The Mediation of Racial Differences in Hypertension by Sleep Characteristics: Chicago Area Sleep Study

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BACKGROUND
Racial disparities in hypertension prevalence in the United States are established. Given our understanding of racial and ethnic disparities in sleep characteristics and demonstrated associations between sleep characteristics and hypertension, we tested whether sleep characteristics mediated racial disparities in hypertension.

METHODS
Analyses were performed in the Chicago Area Sleep Study, a population-based cohort study of 154 Blacks, 128 Whites, 103 Hispanics, and 109 Asians without obstructive sleep apnea. Participants underwent 7 days of wrist actigraphy monitoring. Algorithms were used to determine sleep duration and sleep maintenance (the percent of sleep in the sleep period). Hypertension was determined as systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg or the use of antihypertensive medications. We estimated sample prevalence ratios for hypertension before and after adjustment for sleep characteristics and also conducted mediation analysis.

RESULTS
The sample prevalence of hypertension was highest in Blacks (36%), followed by Hispanics (14%), Asians (8%), and Whites (5%). The sample prevalence ratio for hypertension for Blacks vs. Whites was 5.52 (95% confidence interval (CI): 2.36, 13.23) after adjusting for age, sex, and education. Adjustment for sleep duration had no influence on the effect estimate, but adjustment for sleep maintenance attenuated the sample prevalence ratio to 4.55 (95% CI: 1.91, 11.14). Sleep maintenance mediated 11.4% of the difference in hypertension prevalence between Blacks and Whites in this sample.

CONCLUSIONS
Sleep maintenance mediated a small but significant portion of the disparity in hypertension between Blacks and Whites. Future research should investigate the mechanisms underlying these findings.

Keywords: blood pressure; sleep maintenance; hypertension; mediation; racial disparities.

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Racial disparities in prevalent hypertension in the United States are well known. A recent analysis of 2009–2010 NHANES data showed the prevalence of hypertension was 26.3% in Mexican American men, 29.8% in White men, and 39.6% in African American men with similar disparities observed in women.[1] This same paper demonstrated that the rates of hypertension and the racial disparities have not improved from 1999–2010.[1] Despite the long-term persistence of racial disparities in hypertension, reasons underlying the disparity are poorly understood.[2]

Recently, racial disparities in sleep characteristics were characterized in the Chicago Area Sleep Study (CASS).[3] Sleep duration (minutes), minutes of wake after sleep onset (WASO), and sleep fragmentation were each less favorable in Black, Hispanic, and Asian participants than in White participants following statistical adjustment for health behaviors and clinical factors. Adverse sleep characteristics are associated with higher blood pressure and hypertension in many studies. A recent review documented extensive evidence from both cross-sectional and longitudinal epidemiologic studies that short sleep duration is associated with higher blood pressure and hypertension.[4] Short sleep duration and lower sleep maintenance (the percent of time during the sleep period spent sleeping) were associated with higher systolic and diastolic blood pressure after adjustment and exclusion of participants on antihypertensive medications.[5] A trial is currently underway to prevent hypertension using a multicomponent online sleep intervention.[6]

Given the documented disparities in sleep characteristics in CASS and demonstrated associations between sleep characteristics and hypertension, we sought to examine whether sleep characteristics (i.e., duration, sleep maintenance, fragmentation, and WASO) mediated racial disparities in hypertension prevalence in CASS. We hypothesized that differences in sleep characteristics would mediate racial disparities in hypertension.

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METHODS

Study design

CASS is a cross-sectional study explained in detail previously.[3] All participants attended 2 clinical examinations approximately 1 week apart. Women were scheduled to attend their first examination during the mid-follicular phase of their menstrual cycle. At the first examination, participants gave their consent and the procedures for wearing the Apnealink Plus apnea-screening device and the wrist actigraph (Actiwatch) were explained. Participants were given the equipment and a set of questionnaires to complete prior to the next examination that was scheduled to take place a minimum of 8 days later and a maximum of 14 days later. On the morning of the clinical examination, participants were instructed to arrive between 7:30 and 11:00 AM after having fasted for a minimum of 12 hours, and to bring all prescription medications and over-the-counter supplements that they were currently taking. All clinical measurements including blood pressure were conducted during a 3-hour examination at the second visit.

A study design feature was to include equal representation of adults from 4 racial/ethnic groups—White, Black, Hispanic/Latino, and Asian. Adults ages 35–64 years old were recruited from neighborhoods in Chicago, IL, and surrounding suburbs with a high proportion of the targeted racial and ethnic groups based on data from the US census. Participants were categorized based on their self-reported race/ethnicity at the time of the examination.

To restrict the sample to participants with a low likelihood of obstructive sleep apnea, CASS staff prescreened participants by telephone to disqualify those at high likelihood of sleep apnea. Additionally, at the first visit, participants wore the ApneaLink Plus apnea-screening device for 1 night. *Post hoc* exclusions for analysis were made for those participants with an apnea–hypopnea index <15 (a common cutoff for moderate sleep apnea) or an oxygen desaturation index (<10) based on a minimum of 4 hours of wear time and using a combination of devices including the nasal cannula, a chest belt to detect respiratory effort, and a pulse oximeter.

Measurements

Measurements of sleep characteristics in the study have been described in detail previously.[3,7] In brief, participants wore the Actiwatch 2 device (Phillips Respironics, Bend, OR) on their wrists for 7 days. Participants kept a daily sleep log to record when they went to sleep and awoke each day and the times that they napped during the preceding 24-hour interval. If the participants did not use the marker on the Actiwatch device to indicate time in bed, self-reports based on the Karolinska sleep diary were used to identify the bedtimes and wake times. Sleep characteristics were determined using the device software algorithms. Nocturnal sleep duration was quantified as the amount of actual sleep during time in bed. The sleep period is the interval between sleep onset and sleep end, both estimated by the algorithm. There are 3 indicators of sleep quality examined in these analyses. First, the number of minutes of WASO were calculated. Second, sleep maintenance was calculated as the percentage of time the participant was asleep during the sleep period, which is the interval between sleep onset to sleep end. Both sleep onset and sleep end are determined by the software algorithm. Third, sleep fragmentation is an index of restlessness during the sleep period expressed as a percentage. It is calculated by summing the following 2 percentages: (i) the percentage of the sleep period spent moving (an epoch with >2 activity counts is considered moving) and (ii) the percentage of the number of immobile phases (consecutive epochs with no movement) that are only 1 minute long or less. The average values for each of the sleep characteristics were calculated for the 7 days.

At the clinical examination, blood pressure was measured using an Omron automated cuff from participants in a seated position after 5 minutes of rest. Three measurements were collected and the final 2 were averaged. Hypertension was defined if participants had systolic blood pressure >140, diastolic blood pressure >90, or self-reported using antihypertensive medications.

Years of completed education completed was captured as a measure of socioeconomic status. Work status (i.e., full time, part time, or unemployed) and schedule (i.e., regular day shift, night shift, or swing shift) were queried as both an additional measure of socioeconomic status and an indicator of regular sleep patterns. Questionnaires were used to ascertain smoking status, which was categorized into current, former, and never and alcohol consumption which was measured in drinks per week. Physical activity was assessed using the Global Physical Activity Questionnaire (GPAQ), a self-reported surveillance instrument that captures the frequency and duration of engagement in 3 domains of activity (i.e., work, leisure, and transportation) and sedentary behavior.[8] Depressive symptoms were assessed using the Centers for Epidemiologic Studies Depression Scale (CES-D).[9] Height and weight were measured in light examination clothes and no shoes. BMI was calculated as weight in kilograms divided by the height in meters squared.

Statistical methods

All statistical analyses were carried out in SAS v9.4. Analysis of variance and chi-square tests were used to examine the univariate associations of covariates across each of the 4 self-identified racial and ethnic groups. In order to investigate the effect of sleep on the association between race and hypertension, and to calculate prevalence ratios before and after adjusting for sleep, we fit a series of multivariable Poisson regression models.[10] Fully adjusted models included the following confounders: age, sex, years of education, smoking status, alcohol intake, depressive symptoms, BMI, and work schedule—all of which have been shown to be associated with hypertension or sleep characteristics in previous studies. Sleep characteristics were modelled continuously. Sample prevalence ratios were estimated instead of odds ratios because hypertension is not a rare outcome.[10]

We conducted a mediation analysis using the approach and SAS macro developed by Valeri and VanderWeele.[11] This approach allows us to derive estimates for the direct and indirect effects of race on hypertension by fitting 2 models: (i) log-linear model (Poisson model) for hypertension, and (ii) linear regression model for sleep characteristics. In the fully adjusted model, the log-linear model includes race, sleep

characteristics, and a set of confounders while the linear regression model includes race and the same set of confounders. We also calculated the proportion of the total effects mediated by sleep characteristics from these combined models. The proportion of the total effects mediated by sleep is defined as the ratio of the natural indirect effect over the total effect.

RESULTS

Table 1 shows the characteristics of the study population (n = 494) in total and stratified by self-identified racial and ethnic group. The sample prevalence of hypertension differed significantly between Whites (hypertension prevalence = 5%) and Blacks (hypertension prevalence = 36%) in our sample with Hispanics and Asians having a prevalence of hypertension between Whites and Blacks. As reported previously,[3] sleep characteristics including sleep duration, sleep maintenance, WASO, and sleep fragmentation all differed significantly across the 4 racial and ethnic groups. In all cases, Whites had, on average, the most favorable sleep characteristics and Blacks had, on average, the least favorable sleep characteristics (i.e., shorter duration and smaller maintenance and greater fragmentation and WASO).

Before starting formal mediation analyses, the associations of all sleep characteristics (modelled in quartiles) with sample hypertension prevalence were examined to better understand the relationships of the variables. Sleep maintenance, WASO, and sleep fragmentation were all significantly associated with prevalent hypertension ($P < 0.001$). The similarity of results for these 3 traits is not surprising given the correlations between the 3 are all strong and highly significant ($P < 0.001$) (sleep maintenance and WASO $r = -0.93$, sleep maintenance and fragmentation $r = -0.83$, fragmentation and WASO $r = 0.75$). Sleep duration was not significantly associated with sample hypertension prevalence ($P = 0.66$). Unadjusted and adjusted prevalence ratios for hypertension by quartile of sleep maintenance and sleep duration are presented in Supplementary Table 1. Because of the high correlation between sleep maintenance, WASO, and sleep fragmentation and because of the lack of association of sleep duration with hypertension prevalence in this sample, we chose to focus in this paper on the results for sleep maintenance and present the results for the other sleep characteristics in a supplementary table (Supplementary Table 2).

Table 2 presents a series of sample prevalence ratios for hypertension by race before and after adjustment for sleep maintenance. Model 1 shows that, in this sample, with minimal adjustment for age gender, and education, Blacks had 5.5 times the prevalence of hypertension as Whites (prevalence ratio = 5.52 (95% confidence interval (CI): 2.33, 13.08)). Asian Americans and Hispanics also had a higher sample prevalence of hypertension than Whites, but these prevalence ratios were not statistically significant. Model 2 showed that additional adjustment for sleep maintenance decreased the sample prevalence ratio for hypertension between Blacks and Whites from 5.5 to 4.6, but the association remained statistically significant. Small decreases were also seen in the sleep maintenance-adjusted hypertension prevalence ratios for

Table 1. Study characteristics by race/ethnicity

Characteristic	All (n = 494)	Black (n = 154)	White (n = 128)	Hispanic (n = 103)	Asian (n = 109)	P*
Age (years)	48 (8)	49 (8)	46 (8)	47 (8)	49 (8)	0.0030
Sex, % female	60	66	49	66	60	0.0206
Hypertension (%)	17	36	5	14	8	<0.0001
Sleep maintenance (%)	90 (5)	88 (5)	92 (4)	90 (4)	91 (5)	<0.0001
Wake after sleep onset (minutes)	44 (22)	53 (27)	37 (16)	43 (20)	39 (18)	<0.0001
Sleep duration (minutes)	420 (64)	409 (67)	443 (49)	417 (80)	413 (51)	<0.0001
Sleep fragmentation (%)	20 (8)	23 (8)	18 (7)	20 (8)	18 (8)	<0.0001
Education, years	16 (4)	15 (3)	17 (3)	12 (4)	18 (3)	<0.0001
Current smoking (%)	19	32	15	20	5	<0.0001
Current alcohol (drinks per week)	4 (7)	3 (6)	8 (10)	2 (4)	1 (2)	<0.0001
Depressive symptoms (CES-D score)	11 (10)	13 (9)	10 (11)	12 (9)	10 (10)	0.1467
Work schedule, %						
Retired/unemployed	31	45	18	36	19	<0.0001
Employed—day shift	51	36	59	42	70	
Employed—other shift	19	18	23	22	11	
Weight status, %						
Normal weight	45	28	55	18	81	<0.0001
Overweight	32	31	34	48	17	
Obese	23	41	12	34	3	

Mean (SD). *P for comparison across all four groups per chi-square or ANOVA. Abbreviation: ANOVA, analysis of variance; CES-D, Centers for Epidemiologic Studies Depression Scale.

Hispanics and Whites and Asians and Whites. Models 2 and 3 show that a difference of 1 SD in sleep maintenance (about 5 percentage points) was associated with a statistically significant 20% lower prevalence of hypertension (prevalence ratio = 0.80 (95% CI: 0.65, 0.98)) in this sample. Finally, model 3 demonstrated that further adjustment for several potential lifestyle confounders did not meaningfully reduce the association between sleep maintenance and hypertension.

Table 3 presents the results of the mediation analysis. In a fully adjusted model, the total effect, or observed sample hypertension prevalence ratio between Blacks and Whites was 4.30 (95% CI: 1.74, 10.60). The sample prevalence ratio for the effect of race on hypertension prevalence through sleep maintenance (i.e., the indirect effect) was 1.18 (95% CI: 1.01, 1.39). This means 11.4% of the difference in hypertension prevalence between Blacks and Whites was driven by disparities in sleep maintenance in this sample. Proportion of racial and ethnic differences in hypertension explained by sleep maintenance were similar for Asians vs. Whites (9.3%) and Hispanic vs. Whites (10.0%) but we did not consider these proportions significant as the natural indirect effect estimates for the differences between these 2 groups were not significant. We explored whether residual confounding by apnea–hypopnea index (between 0 and 15) was present in the mediation analysis by both adjusting for Apnea–hypopnea index as a continuous variable and repeating the analyses in the subset of participants with apnea–hypopnea index less than or equal to 5. In both cases, the results of analysis changed little. For WASO and sleep fragmentation, the natural indirect effect of the sleep characteristic was statistically significant when comparing sample hypertension prevalence in Blacks and Whites, suggesting that these sleep characteristics also mediated a significant portion of the difference in sample hypertension prevalence between these 2 groups. In contrast, the natural indirect effect of sleep duration was not statistically significant when comparing sample hypertension prevalence in any racial and ethnic groups (Supplementary Table 2).

DISCUSSION

In this study, we sought to determine if racial and ethnic differences in sleep characteristics might mediate racial and ethnic disparities in hypertension prevalence in our study sample. Sleep maintenance, WASO, and sleep fragmentation, all significantly mediated the difference in hypertension prevalence between Blacks and Whites; sleep maintenance mediated over 11% of the difference in hypertension prevalence between Blacks and Whites in our sample.

Although several studies have examined the association between self-reported sleep duration and hypertension,[4]

Table 2. Sample prevalence ratios of hypertension by race and sleep maintenance

	Model 1 PR (95% CI)	Model 2 PR (95% CI)	Model 3 PR (95% CI)
Race			
Black vs. White	5.52 (2.33, 13.08)	4.55 (1.88, 10.99)	3.65 (1.45, 9.17)
Asian vs. White	1.58 (0.56, 4.44)	1.50 (0.53, 4.24)	2.00 (0.67, 5.98)
Hispanic vs. White	2.23 (0.79, 6.29)	2.15 (0.76, 6.08)	1.93 (0.66, 5.69)
Sleep maintenance (per SD)		0.80 (0.66, 0.96)	0.80 (0.65, 0.98)

Model 1: adjusted for age, sex and education; model 2: adjusted for model 1 + sleep; model 3: adjusted for model 2 + current smoking, current alcohol intake, depressive symptoms, work schedule, BMI. Abbreviations: BMI, body mass index; CI, confidence interval; PR, sample prevalence ratio.

Table 3. Estimates of direct effects and indirect effects of race on hypertension and the percent mediated by sleep maintenance

	Natural direct effect	Natural indirect effect	Total effect	Percent mediated through sleep maintenance
	PR (95% CI)	PR (95% CI)	PR (95% CI)	%[a]
Model 1				
Black vs. White	4.55 (1.88, 10.99)	1.19 (1.02, 1.39)	5.40 (2.27, 12.86)	10.2
Asian vs. White	1.50 (0.53, 4.24)	1.05 (0.98, 1.13)	1.58 (0.56, 4.47)	11.0
Hispanic vs. White	2.15 (0.76, 6.08)	1.06 (0.98, 1.15)	2.29 (0.81, 6.47)	7.4
Model 2				
Black vs. White	3.65 (1.45, 9.17)	1.18 (1.01, 1.39)	4.30 (1.74, 10.60)	11.4
Asian vs. White	2.00 (0.67, 5.98)	1.07 (0.98, 1.17)	2.15 (0.72, 6.41)	9.3
Hispanic vs. White	1.93 (0.66, 5.69)	1.08 (0.98, 1.18)	2.08 (0.71, 6.10)	10.0

Model 1: adjusted for age, race, sex, education, and sleep; model 2: adjusted for model 1 + smoking status, alcohol intake, depressive symptoms and work schedule, BMI. Abbreviations: BMI, body mass index; CI, confidence interval; PR, sample prevalence ratio.

[a]The proportion of the total effects mediated by sleep maintenance is defined as the ratio of the natural indirect effect over the total effect.

there are few studies that included measures determined objectively *via* actigraphy (i.e., sleep maintenance, WASO, or fragmentation). We observed that sleep maintenance was a significant negative predictor of prevalent hypertension whereas there was no association with sleep duration. Previous research has demonstrated that poor sleep quality is associated with pulsatile cortisol release[12] and autonomic activation[13] which may persistently raise blood pressure.[14] In this population, we hypothesize that minutes of WASO (reflected by sleep maintenance and higher fragmentation), may contribute more to variation in blood pressure (and thus mediate more of the racial differences in blood pressure) than sleep duration. Because sleep duration can vary according to individual sleep needs and be curtailed for a variety of voluntary and involuntary reasons, measures that reflect sleep quality may be more strongly associated with cardiovascular risk.

There are several strengths to this study. CASS employed high-quality "objective" assessment of sleep characteristics. Objective assessments of sleep duration *via* actigraphy have been demonstrated to be superior to self-reported sleep duration which is biased by habitual over reporting.[15] Additionally, CASS included a study population without obstructive sleep apnea thus assessing sleep characteristics (and variable associations with sleep characteristics) without potential confounding from obstructive sleep apnea. CASS included a large sample size of 4 different racial and ethnic groups which permitted examination of racial and ethnic disparities in multiple groups. Finally, we conducted a formal statistical assessment of mediation.

An important limitation to the generalizability of our findings is that the inclusion criteria for the study (which sought to only include people with a low likelihood of prevalent obstructive sleep apnea) lowered the prevalence of hypertension in this population compared to population-based studies. Consequently in our sample, whites had much a lower prevalence of hypertension than similarly aged whites according to the most recent hypertension prevalence estimates from NHANES[1]; however, our prevalence estimates for Black participants were more similar to those in NHANES. Our inclusion criteria would have only biased our mediation estimates if our strategies to determine apnea risk (i.e., questionnaires and the ApneaLink Plus apnea-screening device) differentially determined risk based on self-identified race, which we believe to be unlikely. However, whether our results could be extended to a population with or at high risk for sleep apnea is unknown.

Another limitation is a cross-sectional design, which did not permit assessment of temporality; our model assumes that lower sleep maintenance increases hypertension, but it is possible that hypertension leads to a lower sleep maintenance. Also, although this study was larger than many others, the sample sizes in each of the racial and ethnic groups limited the power for some analyses. Finally, the estimation of natural direct and indirect effects assumes appropriate control of confounding for the exposure—outcome, exposure—mediator, and mediator-outcome relationships, as described in detail by Vanderweele.[16] As the relationships of sleep maintenance to hypertension and race are, as yet, incompletely understood, we may not have included all relevant confounders in regression models.

In conclusion, our results suggest that sleep maintenance (as well as the highly correlated traits sleep fragmentation and WASO) may mediate part of the racial and ethnic disparity in US hypertension prevalence between Blacks and Whites. Future research should investigate the mechanisms underlying these findings.

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DISCLOSURE

The authors declared no conflict of interest.

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