4.0 Hz. Outcomes in the present analyses included three indices of sHRV: LF-HRV, HF-HRV, and the ratio of low-to-high frequency power (LF/HF) which provide a comprehensive assessment of the race-sHRV relationship and for comparability with the published literature on race and HRV during wakefulness. Analyses were conducted using both absolute and normalized LF- and HF-HRV as total sHRV power during non-rapid eye movement

(NREM) sleep differed significantly by race ($F(2,329)=4.83, p<.009$). Nomalized variables were identified as nLF-HRV and nHF-HRV.

Time series data files were used to align sleep and HRV data, with a total of six 20-second PSG epochs for each 2-minute HRV epoch. Heart rate variability epochs that contained either stage 2 NREM sleep or rapid eye movement (REM) sleep for the entire 120 seconds were extracted for analysis and averaged across the night. Stage 2 NREM and REM sleep were selected for analysis as they comprise the majority of the sleep period in midlife women.

Only participants with at least fifteen 2-minute epochs of stage 2 NREM (n=332) or REM sleep (n=321) were included in the analyses, to ensure that sufficient data were available to render reliable estimates. There were too few participants with fifteen 2-minute epochs of stage 3+4 NREM sleep (n=11) to evaluate race differences in HRV during slow-wave sleep, which is known to differ as a function of race (23). Epochs of stage 1 NREM sleep were not included as it is a transitional sleep stage with EEG characteristics similar to wakefulness. Heterogeneous HRV epochs, which contained a mixture of sleep stages, were not used in analyses due to recognized differences in HRV across sleep stages (25, 26). For each participant, HRV data were generated for either Night 2 or 3 of sleep given the high short-term stability of sHRV (27). Thus, ten variables were created for each participant based on all-night averages of homogeneous HRV epochs: LF-HRV, nLF-HRV, HF-HRV, nLF-HRV and the LF/HF ratio during both stage 2 NREM sleep and during REM sleep. Respiration rate was also collected for each 2-minute epoch of sleep based on the respiratory effort signal.

Potential covariates included sociodemographic, psychological, physiological, and behavioral factors previously linked to racial differences in HRV and/or cardiovascular risk (28). *Age* was established by self-report. *Marital status* at the time of sleep studies was coded as “married/living as married” or “unmarried;” this latter category included participants who were single, separated, divorced, or widowed. *Educational attainment* was used as an indicator of socio-economic status and was dichotomized as a comparison of those participants with a college or advanced degree versus those women without a college degree.

Daily sleep diaries used throughout the study were used to assess vasomotor symptoms and smoking status. Each morning upon awakening, participants were asked to report the number of hot flashes and the number of night sweats they experienced on the previous night of sleep. Total number of reported hot flashes and night sweats was calculated and *vasomotor symptoms* were dichotomized as none reported on HRV nights versus at least one reported on HRV nights. Each evening before going to bed, participants recorded the number of cigarettes smoked during the previous waking day. Participants who reported any cigarette use on the majority of days were coded as *current smokers*. *Body mass index* (BMI) was calculated as weight in kilograms/height in meters-squared. Daily *medication use* was coded according to the World Health Organization ATC classification (http://www.whocc.no/atcddd). The use of *medications that affect sleep*, including opioids, antiepileptics, anxiolytics, sedatives and hypnotics, antidepressants, and antihistamines; use was dichotomized as “present” or “absent.” *Beta-blocker use* concurrent with sleep studies was also dichotomized as “present” or “absent.” National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) guidelines for women were used to identify *hypertension* and *diabetes* as follows: Hypertension was defined as blood pressure of > 130 mm/Hg systolic, > 85 mm Hg diastolic or use of antihypertensive medication; diabetes was defined as fasting serum glucose of > 100 mg/dL, use of diabetic medication or having ever been classified as diabetic (29). Fasting blood draws were collected during the morning

hours and blood pressure was recorded using standard mercury sphygmomanometers following a 5-minute rest in the seated position. Two sequential readings were taken on the right arm, with a 2-minute intervening rest and values were averaged for each participant. These measures were collected in conjunction with Core SWAN annual visits immediately preceding the Sleep Study.

Self-reported *symptoms of depression* were measured concurrently with sleep studies using the 16-item Inventory of Depressive Symptomatology (IDS) (30). The IDS, minus sleep items, was calculated as a continuous variable. *Symptoms of anxiety* and *perceived stress* were assessed concurrently with sleep studies using the 20-item Spielberger State Anxiety Inventory (STAI) and the 4-item Perceived Stress Scale, respectively (31, 32). Finally, *respiration rate, sleep-disordered breathing* (apnea-hypopnea index; AHI) *and leg movements* (leg movement arousal index; LMAI), assessed by polysomnography, were included as covariates because of their known association with HRV (33, 34).

Statistical Analyses—Descriptive statistics were used to characterize the study sample. The following sHRV variables were transformed by natural logarithm to reduce skewness: absolute LF-HRV, absolute HF-HRV and the LF/HF ratio. Normalized LF- and HF-HRV were not transformed for analyses. Differences in background characteristics between the races were assessed using analysis of variance (ANOVA) for continuous variables and chi-square tests for categorical variables. Analysis of covariance (ANCOVA) was used to evaluate race differences in HRV during stage 2 NREM and REM sleep, with significance set at $p<.01$. Post-hoc tests (Tukey's Honestly Significant Difference) were used to evaluate significant race differences. Covariates were age, education, marital status, vasomotor symptoms, BMI, hypertension, smoking, use of medications that affect sleep and/or beta blockers, symptoms of depression, respiration rate, apnea-hypopnea index, and leg movement arousal index. Diabetes, symptoms of anxiety and perceived stress were not included in the final models as they were unrelated to race and/or sHRV in our sample. Sensitivity analyses were conducted in participants with AHI values less than 15 (n=259) to confirm that sleep disordered breathing did not confound race differences in HRV during sleep. Race-by-AHI interactions were also used to evaluate possible confounding by sleep-disordered breathing. Interaction terms were calculated using the median split for AHI (AHI = 5.05).

RESULTS

On average, participants were 51 years of age (range 46 – 57), married or living with a partner, and overweight (Table 1). As previously reported in this cohort (35), race was a significant correlate of sociodemographic, mental and physical health, and health behavior characteristics. Compared to their white and Chinese counterparts, African American participants were more likely to be unmarried, less educated, smokers, have a higher BMI, meet criteria for hypertension, and report more depressive and nighttime vasomotor symptoms. These sample characteristics were among the covariates included in statistical models of the race-sHRV relationship. As shown in Table 2, participants spent an average of 64 ± 8% of the night in Stage 2 NREM sleep and 25 ± 5% of the night in REM sleep. Significant race effects were observed during NREM and REM sleep. Percent Stage 1 NREM sleep was lower in whites compared to African Americans (p=.014) and percent slow-wave sleep was greater in Whites compared both to African American (p=.001) and Chinese participants (p=.017). Finally, percent REM sleep was lower in African American compared to Chinese participants (p=.039). Other sleep parameters did not differ as a function of race.

Figure 1 illustrates the contribution of LF- and HF-HRV to total power during NREM and REM sleep by race. As shown in Table 3, significant race effects were observed for LF-HRV (absolute and normalized), normalized HF-HRV and the LF/HF ratio during both stage 2 NREM and REM sleep. Absolute LF-HRV was significantly higher in White compared to Chinese participants during stage 2 NREM (p=.001) and REM sleep (p=.004). Whites also exhibited higher absolute LF-HRV during stage 2 NREM sleep compared to African American participants (p=.001). Normalized LF-HRV was significantly higher in White compared to African American and Chinese participants during both stage 2 NREM (p=.001) and REM sleep (p=.001). Although absolute HF-HRV during sleep did not differ as a function of race, significant effects were observed for normalized HF power during stage 2 NREM sleep (p<.001) and REM sleep (p<.001). Normalized HF-HRV was lower in White compared to African American and Chinese participants during stage 2 NREM and REM sleep (p's<.001). The LF/HF ratio during both NREM and REM sleep was significantly lower in African American and Chinese, compared to White participants (p's<.010). Chinese and African American participants did not differ on LF/HF ratio values during NREM or REM sleep. These results were observed after adjusting for all covariates.

Exploratory analyses showed that the race-sHRV relationship did not differ as a function of sleep-disordered breathing. Sensitivity analyses revealed that results were unchanged by excluding participants with moderate to severe sleep apnea as defined by an AHI > 15 for all outcomes except for absolute LF-HRV during NREM sleep, which no longer differed by race (p=.064; data not shown). Nor were there significant race-by-AHI interactions for any of the sHRV outcomes.

DISCUSSION

Emerging evidence suggests that HRV is a critical biological mechanism affecting cardiovascular risk and that race and/or ethnicity play a significant role in its expression (1, 9, 36). Yet, few studies of race and HRV have been conducted in women, and none has evaluated HRV during sleep, despite its importance to cardiovascular health (13). We report here the first data regarding racial/ethnic differences in HRV during sleep. Our major finding is that African American and Chinese women exhibited increased cardiac parasympathetic control (nHF-HRV) during NREM and REM sleep in comparison to White women. Conversely, LF-HRV and the LF/HF ratio were elevated during sleep in White compared to African American and Chinese participants. Race effects on HRV during sleep were unrelated to sleep-disordered breathing.

We found robust race differences in nHF-HRV during stage 2 NREM and REM sleep, after adjusting for other socio-demographic, psychological, behavioral and medical factors known to influence HRV. Our results for sHRV are consistent with the majority of studies that have evaluated race effects on HF-HRV during wakefulness (2–8). For instance, Earnest and colleagues reported that cardiac vagal activity during wakefulness was higher in postmenopausal African American compared to Cuacasian participants (37). We know of only one study that has compared HF-HRV in European and South Asian adults, all of whom were men (38). In that study, HF-HRV during wakefulness did not vary as a function of race/ethnicity. In addition to studies that assessed HRV during wakefulness, some (39) but not all (10) studies based on 24-hour Holter monitoring have found HF-HRV differences between African Americans and Whites. However, because of small sample sizes, not all effects were statistically reliable. Guzetti and colleagues reported an effect size of d=0.47 but had only 26 participants in each ethnic group, while Lampert et al reported higher HF-HRV in Whites but had only 41 African American participants (10, 39). While it has been noted that ambulatory studies introduce confounds associated with waking behaviors that may differ as a function of race, race differences in sleep, too, may confound 24-hour

monitoring (23). For this reason, we restricted the current comparisons of HRV and race to stage 2 NREM and REM sleep. Different outcomes for absolute and normalized HF-HRV suggest that while White women exhibit higher total power during sleep compared to African American and Chinese women, relatively less power can be attributed to vagal modulation of the heart. It is important to note that, whereas the greater HF-HRV in the Chinese women is consistent with their generally better cardiovascular risk profile, the greater HF-HRV in the African Americans is not consistent with their generally poorer cardiovascular risk profiles. More research is to further explicate this HRV race paradox.

We observed significant race effects for LF-HRV and the LF/HF ratio during stage 2 NREM and REM sleep. Several previous studies have similarly reported increased LF-HRV during wakefulness and during 24-hour Holter recordings in White compared to African American participants (3, 9, 10, 39). In contrast, results for race and the LF/HF ratio have not been consistent across studies. Choi and colleagues reported no significant race differences in their sample of younger (23–54 years of age) African American and White men and women (9) while the LF/HF ratio was significantly lower in White compared to African American participants in the Atherosclerosis Risk in Communities (ARIC) cohort, irrespective of age and sex (3). In contrast, LF/HF ratio values were higher in White compared to African American participants both in our study of sHRV and in a 24-hour Holter monitoring study of 52 unmedicated essential hypertension patients. Similar to results for HF-HRV, European and South Asian men did not differ in terms of LF-HRV or the LF/HF ratio (38). Too few studies have evaluated Chinese or other Asian populations in comparison to African American and White participants to warrant firm conclusions about HRV in these racial/ethnic groups.

Our understanding of the meaning of LF and the LF/HF ratio continues to evolve. There is a growing consensus that LF power (either absolute or normalized) may reflect modulation of cardiac autonomic outflow via the baroreflex (40) rather than sympathetic activity, as previously thought. Similarly, most criticisms of the LF/HF ratio highlight the lack of association of LF power with beta-adrenergic activity (41). However, the baroreflex is comprised of at least three related feedback loops, only one of which has been explicitly linked to LF power (40, 42). A major unexplored association is with the vascular limb of the baroreflex, which would be primarily alpha-adrenergic. Indeed, the best evidence linking LF and, thus, the LF/HF ratio to sympathetic activity comes from studies of orthostasis, where LF power has a graded relationship with the angle of the tilt (41); tilt induces alpha-adrenergic vasoconstriction consistent with the increased blood pressure needed to avoid syncope. Thus, broad statements that LF is not related to sympathetic activity are not consistent with the complex physiology of the sympathetic nervous system. Regardless of the precise autonomic origins of the LF/HF ratio, a recent study suggests important functional consequences of larger LF/HF ratios. In a large study of healthy middle-aged adults, it was found that a time domain measure of the LF/HF ratio was positively associated with elevated cholesterol levels after controlling for a large number of potential confounders including overnight urinary norepinephrine — a measure of beta-adrenergic activity (43). Thus, elevated LF/HF values, regardless of explicit knowledge about their autonomic origins, appears to be deleterious and inversely related to healthy vagal modulation, as found in the present study.

Taken as a whole, our data suggest robust race differences in sHRV. The relevance of HRV during sleep to cardiovascular health remains underexplored. A burgeoning literature continues to document the impact of sleep disturbances (e.g., short sleep duration, shift work) and disorders (e.g., sleep apnea, insomnia) on cardiovascular risk (13, 44–46). Alterations in autonomic tone, in turn, have been documented in each of these sleep disturbances and disorders, suggesting one plausible mechanism through which sleep affects

cardiovascular health (1, 13). That many of these sleep disturbances and disorders are more prevalent in African Americans and, in some cases, other racial and ethnic minorities suggests that links between race, autonomic imbalance during sleep, and cardiovascular disease are likely complex and multiply determined. For example, the increased prevalence of hypertension in racial and ethnic minorities has been hypothesized to be due at least in part to greater sympathetic drive in at-risk minorities (47, 48). Alterations in autonomic tone, as defined by increased LF-HRV and the LF/HF ratio during NREM sleep in Whites compared to African-Americans and Chinese in the current study is at odds with this hypothesis. Clearly, if one is to understand these important health disparities, further research is needed to examine autonomic control in various racial and ethnic groups by including measures of alpha-adrenergic and beta-adrenergic influences in addition to parasympathetic factors.

Several limitations to the present study should be considered. The sample did not include certain populations at increased risk for cardiac autonomic imbalance and CVD including men, other minority racial/ethnic groups (e.g., Hispanics), and shiftworkers. Nor can results be generalized to younger or elderly women, given age-related changes in sleep and HRV (28, 49). As noted above, absolute LF power and the LF/HF ratio are multiply determined, complicating interpretation of these differences and their implications for cardiovascular morbidity and mortality. However, evidence does exist that larger LF/HF ratios are associated with cardiovascular risk factors (43). Finally, we were not able to generate estimates of HRV during NREM stage 3+4 sleep due to the limited number of consolidated 2-minute epochs of slow-wave sleep. In future studies, time series modeling techniques may prove especially useful for characterizing the moment-to-moment dynamic interplay between HRV and sleep, including the extent to which these relationships differ by race and impact cardiovascular risk. It may also be useful to examine these relationships in younger individuals who have more slow-wave sleep than do midlife women.

Numerous strengths offset these limitations, including the large sample size, direct comparison of three racial groups, and statistical adjustment for multiple factors known to affect HRV. In addition, we collected EKG signals concurrently with PSG, which permitted accurate quantification of HRV in relation to specific stages of sleep. This level of precision limits the amount of random error attributable to environmental influences that may affect daytime laboratory or 24-hour ambulatory recordings. Other strengths of this study include the use of in-home PSG to enhance the ecological validity of the data. Power spectral analysis of HRV data was performed on Night 2 or 3 of sleep studies in order to reduce the possible influence of physiological habituation to PSG monitoring on cardiac autonomic tone during sleep. Our study also restricted analyses to equivalent sleep stages (stage 2 NREM and REM), which is critical given marked racial differences in sleep duration, fragmentation, and depth (23).

In conclusion, marked racial/ethnic differences are observed during stage 2 NREM sleep and REM sleep in midlife women. These differences are observed among African American and Chinese compared to White women and after controlling for known cardiovascular risk factors such as smoking, BMI, hypertension, medication use, and sleep disordered breathing. It will be important for future studies to evaluate the extent to which racial and/or ethnic differences in sHRV contribute to cardiovascular morbidity and mortality, including mechanisms that underlie this relationship. Our data suggest that the pathways that link race, sHRV and cardiovascular outcomes may differ from the pathways which contribute to health disparities in cardiovascular morbidity and mortality in African American and other ethnic minorities.

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Abbreviations

BMI	body mass index
HRV	heart rate variability
sHRV	heart rate variability during sleep
PSG	polysomnography
EKG	electrocardiogram
LF	absolute low frequency heart rate variability
nLF	normalized low frequency heart rate variability
HF	high frequency heart rate variability
nHF	normalized high frequency heart rate variability
LF/HF ratio	ratio of low-to-high frequency heart rate variability

REM	rapid eye movement
NREM	non-rapid eye movement
SWAN	Study of Women Across the Nation
IDS	Inventory of Depressive Symptomatology
AHI	apnea-hypopnea index
LMAI	leg movement arousal index
ANCOVA	analysis of covariance

Reference List

1. Thayer JF, Yamamoto SS, Brosschot JF. The relationship of autonomic imbalance, heart rate variability and cardiovascular disease risk factors. Int J Cardiol. 2010; 141:122–131. [PubMed: 19910061]
2. Gutin B, Howe C, Johnson MH, Humphries MC, Snieder H, Barbeau P. Heart rate variability in adolescents: relations to physical activity, fitness, and adiposity. Med Sci Sports Exerc. 2005; 37:1856–1863. [PubMed: 16286853]
3. Liao D, Barnes RW, Chambless LE, Simpson RJ Jr, Sorlie P, Heiss G. Age, race, and sex differences in autonomic cardiac function measured by spectral analysis of heart rate variability--the ARIC study. Atherosclerosis Risk in Communities. Am J Cardiol. 1995; 76:906–912. [PubMed: 7484830]
4. Ohira T, Diez Roux AV, Prineas RJ, Kizilbash MA, Carnethon MR, Folsom AR. Associations of psychosocial factors with heart rate and its short-term variability: multi-ethnic study of atherosclerosis. Psychosom Med. 2008; 70:141–146. [PubMed: 18256350]
5. Propper C, Moore GA, Mills-Koonce WR, Halpern CT, Hill-Soderlund AL, Calkins SD, Carbone MA, Cox M. Gene-environment contributions to the development of infant vagal reactivity: the interaction of dopamine and maternal sensitivity. Child Dev. 2008; 79:1377–1394. [PubMed: 18826531]
6. Martin LA, Doster JA, Critelli JW, Lambert PL, Purdum M, Powers C, Prazak M. Ethnicity and Type D personality as predictors of heart rate variability. Int J Psychophysiol. 2010; 76:118–121. [PubMed: 20211208]
7. Wang X, Thayer JF, Treiber F, Snieder H. Ethnic differences and heritability of heart rate variability in African- and European American youth. Am J Cardiol. 2005; 96:1166–1172. [PubMed: 16214458]
8. Sloan RP, Huang MH, McCreath H, Sidney S, Liu K, Dale WO, Seeman T. Cardiac autonomic control and the effects of age, race, and sex: the CARDIA study. Auton Neurosci. 2008; 139:78–85. [PubMed: 18304893]
9. Choi JB, Hong S, Nelesen R, Bardwell WA, Natarajan L, Schubert C, Dimsdale JE. Age and ethnicity differences in short-term heart-rate variability. Psychosom Med. 2006; 68:421–426. [PubMed: 16738074]
10. Lampert R, Ickovics J, Horwitz R, Lee F. Depressed autonomic nervous system function in African Americans and individuals of lower social class: a potential mechanism of race- and class-related disparities in health outcomes. Am Heart J. 2005; 150:153–160. [PubMed: 16084163]
11. Karlamangla AS, Merkin SS, Crimmins EM, Seeman TE. Socioeconomic and ethnic disparities in cardiovascular risk in the United States, 2001–2006. Ann Epidemiol. 2010; 20:617–628. [PubMed: 20609342]
12. Roger VL, Go AS, Lloyd-Jones DM, Adams RJ, Berry JD, Brown TM, Carnethon MR, Dai S, de SG, Ford ES, Fox CS, Fullerton HJ, Gillespie C, Greenlund KJ, Hailpern SM, Heit JA, Ho PM, Howard VJ, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Makuc DM, Marcus GM, Marelli A, Matchar DB, McDermott MM, Meigs JB, Moy CS, Mozaffarian D, Mussolino ME, Nichol G, Paynter NP, Rosamond WD, Sorlie PD, Stafford RS, Turan TN, Turner

MB, Wong ND, Wylie-Rosett J. Heart disease and stroke statistics--2011 update: a report from the American Heart Association. Circulation. 2011; 123:e18–e209. [PubMed: 21160056]

13. Knutson KL. Sleep duration and cardiometabolic risk: a review of the epidemiologic evidence. Best Practice & Research Clinical Endocrinology & Metabolism. 2010; 24:731–743. [PubMed: 21112022]
14. Thomas RJ, Weiss MD, Mietus JE, Peng CK, Goldberger AL, Gottlieb DJ. Prevalent hypertension and stroke in the Sleep Heart Health Study: association with an ECG-derived spectrographic marker of cardiopulmonary coupling. Sleep. 2009; 32:897–904. [PubMed: 19639752]
15. Hansen TW, Li Y, Boggia J, Thijs L, Richart T, Staessen JA. Predictive role of the nighttime blood pressure. Hypertension. 2011; 57:3–10. [PubMed: 21079049]
16. Hall M, Vasko R, Buysse DJ, Ombao H, Chen Q, Cashmere JD, Kupfer D, Thayer JF. Acute stress affects heart rate variability during sleep. Psychosomatic Medicine. 2004; 66:56–62. [PubMed: 14747638]
17. Hall M, Thayer JF, Germain A, Moul D, Vasko R, Puhl M, Miewald J, Buysse DJ. Psychological stress is associated with heightened physiological arousal during NREM sleep in primary insomnia. Behav Sleep Med. 2007; 5:178–193. [PubMed: 17680730]
18. Boyd RL. The northern"Black Metropolis" of the early twentieth century: a reappraisal. Sociol Inq. 2011; 81:88–109. [PubMed: 21337739]
19. Manfredini R, Boari B, Smolensky MH, Salmi R, la CO, Maria MA, Haus E, Manfredini F. Circadian variation in stroke onset: identical temporal pattern in ischemic and hemorrhagic events. Chronobiol Int. 2005; 22:417–453. [PubMed: 16076646]
20. Nakanishi H, Sun Y, Nakamura RK, Mori K, Ito M, Suda S, Namba H, Storch FI, Dang TP, Mendelson W, Mishkin M, Kennedy C, Gillin JC, Smith CB, Sokoloff L. Positive correlations between cerebral protein synthesis rates and deep sleep in Macaca mulatta. Eur J Neurosci. 1997; 9:271–279. [PubMed: 9058047]
21. Tononi G, Cirelli C. Modulation of brain gene expression during sleep and wakefulness: a review of recent findings. Neuropsychopharmacology. 2001; 25:S28–S35. [PubMed: 11682270]
22. Hayes SN, Wenger NK, Greenberger P, Tate LM. 10Q Report: Advancing women's hearth health through improved research, diagnosis and treatment. 2011
23. Hall M, Matthews KA, Kravitz HM, Gold EB, Buysse DJ, Bromberger JT, Owens JF, Sowers MF. Race and financial strain are independent correlates of sleep in mid-life women: The SWAN sleep study. Sleep. 2009; 32:73–82. [PubMed: 19189781]
24. Rechtschaffen, A.; Kales, A. Washington DC: US Government Printing Office; 1968. A manual of standardized terminology, techniques and scoring system for sleep stages of human subjects.
25. Berlad I, Shlitner A, Ben Haim S, Lavie P. Power spectrum analysis and heart rate variability in Stage 4 and REM sleep: evidence for state-specific changes in autonomic dominance. J Sleep Res. 1993; 2:88–90. [PubMed: 10607076]
26. Bonnet MH, Arand DL. Heart rate variability: sleep stage, time of night, and arousal influences. Electroencephalogr Clin Neurophysiol. 1997; 102:390–396. [PubMed: 9191582]
27. Israel B, Buysse DJ, Krafty RT, Begley A, Miewald J, Hall M. Short-term stability of sleep and heart rate variability in good sleepers and patients with insomnia: For some measures, one night is enough. Sleep. 2012; 35:1285–1291. [PubMed: 22942507]
28. Britton A, Shipley M, Malik M, Hnatkova K, Hemingway H, Marmot M. Changes in heart rate and heart rate variability over time in middle-aged men and women in the general population (from the Whitehall II Cohort Study). Am J Cardiol. 2007; 100:524–527. [PubMed: 17659940]
29. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, Gordon DJ, Krauss RM, Savage PJ, Smith SC, Spertus JA, Costa F. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation. 2005; 112:2735–2752. [PubMed: 16157765]
30. Rush AJ, Trivedi MH, Ibrahim HM, Carmody TJ, Arnow B, Klein DN, Markowitz JC, Ninan PT, Kornstein S, Manber R, Thase ME, Kocsis JH, Keller MB. The 16-Item Quick Inventory of Depressive Symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. Biol Psychiatry. 2003; 54:573–583. [PubMed: 12946886]

31. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. J Health Soc Behav. 1983; 24:385–396. [PubMed: 6668417]
32. Spielberger CD. State-trait anxiety inventory for adults: Permissions set, manual, test booklet, and scoring key. Mind Garden. 1983 1983.
33. Guggisberg AG, Hess CW, Mathis J. The significance of the sympathetic nervous system in the pathophysiology of periodic leg movements in sleep. Sleep. 2007; 30:755–766. [PubMed: 17580597]
34. Perakakis P, Taylor M, Martinez-Nieto E, Revithi I, Vila J. Breathing frequency bias in fractal analysis of heart rate variability. Biol Psychol. 2009; 82:82–88. [PubMed: 19559748]
35. Hall M, Matthews KA, Kravitz HM, Gold EB, Buysse DJ, Bromberger JT, Owens JF, Sowers MF. Race and financial strain are independent correlates of sleep in mid-life women: The SWAN sleep study. Sleep. 2009; 32:73–82. [PubMed: 19189781]
36. Kop WJ, Stein PK, Tracy RP, Barzilay JI, Schulz R, Gottdiener JS. Autonomic nervous system dysfunction and inflammation contribute to the increased cardiovascular mortality risk associated with depression. Psychosom Med. 2010; 72:626–635. [PubMed: 20639389]
37. Earnest CP, Lavie CJ, Blair SN, Church TS. Heart rate variability characteristics in sedentary postmenopausal women following six months of exercise training: the DREW study. PLoS One. 2008; 3:e2288. [PubMed: 18523583]
38. Bathula R, Francis DP, Hughes A, Chaturvedi N. Ethnic differences in heart rate: can these be explained by conventional cardiovascular risk factors? Clin Auton Res. 2008; 18:90–95. [PubMed: 18414771]
39. Guzzetti S, Mayet J, Shahi M, Mezzetti S, Foale RA, Sever PS, Poulter NR, Porta A, Malliani A, Thom SA. Absence of sympathetic overactivity in Afro-Caribbean hypertensive subjects studied by heart rate variability. J Hum Hypertens. 2000; 14:337–342. [PubMed: 10822322]
40. Goldstein BI, Liu SM, Zivkovic N, Schaffer A, Chien LC, Blanco C. The burden of obesity among adults with bipolar disorder in the United States. Bipolar Disord. 2011; 13:387–395. [PubMed: 21843278]
41. Eckberg DL. Physiological basis for human autonomic rhythms. Ann Med. 2000; 32:341–349. [PubMed: 10949066]
42. Vaschillo EG, Vaschillo B, Buckman JF, Pandina RJ, Bates ME. Measurement of vascular tone and stroke volume baroreflex gain. Psychophysiology. 2012; 49:193–197. [PubMed: 22092290]
43. Thayer JF, Fischer JE. Heart rate variability, overnight urinary norepinephrine, and plasma cholesterol in apparently healthy human adults. Int J Cardiol. 2013; 162:240–244. [PubMed: 21641664]
44. Chien KL, Chen PC, Hsu HC, Su TC, Sung FC, Chen MF, Lee YT. Habitual sleep duration and insomnia and the risk of cardiovascular events and all-cause death: report from a community-based cohort. Sleep. 2010; 33:177–184. [PubMed: 20175401]
45. Hall M, Okun ML, Sowers MF, Matthews KA, Kravitz HM, Hardin K, Buysse DJ, Bromberger JT, Owens JF, Karpov I, Sanders MH. Sleep is associated with the metabolic symdrome in a multi-ethnic cohort of midlife women: The SWAN sleep study. Sleep. 2012; 35:783–790. [PubMed: 22654197]
46. Leclerc A. Shift-work and cardiovascular disease. Eur J Epidemiol. 2010; 25:285–286. [PubMed: 20422441]
47. Lang CC, Stein CM, Nelson RA, He HB, Belas FJ, Blair IA, Wood M, Wood AJ. Sympathoinhibitory response to clonidine is blunted in patients with heart failure. Hypertension. 1997; 30:392–397. [PubMed: 9314422]
48. Stein CM, Lang CC, Singh I, He HB, Wood AJ. Increased vascular adrenergic vasoconstriction and decreased vasodilation in blacks. Additive mechanisms leading to enhanced vascular reactivity. Hypertension. 2000; 36:945–951. [PubMed: 11116105]
49. Ohayon MM, Carskadon MA, Guilleminault C, Vitiello MV. Meta-analysis of quantitative sleep parameters from childhood to old age in healthy individuals: developing normative sleep values across the human lifespan. Sleep. 2004; 27:1255–1273. [PubMed: 15586779]

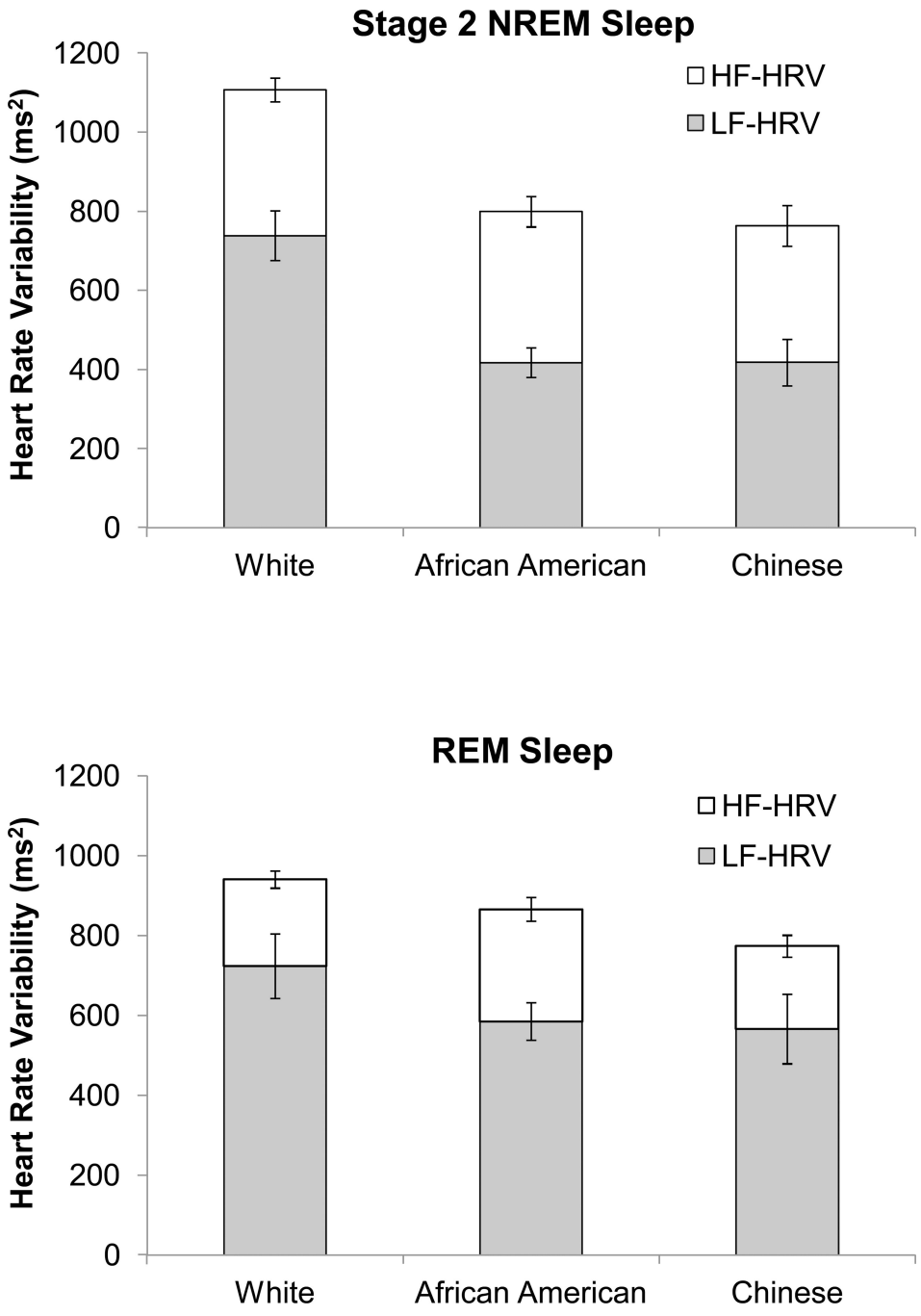

Figure 1.
Mean HRV (SE) during Stage 2 NREM and REM sleep. LF-HRV refers to absolute power integrated in the low frequency band (0.04–0.15 Hz) and HF-HRV refers to absolute power integrated in the high frequency band (0.15–0.40 Hz).

Table 1

Sample characteristics by race

	Full Sample n = 332	White n = 160	African American n = 119	Chinese n = 53	Test Statistic[1]
Mean (SD) age, years	51.17 (2.17)	51.16 (2.17)	50.96 (2.16)	51.70 (2.18)	2.15
No. (%) without a high school or college degree	152 (46.3%)	61 (38.4%)	71 (61.2%)	20 (37.7%)	15.96***
No. (%) unmarried, divorced, widowed	115 (34.6%)	38 (23.8%)	62 (52.1%)	15 (28.3%)	25.35***
No. (%) current smoker	32 (9.7%)	7 (4.4%)	25 (21.2%)	0 (0%)	28.41***
Mean (SD) body mass index	29.70 (7.45)	29.40 (7.05)	32.95 (7.53)	23.35 (2.71)	40.89***
No. (%) reporting at least 1 vasomotor symptom	12.3 (38.2%)	49 (31.2%)	61 (53.5%)	13 (25.5%)	18.06***
No. (%) taking medications that affect sleep	88 (27.0%)	45 (28.3%)	31 (27.0%)	12 (23.1%)	0.54
No. (%) taking medications beta blockers	26 (7.8%)	10 (6.2%)	14 (11.8%)	2 (3.8%)	4.31
No. (%) meeting hypertension criteria	131 (40.1%)	52 (33.1%)	70 (59.8%)	9 (17.0%)	33.95***
No. (%) meeting diabetes criteria	52 (16.0%)	22 (14.0%)	20 (17.4%)	10 (18.9%)	0.95
Mean (SD) symptoms of depression	4.78 (3.03)	4.50 (2.64)	5.33 (3.39)	4.38 (3.16)	3.12*
Mean (SD) symptoms of anxiety	14.95 (5.19)	14.62 (4.89)	15.08 (5.19)	15.64 (6.03)	0.83
Mean (SD) perceived stress	3.92 (2.92)	3.64 (2.77)	4.23 (3.09)	4.08 (2.94)	1.45

[1] Test statistic = Chi square for all but age, BMI, symptoms of depression, anxiety and perceived stress (ANOVA F test); for tests of significance,

* p<.050,

** p < .010,

*** p < .001

Table 2

Sleep characteristics by race

	Full Sample n = 332	White n = 160	African American n = 119	Chinese zn = 53	F Test Statistic[1]
Mean (SD) stage 1 NREM sleep percent[1]	6.91 (4.77)	6.28 3.99)	7.93 (5.82)	6.65 (4.12)	4.01*
Mean (SD) stage 2 NREM sleep percent	64.95 (7.64)	64.58 (8.04)	65.48 (7.53)	64.59 (6.53)	0.73
Mean (SD) slow-wave NREM sleep percent	3.42 (4.56)	4.16 (4.87)	2.71 (4.17)	2.66 (4.00)	8.16***
Mean (SD) REM sleep percent[1]	24.71 (5.89)	24.98 (5.71)	23.67 (6.49)	26.10 (4.65)	3.34*
Mean (SD) apnea-hypopnea index	10.07 (14.97)	10.65 (16.87)	10.04 (14.28)	8.48 (9.73)	0.41
Mean (SD) leg movement index	3.96 (5.55)	4.55 (6.58)	3.75 (4.69)	2.57 (3.07)	2.51
Mean (SD) minutes of Stage 2 sleep	180.27 (52.27)	183.27 (53.59)	174.13 (50.75)	185.02 (51.91)	1.30
Mean (SD) respiration rate during Stage 2 sleep	14.48 (4.24)	14.40 (5.08)	14.73 (3.61)	14.16 (2.34)	0.27
Mean (SD) minutes of REM sleep	80.81 (27.60)	84.41 (28.02)	73.01 (26.76)	87.02 (24.63)	7.42***
Mean (SD) respiration rate during REM sleep	14.19 (4.50)	14.25 (5.63)	14.07 (3.32)	14.25 (2.47)	0.56

* $p < 0.05$;

** $p < 0.01$,

*** $p < 0.001$

Table 3

Heart Rate Variability by Race, Adjusted for Covariates

	White Mean (SE)	African American Mean (SE)	Chinese Mean (SE)	ANCOVA F test[2]	Tukey's HSD[3]
Low Frequency Power					
Absolute[1]					
Stage 2 NREM Sleep (ms^2)	472.01 (1.08)	328.65 (1.11)	246.41 (1.15)	10.34^{***}	$1>2,3^{**}$
REM Sleep (ms^2)	475.33 (1.08)	455.32 (1.11)	292.07 (1.16)	4.35^{**}	$1,2>3^{*}$
Normalized					
Stage 2 NREM Sleep (ms^2)	.66 (0.01)	.58 (0.02)	.53 (0.03)	13.70^{***}	$1>2,3^{***}$
REM Sleep (ms^2)	.77 (0.01)	.71 (0.02)	.68 (0.02)	10.77^{***}	$1>2,3^{**}$
High Frequency Power					
Absolute[1]					
Stage 2 NREM Sleep (ms^2)	232.76 (1.09)	233.69 (1.12)	213.15 (1.18)	0.12	
REM Sleep (ms^2)	123.59 (1.10)	164.84 (1.14)	127.87 (1.20)	1.41	
Normalized					
Stage 2 NREM Sleep (ms^2)	.35 (0.01)	.43 (0.02)	.47 (0.03)	13.70^{***}	$1<2,3^{***}$
REM Sleep (ms^2)	.23 (0.01)	.29 (0.02)	.33 (0.02)	10.77^{***}	$1<2,3^{**}$
Low:High Frequency Power[1]					
Stage 2 NREM Sleep (LF/HF)	2.42 (1.07)	1.69 (1.09)	1.35 (1.07)	13.73^{***}	$1>2,3^{***}$
REM Sleep (LF/HF)	5.05 (1.07)	3.51 (1.09)	2.88 (1.13)	11.58^{***}	$1>2,3^{**}$

[1] Variables were log transformed (LN) prior to analyses, values in table were back-transformed (exponential);

[2] Covariates were age, education, marital status, vasomotor symptoms, body mass index, smoking, use of medications that affect sleep and/or beta blockers, hypertension, symptoms of depression, respiration rate, apnea-hypopnea index, and leg movement arousal index;

[3] Groups: 1=White, 2=African American, 3=Chinese;

$^{*}p < 0.05$;

$^{**}p < 0.01$,

*** $p < 0.001$.