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Diurnal Cortisol Slope and Nighttime Blood Pressure: A Study in European Americans and African Americans

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Objectives: African Americans (AAs) have higher nighttime blood pressure (BP) than European Americans (EAs). Stress has been suggested to play a role in this difference, but the mechanism is not well-understood. Flatter diurnal cortisol slope (DCS) is a well-known biological marker of stress. The objectives of this study were to: 1) examine ethnic differences in DCS; 2) evaluate the association between DCS and nighttime BP; and 3) determine the extent to which ethnic differences in nighttime BP can be explained by ethnic differences in DCS.

Methods: A total of 510 participants (age range: 14-35 years; 49.6% AAs, 54.5% females) provided four salivary cortisol samples at bedtime, wakeup, 30-minutes post-wakeup, and 60-minutes post-wakeup. Additionally, participants wore an ambulatory BP monitor for 24 hours. DCS was calculated as the average of the three morning samples minus the bedtime measurement.

Results: After adjustment for age, sex, BMI, and smoking, AAs had blunted DCS (P=.018) and higher nighttime systolic BP (SBP) and diastolic BP (DBP) (Ps<.001) compared with EAs. The DCS was inversely related to nighttime SBP and this relationship did not depend on ethnicity. The ethnic difference of nighttime SBP was significantly attenuated upon addition of DCS to the model. Mediation test showed that 9.5% of ethnic difference in nighttime SBP could be explained by DCS (P=.039).

Conclusion: This study confirms ethnic differences in DCS and nighttime BP and further demonstrates that the ethnic differences in DCS can, at least partially, explain the ethnic differences found in nighttime BP. *Ethn Dis*. 2021;31(4):481-488; doi:10.18865/ed.31.4.481

Introduction

The leading cause of death in the United States is cardiovascular disease (CVD).[1] Psychosocial stress is often rooted in factors leading to CVD, but their association is not well understood.[2] Understanding of the stress risk factor and the application of stress management in the clinical setting is increasing but still relatively limited.[2] Learning more about the connections between stress and CVD is vital for greater clinical application in its prevention.

A well-known biological marker of stress is cortisol. The physiological response to stress initially involves the activation of the hypothalamic-pituitary-adrenal (HPA) axis. This HPA axis activation leads to the adrenocorticotropic hormone (ACTH) release from the pituitary gland, which acts on the adrenal cortex to release cortisol. Cortisol acts in a negative feedback loop on the HPA axis; increasing cortisol concentrations in the blood will inhibit further ACTH release, thus maintaining an appropriate cortisol level for the stress response. While the natural "fight, flight, or freeze" response during acute stress is normal and healthy, prolonged chronic stress leads to irregular HPA axis activity that causes negative physiological and psychological health outcomes.[3]

Cortisol levels follow a diurnal pattern, in which concentrations peak in the morning, decline during the day into the late evening, and rise during the night.[4] Disruptions or variations to typical cortisol circadian rhythms have been extensively studied and linked to poor health outcomes.[5-7] For example, a meta-analysis reported associations between flatter diurnal cortisol slopes

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and poorer health, including depression, cancer, CVD, and other mental and physical health outcomes.[5]

Studies have also examined ethnic differences in cortisol variation and have found that ethnic groups exhibit distinct diurnal cortisol patterns.[8-11] When compared with European Americans (EAs), African Americans (AAs) have flatter diurnal cortisol slopes (DCS), lower cortisol secretion in the morning and throughout the day, and higher bedtime cortisol; all of these have been observed in youth as well as middle-aged and older adults.[8-11] These findings are more pronounced in low socio-economic AAs.[10] These distinct ethnic cortisol patterns among AAs (ie, blunted cortisol profiles) are shown to be stable over time.[12]

We hypothesized that AAs have flatter DCS that can at least partially explain AAs' higher nighttime BP.

Just as cortisol is a common marker of the body's physiological response to stress, blood pressure (BP) is a common indicator of cardiovascular health, particularly nighttime BP or nighttime BP fall as a predictor of cardiovascular events and mortality.[13,14] Similar to cortisol, BP also follows a circadian rhythm of falling at night and rising in the morning. Previous studies have shown that AAs have higher nighttime BP and therefore blunted nocturnal decline of BP compared with EAs[15]; this has been seen in AAs as early as aged 10 years.[16] While this ethnic difference in nighttime BP has been observed, the underlying mechanism is still not completely understood. It is known that long-term health problems exist when BP varies from "normal" patterns, eg, blunted decline in nocturnal BP is a risk factor for cardiac mortality.[17] Therefore, investigating this mechanism is important in order to understand how to help lessen the apparent ethnic health disparities.

One study observed that decreased diurnal variation in cortisol is associated with decreased diurnal variation in BP in a sample consisting of a majority of Caucasians.[18] Since ethnic health disparities can be rooted in psychosocial stressors and AAs exhibit a distinct cortisol profile, comparing ethnic differences in DCS may provide insight into the mechanisms underlying the ethnic difference found in BP differences. No studies have specifically examined the ethnic differences in DCS as they relate to ethnic differences in nocturnal BP.

The objectives of this study were to: 1) examine ethnic differences in DCS; 2) evaluate the association between DCS and nighttime BP; and 3) determine the extent to which ethnic differences in nighttime BP can be explained by ethnic differences in DCS. We hypothesized that AAs have flatter DCS that can at least partially explain AAs' higher nighttime BP.

Methods

Participants

This study included 510 participants (age range: 14-35 years; 49.6% AAs, 54.5% females) who were enrolled in either the Georgia Cardiovascular Twin Study (n=297, 118 twin pairs and 61 singletons) or the Georgia Stress and Heart Study (n=213, 153 individuals and 60 siblings) with salivary cortisol samples obtained at four time points (bedtime, wakeup, 30-minutes post-wakeup, and 60-minutes post-wakeup). Participants came in for one visit between 2007 and 2010. Criteria for classifying participants as AAs or EAs as well as study design and selection criteria have previously been described.[19,20] Of the 510 participants, 13 were taking antihypertensive medications. When participants on antihypertensive medication were excluded from the analyses, the results were virtually unchanged, so results for the entire sample are reported here.

The institutional review board at the Medical College of Georgia gave approval for the studies. Each participant or their parents, if participants were aged <18 years, gave written consent prior to any involvement, in accordance with the institutional guidelines.

At the laboratory, anthropometric measurements were obtained, including height on a wall-mounted stadiometer and weight on a digital scale. Body mass index (BMI) was calculated as weight/height^2 (kg/m^2). Participants self-reported their smoking status; a participant was considered a smoker if

they smoked at least five cigarettes in the past 30 days. Of the 510 participants, 126 were smokers.

Blood Pressure

Participants underwent ambulatory BP monitoring for 24 hours. Our procedures for these measurements have been described previously in detail.[16] Briefly, the cuff was fitted on the non-dominant arm (model 90207; SpaceLabs, Redmond, WA). Recordings took place every 20 minutes during the day (8 AM to 10 PM) and every 30 minutes at night (midnight to 6 AM). Transitional periods from 6 AM to 8 AM and 10 PM to midnight were excluded from analyses. The adequacy of recordings was defined as ≥ 14 readings during the 14 h designated as daytime and ≥ 6 readings during the 6 h designated as nighttime, as recommended by the European Society of Hypertension Working Group on Blood Pressure Monitoring.[21] Acceptable readings were defined according to the following criteria: pulse pressure ≥20 mm Hg; pulse pressure ≤140 mm Hg; heart rate ≥40 beats/min; and heart rate ≤180 beats/min.

Cortisol

Salivary cortisol samples were obtained at four time points: a) bedtime; b) wake-up time; c) 30-minutes post-wakeup; d) 60-minutes post-wakeup. Participants were instructed to not eat, drink, brush their teeth or smoke at least 30 minutes before collecting their sample. The passive drool technique was used, in which participants expelled unstimulated saliva through a small plastic straw into a 2 mL polypropylene vial. They were instructed to place collection tubes in the freezer after each sample collection. For recording collection times, the Medication Event Monitoring System (MEMS; Aardex Ltd., Switzerland) was used. This device timestamps each occurrence when the subject removes a collection tube from the MEMS and increases likelihood of compliance.[22] At the end of the collection period, participants brought the samples to the lab where it was immediately stored at -80ºC until shipped for assay to Trier University in Germany. Cortisol concentrations were measured using time-resolved immunoassays with fluorescence detection and intra- and inter-assay coefficients of variance below 6.7% and 9.0%.[23] To compute DCS, we took the average of the three morning samples minus the bedtime measurement.

Table 1. General characteristics of the participants

	European Americans	African Americans	P
N	257	253	
Females	49.42%	59.68%	.02
Age, yr	23.3 ± 4.4	24.2 ± 5.0	.01
BMI[a] , kg/m^2	25.8 ± 6.0	28.7 ± 8.0	.001
Smoker	32.30%	17.00%	<.001
Bedtime cortisol[b] , nmol/l	1.83 ± 2.44	1.86 ± 2.17	NS
Wakeup cortisol[b] , nmol/l	8.31 ± 4.12	7.64 ± 3.63	NS
DCS[b] , nmol/l	6.5 ± 4.7	5.8 ± 3.9	.018
Nighttime SBP[b,c] ,mm Hg	107.3 ± 9.6	110.3 ± 10.3	<.001
Nighttime DBP[b,c] , mm Hg	59.1 ± 7.2	62.4 ± 8.2	<.001
Daytime SBP[b,d] , mm Hg	119.5 ± 8.9	119.5 ± 9.5	NS
Daytime DBP[b,d] , mm Hg	71.9 ± 7.4	72.6 ± 7.8	NS

Values are mean ± standard deviation, unless otherwise indicated.
BMI, body mass index; DCS, diurnal cortisol slope; SBP, systolic blood pressure; DBP, diastolic blood pressure
.
a. For the test of race difference, age and sex were included in the model as covariates.
b. For the test of race difference, age, sex, BMI, and smoking were included in the model as covariates.
c. A smaller sample size of 460 participants with 237 EAs and 233 AAs.
d. A smaller sample size of 488 participants with 247 EAs and 241 AAs.

Statistical Analysis

All analyses were performed using Stata software. BP was log transformed for normality and these transformed BP values were used in statistical analysis. Generalized estimating equations (GEE) were used to account for family correlation (siblings and twins) when testing the associations. These GEE models (adjusted for age, sex, BMI, and smoking) tested whether ethnic differences exist in DCS and BP. We also examined the association between DCS and BP using GEE models adjusted for age, sex, ethnicity, BMI, and smoking. Linear mixed model was also used to confirm the results from GEE with either family or family and zygosity (this is, allowing the parameter estimations to be different between identical twins and non-identical twins) as random intercepts. Since similar results were obtained from all three models (ie, GEE, mixed model

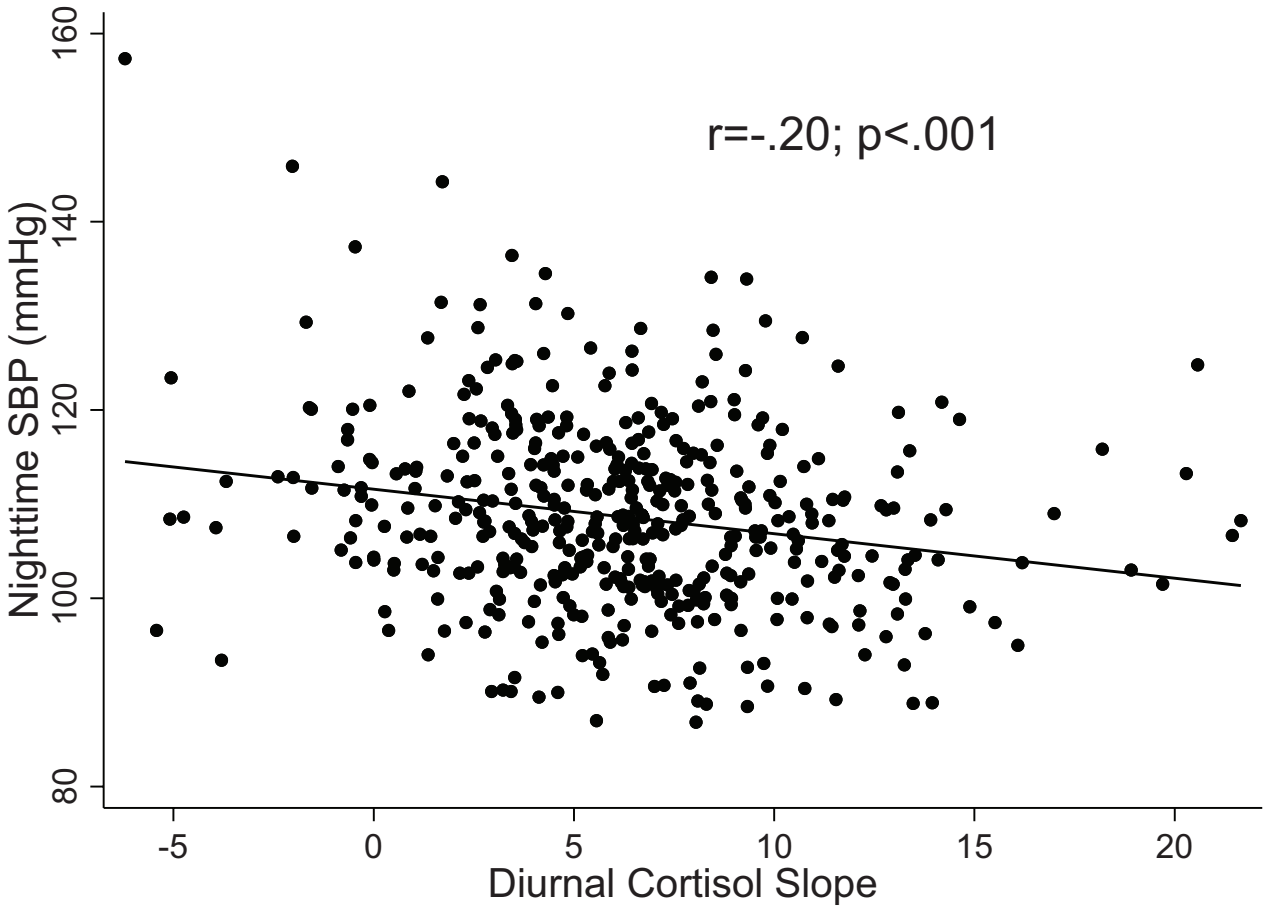

Figure 1. Correlation between diurnal cortisol slope and nighttime systolic blood pressure (SBP)

with family as random intercept or mixed model with family and zygosity as random intercepts), only the results from GEE model were reported.

Mediation was suspected when upon addition of DCS to the model, the effect size of the ethnic difference in BP decreased. We performed mediation analysis to test whether DCS can mediate the ethnic differences in BP.[24] We used bootstrapping to test for mediation significance.[25] The covariates in all models included age, sex, BMI, and smoking.

Results

Participant characteristics, grouped by ethnicity, are presented in Table 1. Compared with AAs, more EAs were smokers (P<.001). After adjustment for age and sex, AAs had significantly higher BMI than EAs (P=.001). After adjustment for age, sex, BMI, and smoking, AAs had significantly lower DCS compared with EAs (P=.018). However, AAs had significantly higher nighttime SBP (P<.001) and DBP than EAs (P<.001). There was no significant difference in bedtime cortisol, wakeup average cortisol, daytime SBP and daytime DBP between AAs and EAs although the difference in the wakeup average cortisol levels was borderline significant (P=.073).

There was a statistically significant correlation between DCS and nighttime SBP (r=-.20, P<.001; Figure 1) and DBP (r=-.10, P=.04) as well as daytime SBP (r= –.11, P=.02). There was also a statistically significant correlation of bedtime cortisol (r=.13, P=.006) and wakeup

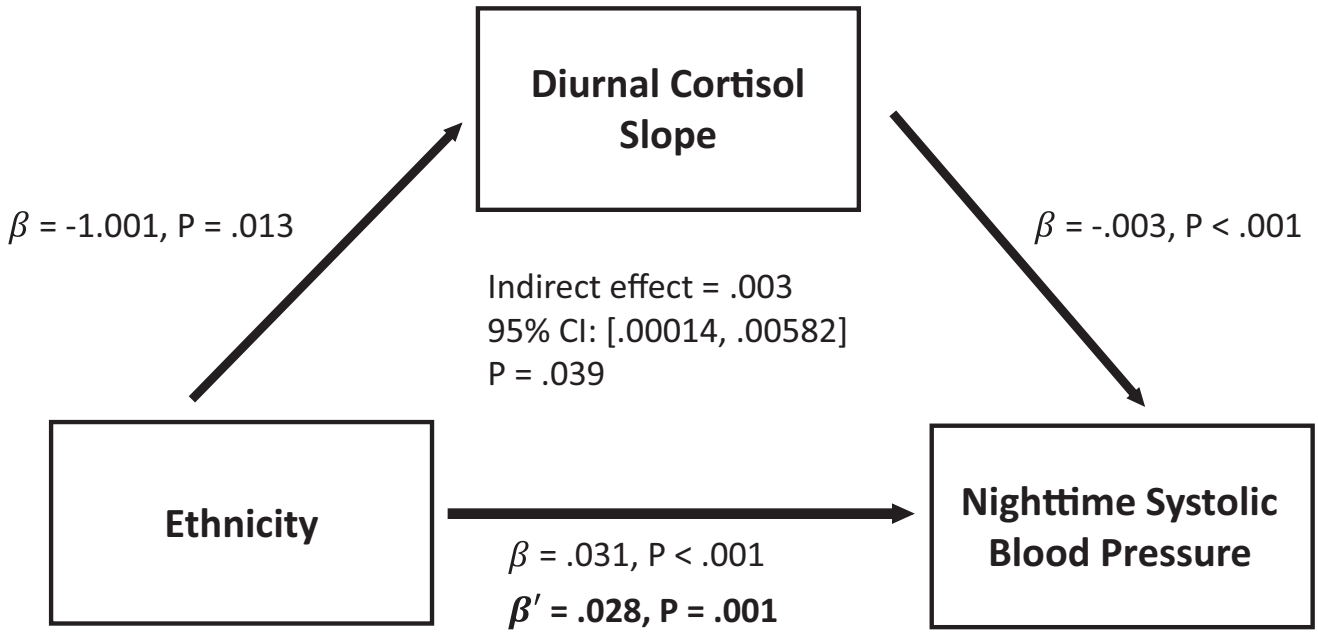

Figure 2. Partial mediation model illustrating diurnal cortisol slope mediating the effect of ethnicity on nighttime systolic blood pressure.
When the mediator is present, change in beta is in bold. The numbers in the center show the output from bootstrapping. Our mediation analysis indicates that 9.5% of the ethnicity difference in nighttime SBP could be explained by DCS.

average cortisol (r=-.17, P<.001) with nighttime SBP. No significant correlation of DCS with daytime DBP was observed. After including age, sex, ethnicity, BMI, and smoking as covariates into the regression model, the association between DCS and nighttime SBP remained significant (P=.026). No significant interaction between ethnicity and DCS on nighttime SBP was identified, indicating the inverse association between DCS and nighttime SBP exists in both EAs and AAs.

We performed mediation analysis to test whether ethnic differences in DCS can explain the ethnic differences in nighttime SBP (Figure 2). Upon addition of DCS to the model, the ethnic difference in nighttime SBP was attenuated. A bootstrapping test for significance revealed that the mediation effect was significant (P=.039) and the DCS explains 9.5% of the ethnicity difference in nighttime SBP.

Discussion

The primary aim of this study was to investigate ethnic differences in DCS as a means for explaining the blunted nocturnal BP dip seen in AAs. We observed that AAs experienced flattened DCS as compared with EAs. Moreover, the flattened DCS was associated with higher nighttime SBP in both AAs and EAs. To our knowledge, this is the first study to demonstrate that the ethnic differences in DCS can, at least partially, explain the ethnic differences found in nighttime BP.

It has been well-established that a flattened cortisol profile from morning to evening has been associated with negative mental and physical health outcomes.[5,26,27] With this foundation, recent studies have specifically examined the relationship between diurnal cortisol patterns and health outcomes related to CVD; however, the research is limited. One recent meta-analysis[5] found a lack of significant association between DCS and CVD, but only considered four studies to reach that conclusion.

In order to further investigate cortisol's effect on CVD, our study focused on DCS as it relates to nighttime SBP and found they had a statistically significant inverse rela-

tionship, regardless of age, sex or ethnicity; namely, a flattened cortisol rise was associated with a high nighttime BP. Since nighttime BP is a reliable indicator of cardiovascular health, our findings can support the link between flattened diurnal cortisol patterns and CVD. Other studies have similar findings related to coronary calcification[27] and atherosclerosis.[26]

More research is needed to investigate the association between cortisol patterns and CVD, particularly long-term follow-up studies. It is also important to point out that the observed correlation coefficient (r=-.2) between DCS and nighttime SBP in the current study is in the range of .1-.3, a correlation coefficient range that indicates a weak association. The weak association might be due to the fact that this is an observational study with the data collected from participants in the real-life setting rather than a well-controlled experimental setting. Future studies in the experimental setting are warranted to confirm the association.

To our knowledge, this is the first study to demonstrate that the ethnic differences in DCS can, at least partially, explain the ethnic differences found in nighttime BP.

We hypothesize that the inverse relationship between DCS and nighttime SBP is a result of abnormal physiologic stress response. Chronic stress leads to persistent HPA axis activation, ultimately causing its wear and tear.[28] Thus, variations seen in the stress hormone cortisol may be an indicator of variations in stress response. Our results showed that AAs had a flattened DCS compared with EAs. This difference in cortisol pattern is likely linked to underlying stress differences between the two groups. Studies have found that dysregulation of the stress systems (eg, blunted cortisol patterns) are linked to psychosocial stressors, such as racial discrimination[29] and low socioeconomic status,[30] all of which are stressors that AAs are more likely to experience.[31, 32] Additional studies are needed to clarify the role of psychosocial stressors in the ethnic differences of cortisol and BP observed in our and other studies.

Ethnic differences in circadian BP patterns are well-established. Our study supports the notion that AAs typically have less of a dip in nocturnal BP as compared with EAs.[15] However, the reasons for this are not well-understood and thus drove us to investigate the possible connections between cortisol and BP. Although the mechanisms are not clear, we demonstrated in this study that the difference in diurnal cortisol secretion between AAs and EAs could be a contributor to the ethnic differences in nighttime SBP. Specifically, our mediation analysis indicates that 9.5% of the ethnic difference in nighttime SBP could be explained by DCS. Although we observed diurnal cortisol secretion pattern as a significant contribution to the ethnic difference in nighttime SBP, these results do not confirm biological mediation and should be validated by prospective interventional studies.

An important element of this study is the method of measurement. Typically, diurnal cortisol patterns are measured from cortisol readings taken during the day and into the evening. However, we chose to measure changes in cortisol secretions from evening to morning. Another study also measured cortisol in this way, claiming that it required fewer samples at more practical times and eliminates confounding daytime effects such as meals and acute stressors.[26] We expect our DCS measurement to provide a similar picture of cortisol variation compared with daytime diurnal cortisol slope since they parallel each other (ie, one looks at the rise while the other looks at the fall of cortisol).

Study Limitations

In addition to the method of measurement, the frequency of the cortisol measurement is a point of debate in research. While one study's results suggest that four collection points is in the optimal range for predicting associations between diurnal cortisol patterns and health outcomes,[5] another study suggested 5-6 samples per day as optimal.[33] Diurnal cortisol patterns are not highly stable from day-to-day,[34] so our cortisol sampling over the course of one day may not be truly representative of diurnal cortisol patterns among EAs and AAs. However, previous re-

search findings have indicated that single day sampling was similar to multi-day sampling in showing associations between diurnal cortisol slopes and health outcomes.[5] It remains unclear if our method of cortisol sample collection is ideal for investigating ethnic differences in cortisol patterns as related to CVD. Since this area of research is still developing, future studies could investigate this relationship under various circumstances (eg, single-day vs multi-day, and varying the number of collection points).

Furthermore, diurnal cortisol patterns are also impacted by shift-work, sleep disorders, or circadian rhythm sleep-wake disorders. Although the lack of measurements on these factors prevents us from exploring their potential confounding effects on the current findings, the impacts should be limited because of the relatively young age of the participants of the current study. In addition, endogenous circadian markers, such as core body temperature, dim light melatonin onset and rest-activity rhythm, should also be measured under constant routine or forced desynchrony circadian protocols for better control of the environmental factors. Another limitation of the methodology is that fixed time period was used to define day and night rather than diary records. We excluded the transitional periods from 06:00 to 08:00 hours and 22:00 hours to midnight to limit the potential impact of variability in sleep onset and offset in the population.

In addition to the afore-mentioned limitations of our study, we only examined DCS and BP in EAs and AAs. Future studies could benefit from examining differences in other ethnic populations, since other populations have also shown distinct cortisol patterns and BP patterns.[8]

Conclusion

Increasing evidence exposes the substantial health disparities between AAs and EAs, including the risk for CVD. Understanding the underlying mechanisms is essential to helping decipher the causes of the ethnic health disparities, in order to reduce the gap. Our study confirmed that AAs, compared with EAs, exhibited a flattened diurnal cortisol slope. Our study also suggested that the ethnic difference in DCS could partly explain the established ethnic difference in nighttime SBP, an important finding that may help the prevention and management of hypertension in AAs.

Acknowledgments

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Conflict of Interest

No conflicts of interest to report.

Author Contributions

Research concept and design: Su, Treiber, Wang; Acquisition of data: Treiber, Snieder; Data analysis and interpretation: Ernst, Su, Wang; Manuscript draft: Ernst, Snieder, Wang; Statistical expertise: Ernst, Su; Acquisition of funding: Treiber, Snieder; Administrative: Treiber,

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