Association Between Sleep and Blood Pressure in Midlife

The CARDIA Sleep Study

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Background: Epidemiological studies have reported an association between self-reported short sleep duration and high blood pressure (BP). Our objective was to examine both cross-sectional and longitudinal associations between objectively measured sleep and BP.

Methods: This study is ancillary to the Coronary Artery Risk Development in Young Adults (CARDIA) cohort study. Blood pressure was measured in 2000 and 2001 and in 2005 and 2006. Sleep was measured twice using wrist actigraphy for 3 consecutive days between 2003 and 2005. Sleep duration and sleep maintenance (a component of sleep quality) were calculated. Analyses included 578 African Americans and whites aged 33 to 45 years at baseline. Outcome measures were systolic BP (SBP) and diastolic BP (DBP) levels, 5-year change in BP, and incident hypertension.

Results: After we excluded the patients who were taking antihypertensive medications and adjusted for age, race, and sex, shorter sleep duration and lower sleep maintenance predicted significantly higher SBP and DBP levels cross-sectionally as well as more adverse changes in SBP and DBP levels over 5 years (all \( P < .05 \)). Short sleep duration also predicted significantly increased odds of incident hypertension (odds ratio, 1.37; 95% confidence interval, 1.05-1.78). Adjustment for 16 additional covariates, including snoring and daytime sleepiness, slightly attenuated the associations between sleep and BP. Sleep duration appeared to mediate the difference between African Americans and whites in DBP change over time (\( P = .02 \)).

Conclusion: Reduced sleep duration and consolidation predicted higher BP levels and adverse changes in BP, suggesting the need for studies to investigate whether interventions to optimize sleep may reduce BP.

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EARLY ONE-THIRD OF Americans have high blood pressure (BP), and 7 million deaths worldwide are attributed to high BP each year. Recently, 2 large epidemiological studies reported an association between self-reported sleep duration and the prevalence or incidence of hypertension. Identifying a novel lifestyle risk factor for high BP could lead to new interventions to prevent or reduce high BP.

Laboratory studies of short-term sleep deprivation have suggested potential mechanisms for a causal link between sleep loss and hypertension. Partial sleep deprivation is associated with increased sympathetic activity estimated from measures of heart rate variability. Other studies have observed increased BP after a night of partial or total sleep deprivation. Therefore, sleep loss may lead to increased sympathetic nervous activity, which could cause high BP if sleep loss were chronic.

On a population level, previous epidemiological studies have observed associations between shorter sleep duration and increased BP. However, most of these studies were cross-sectional and relied on self-reported usual sleep duration, which is only moderately correlated with objectively measured sleep duration. Furthermore, to our knowledge, the possible role of sleep quality independent of sleep duration as a risk factor for high BP has not been explored in adults. The goal of our study was to determine whether objectively measured sleep duration or quality predicted 5-year incidence of hypertension and changes in systolic BP (SBP) and diastolic BP (DBP) levels in a community-based sample of persons in early middle age.
This sleep study is ancillary to a large, ongoing cohort study: the Coronary Artery Risk Development in Young Adults (CARDIA) Study. In 1985 and 1986, CARDIA recruited African American and white adults aged 18 to 30 years from 4 sites in the United States (Chicago, Illinois; Minneapolis, Minnesota; Oakland, California; and Birmingham, Alabama). Our ancillary study included persons examined at the Chicago site. We invited persons who were not pregnant at the CARDIA year 15 examination in 2000 and 2001 (n=814) to participate, and 670 consented. Participants and nonparticipants did not differ with respect to self-reported sleep quality or quantity at the year 15 examination. The protocol was approved by the institutional review boards of Northwestern University, Chicago, and the University of Chicago and by the CARDIA steering committee. Written informed consent was also obtained from each participant. In 2000 and 2001, as part of the year 15 CARDIA examination (termed baseline in this article), BP was measured along with other clinical, demographic, and health variables. The CARDIA clinical examination included self-reported questions about sleep duration and quality. In 2003 and 2005, sleep measures were collected in 2 waves approximately 1 year apart using wrist actigraphy and surveys. After the actigraphy data collection was completed, BP and demographic and self-reported sleep covariates were again measured during the year 20 CARDIA examination in 2005 and 2006 (termed follow-up in this article). Because the actigraphy data collection was closer to the follow-up than to the baseline, our primary cross-sectional analysis used BP and covariate data from the follow-up examination. Longitudinal analyses used data from both the baseline and the follow-up examinations. The 670 participants did not differ significantly from the 144 eligible nonparticipants in self-reported sleep duration (P = .75), sleep quality (P = .84), or BP measurements (SBP, P = .51; DBP, P = .72).

OUTCOME MEASURES

For participants not taking antihypertensive medication at either clinical examination, we examined the 5-year change in SBP and DBP levels. Blood pressure was measured 3 times by trained and certified technicians using standardized methods after the participants rested for 5 minutes. The last 2 measurements of BP were averaged for analyses. At the baseline examination, Hawksley random-zero sphygmomanometers were used, and at the follow-up examination, BP was measured using a digital BP monitor (Omron HEM-907XL; Online Fitness, Santa Monica, California). A calibration study was performed, and calibrated values were used for the follow-up measurements to ensure comparability. In participants without hypertension at baseline, we examined incident hypertension at follow-up, defined as an SBP greater than or equal to 140 mm Hg, a DBP greater than or equal to 90 mm Hg, or antihypertensive medication use.

SLEEP MEASUREMENTS

Sleep measurements were collected between 2003 and 2005. Participants were asked to wear a wrist activity monitor (Actiwatch-16; Mini-Mitter Inc, Bend, Oregon) for 3 consecutive days on 2 occasions approximately 1 year apart. The wrist activity monitors contain highly sensitive omnidirectional accelerometers that count wrist movements in 30-second epochs. Wrist actigraphy has been validated against polysomnography, demonstrating a correlation of more than 0.9 in healthy subjects. Unlike polysomnography, actigraphy does not appear to alter sleep behavior, as there is no “first night effect.” Validated computer software was used to calculate sleep variables, including sleep duration and sleep maintenance, as described below.

SLEEP DURATION

Sleep duration is defined as the amount of time between sleep onset and final morning awakening minus the total duration of all awakenings after sleep onset.

SLEEP MAINTENANCE

This index assesses sleep consolidation, a component of sleep quality, and is the percentage of time between initial sleep onset and final waking that is spent sleeping. For most participants (91%), there were 6 days of actigraphy recording. The remaining 9% contributed 1 to 5 days of actigraphy recording. Analyses that were restricted to participants with 6 days of recordings produced similar results as analyses that included all participants for whom at least 1 day of actigraphy was obtained. For each sleep measure, the average of all days of actigraphy recording was used.

COVARIATES

The sociodemographic covariates that were included in all analyses were race, sex, and age at baseline. Baseline income (7-level ordinal variable ranging from <$16 000 to ≥$100 000) and number of years of education (ranging from 4 to 20 years) were also included in the full models. Other covariates were body mass index (BMI [calculated as weight in kilograms divided by height in meters squared]), smoking, alcohol use, and physical activity. For each of these, both baseline status and 5-year change were included in the full models. The BMI was analyzed as a continuous variable. Antihypertensive medication use, current smoking (yes/no), alcohol use, and physical activity were all determined from interview questions at the baseline and follow-up examinations. Alcohol use was the average number of drinks per week of wine, liquor, and beer. The CARDIA Physical Activity History included questions about 13 categories of sports and exercise over the past 12 months and was used to determine a total physical activity score in exercise units. Risk of sleep apnea was defined based on the Berlin Sleep Apnea Questionnaire. The full questionnaire includes 3 components, and a high risk of sleep apnea is defined by the presence of any 2 of the 3 components: (1) persistent snoring symptoms, (2) persistent daytime sleepiness, and (3) obesity or hypertension. A participant was considered to have persistent snoring symptoms if he or she indicated 2 of 3 following conditions on this questionnaire: (1) snored 3 or more times per week, (2) snoring was louder than talking or very loud, and (3) experienced breathing pauses 3 or more times per week. A participant was considered to have persistent daytime sleepiness if he or she indicated 2 of the 3 following conditions: (1) was tired 3 or more times per week after sleeping; (2) was tired 3 or more times per week during wake time; (3) has fallen asleep while driving. Because we were already including measured BMI and change in BMI as covariates and because BP was our outcome, we did not use the summary apnea risk score. Instead, the sleepiness and snoring components of apnea risk were each included in the full models.

STATISTICAL ANALYSES

Linear regression models were used to examine the cross-sectional association between objective sleep and BP at the follow-up examination after adjustment for age, race, and sex and after participants who were taking antihypertensive medications were excluded. Linear regression models were also used to predict the 5-year change in SBP and in DBP, while controlling for age, race, sex, and baseline BP and excluding those participants who were taking antihypertensive medications at either baseline or follow-up. Modeling the follow-up BP and including baseline BP as a covariate is exactly the same as modeling the 5-year change...
in BP and adjusting for baseline BP. Then, among those without hypertension at baseline, logistic regression analyses were used to predict incident hypertension as a function of sleep after adjustment for age, race, and sex. Finally, all of the covariates were added to the linear and logistic regression models. We also tested whether the associations between sleep and BP varied by race or sex by adding interaction terms between race or sex and the sleep measure to the models. We further examined whether the association between snoring and BP varied by sex by introducing an interaction term between sex and snoring to the sleep duration models. Variables were centered at their means. Separate models were estimated for sleep duration and sleep maintenance. The robust variance estimator was used in linear regression models to calculate confidence intervals and P values. In regression models, sleep duration and sleep maintenance were entered as continuous variables. For data presentation, sleep duration was divided into 5 categories (<4 hours, 4–<5 hours, 5–<6 hours, 6–<7 hours, and ≥7 hours), and sleep maintenance was divided into 5 categories (<80%, 80%–<85%, 85%–<90%, 90%–<95%, and ≥95%).

We also explored whether the race-sex differences in the 5-year change in SBP and DBP levels were mediated by race-sex differences in sleep duration. To do this, we estimated the percentage of the mean 5-year change in SDP and DBP levels for African American men, African American women, and white men relative to white women, which was eliminated by adding sleep duration to the models.20 To determine whether the effect of adding sleep duration to the models had a significant effect on the coefficients of the race-sex groups, we modified the approach suggested by Lin et al.21 Their approach involves doubting the data by making a copy of each observation and running a joint model that estimates the race effect both with and without adjustment for sleep. The joint model permits testing whether the race effect differs after adjustment for sleep by using robust variance-covariance estimation clustering on the individual identification numbers. We used a 3 degrees of freedom χ² test for any mediation across the 4 race-sex groups. All statistical analyses were performed using Stata version 9.2 software (StataCorp, College Station, Texas).

### RESULTS

In the cross-sectional analysis, we excluded the participants who were (1) missing valid actigraphy data (n = 3), (2) taking antihypertensive medication at baseline (n = 45), (3) missing a baseline measure of DBP (n = 1), and (4) missing a follow-up measure of DBP (n = 43), which resulted in a final sample size of 578. In the longitudinal analysis that predicted change in BP, we further excluded those who were taking antihypertensive medication at follow-up (n = 73), which left 505 participants for these analyses. Of the 667 participants with actigraphy data, 53 were missing data for hypertension status at years 15 and/or 20, and an additional 69 participants had hypertension in year 15, which resulted in a sample size of 535 participants for the incident hypertension analyses. The cross-sectional sample (n = 578) included 93 African American men (16%), 146 African American women (25%), 159 white men (28%), and 180 white women (31%). The mean (SD) age at baseline was 40.1 (3.6) years. Table 1 presents summary statistics for key variables. On average, participants slept 6 hours and were awake approximately 11% of the time after falling asleep. The distributions of sleep duration and sleep maintenance are illustrated in Figure 1. Almost half of the sample (43%) slept less than 6 hours per night. Only 7 participants (1%) averaged 8 or more hours of sleep. Over 5 years, on average, SBP increased and DBP decreased. Of participants without hypertension at baseline, 14% (75 of 535) of the full sample developed hypertension. Seventy-five participants (14%) of the full sample reported persistent snoring symptoms and 183 (32%) reported daytime sleepiness. Snoring was more common in men than in women (17% of men vs 11% of women), in African Americans than in whites (17% of African Americans vs 11% of whites), and in the obese (BMI, ≥30) than in the nonobese (20% in the obese vs 10% in the nonobese).

Table 2 presents the results from linear regression models used to examine both cross-sectional and longitudinal associations between sleep and BP after adjustment for age, race, and sex. Figure 2 illustrates the longitudinal associations between the adjusted 5-year change in SBP and DBP by sleep duration and sleep maintenance categories. Shorter sleep duration and lower sleep maintenance were both significantly associated with higher SBP and DBP levels at year 20 as well as with smaller decreases or even increases in SBP and DBP levels over the 5-year period. In logistic regression models that predicted incident hypertension, short sleep duration was significantly associated with increased odds of hypertension (odds ratio [OR], 1.37; 95% confidence interval [CI], 1.05–1.78) after adjustment for age and race-sex groups. Each hour of reduction in sleep duration was associated with a 37% increase in the odds of incident hypertension. Sleep maintenance was not significantly associated with incident hypertension (OR, 0.77 per 10% of maintenance; 95% CI, 0.50–1.20).

### Table 1. Key Variables

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>110.1 (13.1)</td>
<td>NA</td>
<td>114.4 (14.4)</td>
<td>+4.3 (11.7)</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>73.7 (10.1)</td>
<td>NA</td>
<td>71.1 (11.4)</td>
<td>−2.6 (9.8)</td>
</tr>
<tr>
<td>BMI</td>
<td>27.9 (6.3)</td>
<td>NA</td>
<td>28.7 (6.7)</td>
<td>0.7 (2.4)</td>
</tr>
<tr>
<td>Sleep duration, h</td>
<td>NA</td>
<td>6.1 (1.1)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Sleep maintenance, %</td>
<td>NA</td>
<td>88.8 (5.5)</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CARDIA, Coronary Artery Risk Development in Young Adults; NA, not applicable.

Participants who were taking antihypertensive medications at baseline were excluded, leaving a total of 578 study participants.
In the fully adjusted models (Table 3), the associations between sleep duration and BP were reduced; however, sleep duration was still significantly negatively associated with a 5-year change in DBP (P = .03). The associations between sleep maintenance and BP were also somewhat reduced but remained significant for all models. The association between short sleep duration and odds of incident hypertension in the fully adjusted logistic regression model was also attenuated (OR, 1.30; 95% CI, 0.96-1.75). Finally, the interaction terms between race or sex and sleep duration or maintenance were not significant, indicating that the associations between sleep and BP did not vary by race or by sex. The interaction term between sex and snoring was not significant in the cross-sectional or longitudinal models that predicted SBP or DBP; however, it was significant in the logistic model that predicted hypertension (P = .02). When stratified by sex, snoring did not significantly predict incident hypertension in men (OR, 0.75; 95% CI, 0.22-2.57), but it did in women (OR, 4.59; 95% CI, 1.95-10.76).

There were significant race-sex differences in the 5-year changes in SBP and DBP (Table 4). We explored whether these differences were partly explained by differences in sleep duration. White women were chosen as the reference group because they had the smallest average increase in SBP and the longest average sleep duration relative to the other 3 race-sex groups. On average, their SBP increased by 3.61 mm Hg and their DBP decreased by 3.14 mm Hg over 5 years. Compared with white women, white men and African American men experienced significantly greater increases in SBP and African American men and women experienced significantly smaller decreases in DBP over 5 years (Table 4). To determine whether sleep duration mediated the association between race-sex and changes in BP, we compared 2 linear regression models: 1 model predicted change in BP from the race-sex groups with adjustment only for age, and the second model added sleep duration as a predictor (Table 4). For African American men, the change in SBP relative to that in white women was reduced by 36%, and the change in DBP again relative to that in white women was reduced by 84% when sleep duration was included in the model. For white men, the change in SBP relative to white women was reduced by 21%, and for African American women, the change in DBP relative to white women was reduced by 37% when sleep duration was included. The overall mediation effect of including sleep duration on the coefficients of the race-sex groups was statistically significant for the change in DBP (P = .02) but not in SBP (P = .38). When we compared models that included all covariates (age, income, education, smoking, 5-year change in smoking, BMI, 5-year change in BMI, physical activity, 5-year change in physical activity, alcohol use, 5-year change in alcohol use, persistent snoring symptoms, and persistent daytime sleepiness), the effect of adding sleep duration was similar. These results suggest that sleep duration partially mediates the larger increases in BP that are associated with African American race or male sex, particularly for DBP.
Among this sample of early middle-aged adults, shorter objectively measured sleep duration or lower sleep maintenance (1 component of sleep quality) predicted higher levels of SBP and DBP as well as greater increases in SBP and smaller decreases in DBP over 5 years. Sleep duration predicted increased odds of incident hypertension after adjustment for age, race, and sex. Inclusion of numerous socioeconomic, health, and sleep-related covariates weakened some of the associations between sleep and BP; however, most remained statistically significant. When examined separately, no single covariate had a strong effect, but all of them considered together did attenuate the associations. Because the mechanisms underlying the relationship between sleep and BP regulation are not fully understood, some of these covariates may not be confounders but rather may be mediating variables on the causal pathway between sleep and increased BP.

Consistent with other studies, higher BP levels in men, particularly African American men. Also, as described in a previous report from this study, Afri-
can American men slept much less than white women. These 2 observations suggested the intriguing possibility that the well-documented higher BP in African Americans and men might be partly related to sleep duration. Indeed, our results suggest that sleep duration did partially mediate the excess increase in BP that is associated with being male and being African American relative to white women. As previously reported, the race-sex differences in sleep duration persist after controlling for numerous sociodemographic confounders, including income, education, employment status, marital status, and presence of children. Therefore, the present study revealed shorter sleep as a previously unrecognized potential mechanism that may underlie the BP disparities that are associated with African American race. 

In secondary analyses, we found that self-reported frequent snoring was associated with increased odds of incident hypertension in women but not in men. These sex differences could reflect true differential risk of hypertension associated with snoring between men and women. Alternatively, it could be that a greater proportion of men who report frequent snoring may not have obstructive sleep apnea compared with women who report frequent snoring and/or that women who report frequent snoring have more severe sleep apnea than do men who report snoring. These observed associations between objectively measured sleep duration and BP change are consistent with some recent epidemiological studies that have found associations between subjective measures of sleep duration and hypertension. The Sleep Heart Health Study observed a U-shaped cross-sectional association between self-reported sleep duration and prevalent hypertension: the OR for prevalent hypertension was 1.66 for participants who reported sleeping less than 6 hours per night and 1.30 for those who reported sleeping 9 or more hours relative to sleeping 7 to less than 8 hours. A French cross-sectional study observed a significant negative association between self-reported sleep time and DBP but not SBP after adjustment for covariates. A recent study of Japanese women also reported a cross-sectional association between self-reported poor sleep and increased DBP but not SBP. Our study also found that sleep duration was more weakly associated with change in SBP than change in DBP after adjustment for all covariates. Two studies also examined BP prospectively. The NHANES I Epidemiologic Follow-up Study observed that adults aged 32 to 59 years who reported sleeping 5 hours or less per night had an adjusted hazard ratio of 1.60 for the development of hypertension over 8 to 10 years relative to those who reported sleeping 7 to 8 hours. Data from the Whitehall II Study found associations between short sleep duration and increased incident hypertension among women only. However, our analyses did not find a gender difference in the association between sleep and BP. Finally, 2 studies involving elderly adults, 1 in the Netherlands and 1 in Brazil, found no association between sleep duration and BP, which suggests that effect of sleep on BP may be age dependent. Taken together, the results of these studies along with our results support the hypothesis that short sleep duration is associated with higher BP in young to middle-aged adults. One other study used wrist actigraphy in a sample of adolescents and found that low sleep efficiency was associated with increased prevalence of prehypertension (defined as an SBP or a DBP $\geq$90th percentile for age, sex, and height). However, to our knowledge, the present study is the first to obtain objective measures of sleep duration and quality in a large sample of adults and to reveal associations between poor sleep quality and adverse effect on BP regulation and risk of hypertension in early middle-aged adults. 

The strengths of our study include the longitudinal measures of BP and the objective measures of sleep duration and quality from 6 days of wrist activity recordings. Average sleep duration and quality over the 5-year follow-up period were derived from two 3-day recording sessions separated by approximately 1 year. We do not have sleep measurements that span the 5-year follow-up period. Previous analysis of these actigraphy data found that the variability between the 2 years was minimal in this cohort, which suggests that our sleep measures may be valid representations of sleep over the 5 years between clinical examinations. 

An important limitation of the present study is that we used wrist actigraphy, which measures only movement, rather than the criterion standard of sleep mea-

### Table 4. Race-Sex Effect on 5-Year Change in SBP and DBP Associated With Differences in Sleep Duration

<table>
<thead>
<tr>
<th></th>
<th>Sleep Duration, Mean (SD), h</th>
<th>S-5 Change in SBP (95% CI)</th>
<th>S-5 Change in DBP (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Not Adjusted for Sleep Duration, mm Hg</td>
<td>Adjusted for Sleep Duration, mm Hg</td>
<td>Effect of Adjusting for Sleep, %&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Not Adjusted for Sleep Duration, mm Hg</td>
<td>Adjusted for Sleep Duration, mm Hg</td>
<td>Effect of Adjusting for Sleep, %&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>African American men</td>
<td>5.2 (1.1)</td>
<td>+4.45 (1.59 to 7.32)</td>
<td>+2.87 (−0.41 to 6.16)</td>
</tr>
<tr>
<td>African American women</td>
<td>5.9 (0.8)</td>
<td>+1.25 (−1.54 to 4.04)</td>
<td>+0.36 (−2.49 to 3.22)</td>
</tr>
<tr>
<td>White men</td>
<td>6.1 (0.9)</td>
<td>+2.85 (0.56 to 5.15)</td>
<td>+2.26 (−0.04 to 4.55)</td>
</tr>
<tr>
<td>White women</td>
<td>6.7 (0.8)</td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>χ&lt;sup&gt;2&lt;/sup&gt; Test for mediation</td>
<td>NA</td>
<td>NA</td>
<td>1.02</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; DBP, diastolic blood pressure; NA, not applicable; SBP, systolic blood pressure.

<sup>a</sup>The percentage of excess change in blood pressure relative to white women was accounted for by adding sleep duration. This percentage is calculated only when the 5-year change in blood pressure is significantly different ($P<.05$) from that of the reference group (white women). Boldface values indicate statistical significance ($P<.05$). The participants who were taking antihypertensive medications at baseline or follow-up were excluded.
measurment, polysomnography. Therefore, we were not able to assess diagnostic sleep characteristics such as the presence and severity of sleep-disordered breathing (SDB), a well-documented risk factor for hypertension.28,29 Instead, the risk of SDB was estimated using habitual snoring from the Berlin questionnaire, a validated instrument for evaluating the risk of sleep apnea.10 The proportion of snorers among men, African Americans, and the obese in our sample was consistent with current estimations of the prevalence of SDB by sex, race, and weight status.30,31 When snorers were excluded from our analyses, the risk of SDB was estimated using habitual snoring BP3,4,10,11 and by laboratory evidence for increased sympathetic nervous activity as a likely mechanism underlying the increase in BP after sleep loss.32 Because of the major adverse health consequences of high BP, the identification of a new and potentially modifiable risk factor has clinical implications. Intervention studies are needed to determine whether optimizing sleep duration and quality can reduce the risk of increased BP.

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Author Contributions: Dr Knutson had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Knutson, Van Cauter, Yan, Liu, and Lauderdale. Acquisition of data: Knutson, Hulley, and Lauderdale. Analysis and interpretation of data: Knutson, Van Cauter, Rathouz, Yan, Hulley, and Lauderdale. Drafting of the manuscript: Knutson. Critical revision of the manuscript for important intellectual content: Van Cauter, Rathouz, Yan, Hulley, and Lauderdale. Administrative, technical, and material support: Knutson. Study supervision: Van Cauter, Hulley, and Lauderdale.

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REFERENCES