Short Sleep Duration and Incident Coronary Artery Calcification

Christopher Ryan King; Kristen L. Knutson; Paul J. Rathouz; et al.

JAMA. 2008;300(24):2859-2866 (doi:10.1001/jama.2008.867)

http://jama.ama-assn.org/cgi/content/full/300/24/2859

Short Sleep Duration and Incident Coronary Artery Calcification

Christopher Ryan King, BS
Kristen L. Knutson, PhD
Paul J. Rathouz, PhD
Steve Sidney, MD, MPH
Kiang Liu, PhD
Diane S. Lauderdale, PhD

Context Coronary artery calcification is a subclinical predictor of coronary heart disease. Recent studies have found that sleep duration is correlated with established risk factors for calcification including glucose regulation, blood pressure, sex, age, education, and body mass index.

Objective To determine whether objective and subjective measures of sleep duration and quality are associated with incidence of calcification over 5 years and whether calcification risk factors mediate the association.

Design, Setting, and Participants Observational cohort of home monitoring in a healthy middle-aged population of 495 participants from the Coronary Artery Risk Development in Young Adults (CARDIA) cohort Chicago site (black and white men and women aged 35-47 years at year 15 of the study in 2000-2001 with follow-up data at year 20 in 2005-2006). Potential confounders (age, sex, race, education, apnea risk, smoking status) and mediators (lipids, blood pressure, body mass index, diabetes, inflammatory markers, alcohol consumption, depression, hostility, self-reported medical conditions) were measured at both baseline and follow-up. Sleep metrics (wrist actigraphy measured duration and fragmentation, daytime sleepiness, overall quality, self-reported duration) were examined for association with incident calcification. Participants had no detectable calcification at baseline.

Main Outcome Measure Coronary artery calcification was measured by computed tomography in 2000-2001 and 2005-2006 and incidence of new calcification over that time was the primary outcome.

Results Five-year calcification incidence was 12.3% (n=61). Longer measured sleep duration was significantly associated with reduced calcification incidence (adjusted odds ratio, 0.67 per hour [95% confidence interval, 0.49-0.91 per hour]; $P=.01$). No potential mediators appreciably altered the magnitude or significance of sleep (adjusted odds ratio estimates ranged from 0.64 to 0.68 per sleep hour; maximum $P=.02$). Alternative sleep metrics were not significantly associated with calcification.

Conclusion Longer measured sleep is associated with lower calcification incidence independent of examined potential mediators and confounders.

JAMA. 2008;300(24):2859-2866 www.jama.com

CORONARY ARTERY CALCIFICATION, the accumulation of calcified plaques visible by computed tomography,[1] is a subclinical predictor of future coronary heart disease events.[2,3] Risk factors for calcification include established heart disease risk factors such as male sex, older age, glucose intolerance, tobacco use, dyslipidemia, high blood pressure, obesity, raised inflammatory markers, and low educational attainment.[4-6]

Recent experimental and epidemiological data implicate sleep quantity and quality as correlates of several of these risk factors, including glucose and appetite regulation,[7] hypertension,[8] inflammation,[9] sex, age, education,[10] and obesity.[11] However, some of these correlations have only been documented in studies in which sleep is measured by self-report, which may be biased or insufficiently accurate.[12-14] Because of these associations, we set out to test whether objectively measured sleep duration and other sleep characteristics predict calcification and, if so, whether calcification risk factors mediate this relationship.

Using sleep data collected in an ancillary study to the Coronary Artery Risk Development in Young Adults (CARDIA) study, we analyzed whether objective and subjective sleep measures predicted the development of incident calcification over 5 years of follow-up.

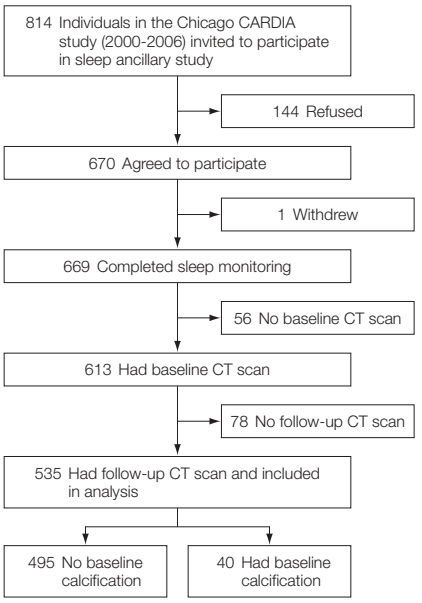
METHODS

Study Sample

CARDIA is an ongoing, prospective, multicenter cohort study of the evolution of cardiovascular risk factors. The original CARDIA cohort was aged 18 to 30 years in 1985-1986 and was balanced by self-identified sex, race (black and white), and education from predefined multiple choice categories. These categories were gathered to control for confounding in risk factor identification. A detailed study description has been presented elsewhere.[15] The ancillary sleep study included participants from 1 (Chicago) of the 4 CARDIA sites.

Author Affiliations: Department of Health Studies, University of Chicago, Chicago, Illinois (Mr King and Drs Knutson, Rathouz, and Lauderdale); Division of Research, Kaiser Permanente, Oakland, California (Dr Sidney); and Department of Preventive Medicine, Northwestern University, Chicago, Illinois (Dr Liu).
Corresponding Author: Diane S. Lauderdale, PhD, Department of Health Studies, University of Chicago, 5841 S Maryland Ave, MC 2007, Chicago, IL 60637 (lauderdale@uchicago.edu).

Figure 1. Study Participant Flow Diagram



CARDIA indicates Coronary Artery Risk Development in Young Adults; CT, computed tomography.

FIGURE 1 illustrates the derivation of the sample used in the main analysis from the initial cohort. Nonpregnant participants in the clinical examination in year 15 of CARDIA (2000-2001) (n=814) were invited to participate in the sleep study in 2003 and 2004, and 670 agreed to do so (82%). CARDIA participants were reexamined in 2005-2006, providing 5-year follow-up. Data on sleep, described below, were collected between CARDIA years 15 (termed baseline in this article) and year 20 (termed follow-up), as described below. All participants provided written informed consent; the protocol was approved by the institutional review boards of Northwestern University and the University of Chicago and by the CARDIA executive committee. Participants were paid $50 for each wave of actigraphy, largely to encourage return of the monitors.

Coronary Artery Calcification

Two scans were obtained using electron beam computed tomography (Imatron C-150, GE Medical Systems, Milwaukee, Wisconsin) at baseline and follow-up for CARDIA participants using a method described previously.[16] Scans were read centrally and each participant's scans were read independently blinded to all participant characteristics. The reader identified a region of interest for each potential focus of calcification, defined as 4 or more adjacent pixels (1.87 mm^2) with a computed tomographic scan number greater than 130 Hounsfield units (field of view=35 cm). Agatston scores[17] were adjusted for between-center differences using a standard calcium phantom scanned underneath each participant, and summed across the 4 major coronary arteries to compute a total calcium score. Biweekly calibrations were conducted using a standard torso insert to guard against between-center and temporal variability. The presence of calcification was defined as having a positive, nonzero Agatston score, using either of 2 scans.[5] Among sleep study participants, 535 have both baseline and follow-up scans.

Sleep Measures

Sleep data were collected by the ancillary study in 2 waves, about 1 year apart. The first wave began approximately 3 years after the baseline examination in 2003. All participants were asked to wear a wrist activity monitor (Actiwatch-16, Mini-Mitter Inc, Bend, Oregon) for Wednesday through Saturday in both waves, 6 total nights per participant. Wrist activity monitors contain highly sensitive omnidirectional accelerometers that count wrist movements in 30-second epochs.[18] For each night of actigraphy data collection, the time in bed when the participant was trying to sleep also was collected, using both an event marker button on the actigraph (which did not affect motion recording) and a sleep log that asked them to record the exact time that they began trying to fall asleep and when they got out of bed (as a backup in case of missing event markers). The software only analyzed these specified periods for sleep. Wrist actigraphy has been validated against polysomnography, demonstrating a correlation of more than 0.9 in healthy individuals for total sleep duration.[19] Unlike polysomnography, actigraphy does not appear to alter sleep behavior because there is no first-night effect.[20] Using manufacturer-supplied software, total sleep duration and sleep fragmentation were calculated. Fragmentation, an index of restlessness, was calculated by summing the percentage of time spent "sleeping" when the individual is moving and the percentage of all immobile periods that last 1 minute or less. This was used as an objective measure of sleep quality. Further explanation of the actigraphy method has been reported elsewhere.[10]

Self-reported habitual sleep duration was collected in the baseline CARDIA questionnaire. The ancillary study also included 3 validated sleep questionnaires: the Pittsburgh Sleep Quality Index,[21] a 21-point scale of overall sleep quality and disturbance; the Epworth Sleepiness Scale, a 24-point scale of daytime sleepiness[22]; and the Berlin Questionnaire, an apnea risk measure that classifies an individual as being at high risk for apnea if 2 of these 3 conditions are present: (1) loud or frequent snoring or frequent breathing pauses, (2) being frequently tired after sleeping or during wake time or having fallen asleep while driving, or (3) having high blood pressure or a body mass index (calculated as weight in kilograms divided by height in meters squared) greater than 30.[23]

Covariates

Baseline questionnaires ascertained demographic information, alcohol consumption, smoking, and self-reported diagnosis or treatment for the following conditions: gout, thyroid disease, human immunodeficiency virus, liver disease, any heart condition, cancer, stroke, peripheral vascular disease, kidney disease, migraine, gallbladder disease, diabetes, dyslipidemia, hypertension, gastrointestinal tract disease, depression, other mental or mood disorders, or asthma. Educational attainment was categorized into 4 levels: less than a high school degree, a high school degree or equivalent, some college, or

college graduate. Alcohol consumption was summarized as weekly intake of mean milliliters of alcohol with the categories of nondrinker, consume less than 7 drinks per week, or consume 7 drinks or more per week. Smoking was categorized as never, former, or current smoker. Additional questionnaires included the Center for Epidemiologic Studies Depression scale,[24] the Cook-Medley hostility subscale of the Minnesota Multiphasic Personality Inventory,[25] and the Framingham type A scale.[26] Total physical activity was assessed by the CARDIA physical activity history questionnaire, which has been described elsewhere.[27] These questionnaires were readministered at follow-up. Hostility was measured at an earlier examination (year 7).

Clinical examination results such as weight and height and most laboratory values were measured at both baseline and follow-up. Blood pressure was measured 3 times for each participant while seated. A Hawksley random-zero sphygmomanometer was used at baseline, and an Omron HEM-907XL (Bannockburn, Illinois) was used at follow-up. The calibrated systolic values and the mean of the second and third readings were used. For 12 hours prior to each examination, participants were asked to fast. For the 2 hours prior to each examination, participants were asked to avoid smoking and heavy physical activity. As reported elsewhere,[5] plasma total cholesterol, high-density lipoprotein cholesterol, and triglycerides were determined using an enzymatic assay by Northwest Lipids Research Laboratory (Seattle, Washington); low-density lipoprotein cholesterol was calculated using the Friedewald equation.[28] Serum glucose was measured using hexokinase coupled to glucose-6-phosphate dehydrogenase by Linco Research (St Louis, Missouri).[4] C-reactive protein was measured using the BNII Nephelometer from Dade Behring (Deerfield, Illinois) with a particle-enhanced immunonepholometric assay.[29] These measures were all available at both the baseline and follow-up examinations. Interleukin 6 was measured by ultrasensitive enzyme-linked immunosorbent assay (R&D Systems, Minneapolis, Minnesota),[29] and was only available at the follow-up examination. Plasma fibrinogen measurements were performed at the follow-up examination using an immunoassay. Total fibrinogen concentration for this assay was determined at the University of Vermont using immunonephelometry (BNII Nephelometer 100 Analyzer, Dade Behring). The amount of immunoreactive fibrinogen present in the sample was quantitatively determined by light scatter intensity.[30]

The Framingham risk score and 10-year estimated risk were calculated from baseline variables according to the recommendation of the National Cholesterol Education Program's Adult Treatment Panel III.[31]

Statistical Analysis

Calcification was dichotomized as incident detectable calcification vs none because of the statistical distribution of the amount of calcification, in which there is a substantial floor effect. The prevalence of detectable calcification was low (40/535) at the baseline examination. Incident calcification was the focus rather than increased calcification because once developed calcification has repeatedly been shown to expand exponentially,[32] a feature that is duplicated in our data set (39/40). Positive follow-up calcification occurred among less than one-fifth of the participants (101/535); among those, the intensity was generally low (<20 Agatston units [AU] in 59%). Sensitivity analyses were conducted using an alternative threshold for calcification of greater than 10 AU rather than greater than 0 AU. Logistic regression was used to analyze the association of incident calcification with actigraphy-measured sleep duration and 4 alternate sleep metrics: self-reported duration, daytime sleepiness, and subjective and objective measures of sleep quality (Pittsburg Sleep Quality Index and fragmentation). These models were all adjusted for the key potential confounders of age, sex-race group, educational attainment, smoking status, and apnea risk. One participant who checked "other" educational attainment was excluded from these regressions.

To explore potential mediators of the calcification-sleep relationship, the following covariates were added to the adjusted model of sleep duration: body mass index, fasting glucose, serum C-reactive protein, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, fibrinogen, interleukin 6, depression scores, systolic blood pressure, alcohol consumption, Framingham type A scores, physical activity, Framingham risk, Cook-Medley hostility scores, and indicator variables for each of the self-reported disease diagnosis and treatment categories ascertained at baseline. If a variable mediates the sleep-calcification association, it is expected to see attenuation of the coefficient for sleep when the mediator is added. For covariates measured at both examinations, both baseline and 5-year change were included as covariates. Each variable was standardized to a z score (mean = 0, variance = 1) using the baseline standard deviation. Because of correlations among the potential mediators, testing all of them simultaneously was not illuminating. The above confounder-adjusted model was regressed with the addition of each potential mediator (and its 5-year change if available) one at a time. A model also was tested simultaneously adjusting for key heart disease risk factors of low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, body mass index, diabetes, age, sex, race, education, smoking, and apnea risk. Ratios of regression coefficients were calculated to quantify how much difference in an established risk factor (systolic blood pressure) was equivalent to a difference of 1 hour of sleep.

Interaction terms between each covariate and sleep were tested for heterogeneity of the sleep effect. Regressions were conducted within racial groups (retaining sex as a covariate), within sex groups (retaining race as a covariate), and within apnea risk groups to further identify heterogeneity among these groups. Regression diagnostics were performed and data points were exam-

ined for excessive influence. Additionally, the regression was repeated using only the participants who reported fasting for 8 hours prior to both clinical examinations. The main analysis also was repeated using relative risk (Poisson) regression in place of logistic regression.

Participants, nonparticipants, and individuals who were not followed up were compared by 2-sided *t* tests and the Fisher exact test where appropriate using a significance threshold of .05 (TABLE 1). Regression coefficients were tested for significance at the .05 level using 2-sided tests. Unadjusted tests for trends among hour groupings were calculated by logistic regression. The 95% confidence intervals (CIs) for hour-group incidence were computed by exact binomial methods. All statistical analysis was performed using Stata software version 9.0 SE (StataCorp, College Station, Texas).

RESULTS

Table 1 compares baseline demographic, self-reported sleep, and cardiovascular risk characteristics of eligible sleep study participants who did vs did not enroll in the sleep study, and sleep study participants at risk for incident calcification with and without follow-up calcification data. Sleep study participation did not vary by self-perceptions of usual sleep hours ($P = .75$). Of the 72 at-risk individuals without follow-up scans, 35 did not return for year 20 follow-up at all, and 37 were not rescanned (scheduling difficulties were often the reason). Measured sleep was similar for those with and without outcome data ($P = .93$).

TABLE 2 provides descriptive statistics of study participants. Where laboratory values were recorded as integers, they have been grouped as close to the tertiles as possible. FIGURE 2 displays the unadjusted relationship between actigraphic and self-reported sleep hours and calcification incidence. There was a moderate correlation between self-reported and actigraphic sleep categories (0.22, $P < .001$), evaluated with a Kendall τ-b statistic. The proportion of persons developing calcification decreases monotonically as actigraphic sleep hours increases. Self-report sums to a lower number of observations due to nonresponse in the initial CARDIA questionnaire.

TABLE 3 presents the associations of sleep metrics and calcification from logistic regression. Unadjusted logistic regression yields a significant reduction in the odds of incident calcification with increasing measured sleep duration (unadjusted odds ratio [OR], 0.57 per hour [95% CI, 0.44-0.73 per hour]). After adjusting for age, sex, race, education, smoking, and apnea risk, longer measured sleep duration was associated with reduced calcification incidence (ad-

Table 1. Characteristics of Study Participants and Nonparticipants

	Eligible for Sleep Substudy			Participants Without Calcification at Baseline		
	Nonparticipants (n = 144)	Participants (n = 670)	*P* Value[a]	Rescanned (n = 495)	Not Rescanned (n = 72)	*P* Value[a]
Self-reported sleep, mean (SD), h	6.5 (1.4)	6.5 (1.2)	.75	6.5 (1.2)	6.5 (1.4)	.57
Measured sleep, mean (SD), h	NA	6.1 (1.1)	NA	6.1 (1.0)	6.1 (1.3)	.93
Baseline calcification prevalence, No./total (%)	13/131 (9.9)	47/616 (7.6)	.38	NA	NA	NA
Follow-up calcification incidence, No./total (%)	11/76 (14.5)	61/496 (12.3)	.60	61/495 (12.3)	NA	NA
Race-sex groups, No. (%)						
White male	44 (30.6)	177 (26.4)	.002	127 (25.7)	20 (27.8)	.29
Black male	38 (26.4)	108 (16.1)		77 (15.6)	17 (23.6)	
White female	25 (17.4)	198 (29.6)		149 (30.1)	19 (26.4)	
Black female	37 (25.7)	187 (27.9)		142 (28.7)	16 (22.2)	
Age, mean (SD), y	39 (3.7)	40 (3.6)	.05	40 (3.5)	39 (3.9)	.04
Educational attainment, No./total (%)[b]						
<High school degree	8/143 (5.6)	27/668 (4.0)	.11	12/494 (2.4)	6/72 (8.3)	.10
High school degree or equivalent	64/143 (44.8)	235/668 (35.2)		175/494 (35.4)	24/72 (33.3)	
Some college	13/143 (9.1)	74/668 (11.1)		56/494 (11.3)	7/72 (9.7)	
College graduate	58/143 (40.6)	332/668 (49.7)		251/494 (50.8)	35/72 (48.6)	
Current smokers, No. (%)	30 (20.8)	141 (21.0)	>.99	90 (18.2)	20 (27.8)	.08
Lipoprotein cholesterol, mean (SD), mg/dL						
High-density	50 (15)	51 (15)	.69	52 (15)	48 (12)	.02
Low-density	115 (32)	113 (32)	.46	111 (30)	118 (34)	.11
Systolic blood pressure, mean (SD), mm Hg	112 (13)	111 (14)	.49	110 (14)	112 (12)	.36
Diagnosed diabetes, No. (%)	11 (7.6)	29 (4.3)	.07	22 (4.4)	4 (5.6)	.84
Framingham 10-year risk score, No. %[c]	1.6 (1.8)	1.8 (2.6)	.39	1.7 (2.3)	2.1 (3.7)	.22

Abbreviation: NA, data not available or not applicable.
SI conversion factors: To convert high-density and low-density lipoprotein cholesterol to mmol/L, multiply by 0.0259.
[a] The *t* test and the Fisher exact test were used.
[b] Three persons had missing or ambiguous educational attainment; only 1 was a scanned sleep study participant.
[c] Calculated per individual per method of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults.[31]

justed OR, 0.67 per hour [95% CI, 0.49-0.91 per hour]). Additionally adjusting for key cardiovascular risk factors had little effect on the OR for measured sleep. None of the alternate metrics was significantly associated with incident calcification (Table 3).

Stratifying by sex suggested a stronger measured sleep duration effect for women (n=291; OR for sleep, 0.48 [95% CI, 0.27-0.85]) than for men (n=203; OR for sleep, 0.76 [95% CI, 0.52-1.10]), however, the interaction term in a combined model was not significant (P=.12). In stratified regression models, there was no suggestion that effects vary by race (OR for whites [n=275], 0.61 [95% CI, 0.39-0.96] and OR for blacks [n=219], 0.64 [95% CI, 0.41-1.02]). In combined regression, the interaction term of race and sleep was not significant (P=.92). Stratifying by apnea risk, there was a suggestion of a stronger effect for those at high risk (OR, 0.38 [95% CI, 0.13-1.10]) compared with low risk (OR, 0.72 [95% CI, 0.52-1.01]), but the interaction was not significant (P=.51).

In all of the models that singly included the potential mediators listed in the "Methods" section (individual results not shown), none of the potential mediators substantially changed the sleep coefficient (although many had main effects on calcification incidence), or caused the P value for the coefficient for sleep to fall above .05; adjusted ORs for measured sleep ranged from 0.64 to 0.68, and the largest P value for sleep hours was .02. No interaction terms between sleep and the other covariates were found to be significant.

The modeled effect of 1 additional hour of sleep on the odds of incident calcification was equal to the modeled effect of a 16.5 mm Hg decrease in systolic blood pressure.

Results for a sensitivity analysis with a higher cut point for positive calcification (>10 AU) were similar (adjusted OR, 0.63 [95% CI, 0.44-0.90]). Use of relative risk regression (Poisson regression) did not substantially change the result (relative risk for gain of 1 hour, 0.75 [95% CI, 0.60-0.93]; P=.01).

COMMENT

We have found a robust and novel association between objectively measured sleep duration and 5-year incidence of coronary artery calcification. One hour more of sleep decreased the estimated odds of calcification by 33%. Figure 2 shows that the (unadjusted) dose-response relationship held up across the range of measured sleep; the lack of significant heterogeneity by race or sex strengthened this finding. Controlling for potential confounders and mediators did not greatly attenuate the relationship, as seen by multiply-adjusted ORs ranging only between 0.64 and 0.68 and significant P values. The magnitude of the observed effect was similar to sizable differences in established coronary risk factors (eg, 1 additional hour of sleep reduced risk similarly to a reduction of 16.5 mm Hg in systolic blood pressure).

Table 2. Study Sample Characteristics Among CARDIA Participants With Baseline and Follow-up Calcification Measurements

Category	Sleep, Mean (SD), h	No./Total (%)	
		Baseline Calcification Prevalence	5-Year Calcification Incidence[a]
All participants	6.1 (1.0)	40/535 (7.5)	61/495 (12.3)
Race-sex groups			
White male	6.1 (0.88)	17/144 (11.8)	26/127 (20.5)
Black male	5.2 (1.1)	8/85 (9.4)	18/77 (23.4)
White female	6.7 (0.84)	8/157 (5.1)	7/149 (4.7)
Black female	5.9 (0.92)	7/149 (4.7)	10/142 (7.0)
Age, y			
<38	6.0 (1.1)	4/121 (3.3)	10/117 (8.5)
38-41	6.1 (1.0)	14/193 (7.3)	18/179 (10.1)
≥42	6.0 (1.0)	21/219 (9.6)	33/198 (16.7)
Smoking status			
Never	6.1 (1.0)	17/337 (5.0)	35/320 (10.9)
Past	6.3 (0.93)	8/93 (8.6)	8/85 (9.4)
Current	5.8 (1.2)	15/105 (14.3)	18/90 (20.0)
High-density lipoprotein cholesterol tertile, mg/dL			
14-43	5.8 (1.0)	18/177 (10.2)	40/159 (25.2)
44-56	6.1 (1.0)	13/179 (7.3)	12/166 (7.2)
57-114	6.3 (1.0)	8/173 (4.6)	9/165 (5.5)
Low-density lipoprotein cholesterol tertile, mg/dL			
39-98	6.1 (1.1)	9/174 (5.2)	16/165 (9.7)
99-124	6.1 (0.96)	9/171 (5.3)	12/162 (7.4)
125-209	6.1 (1.0)	20/175 (11.4)	29/155 (18.7)
Systolic blood pressure tertile, mm Hg			
83-103	6.3 (0.94)	7/170 (4.1)	11/163 (6.8)
104-114	6.1 (1.0)	12/181 (6.6)	22/169 (13.0)
115-181	5.9 (1.1)	21/184 (11.4)	28/163 (17.2)
Diagnosed diabetes			
No	6.1 (1.0)	38/508 (7.5)	57/470 (12.1)
Yes	6.0 (1.1)	1/23 (4.3)	3/22 (13.6)
Framingham 10-year risk, %			
≤1	6.1 (1.0)	19/402 (4.7)	35/383 (9.1)
2-4	6.0 (1.0)	14/97 (14.4)	17/83 (20.5)
≥5	6.0 (0.96)	7/36 (19.4)	9/29 (31.0)
Apnea risk			
Low	6.1 (1.0)	32/465 (6.9)	52/433 (12.0)
High	5.8 (1.0)	8/70 (11.4)	9/62 (14.5)

Abbreviation: CARDIA, Coronary Artery Risk Development in Young Adults.
SI conversion factors: To convert high-density and low-density lipoprotein cholesterol to mmol/L, multiply by 0.0259.
[a] Among those without calcification at baseline.

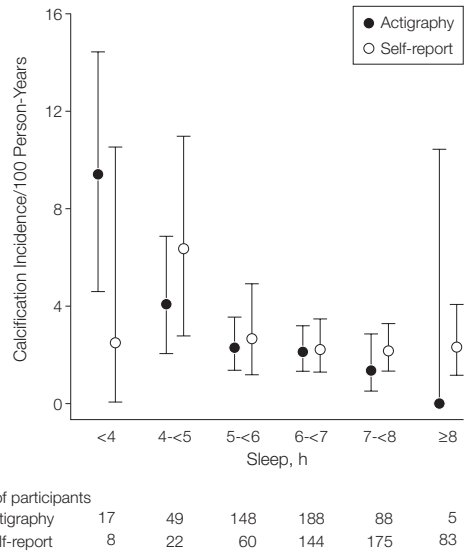
Our study has several limitations. First, too few participants had calcification at baseline for us to examine the rate of further calcification among them. Second, our first wave of sleep measures was taken more than halfway through the period between baseline and follow-up. While calcification may have occurred before sleep measurements, there is no obvious reverse causation mechanism. Further, the level of calcification was not known by the participants at the time of the sleep assessment. Finally, actigraphy is unable to measure potentially important dimensions of sleep such as sleep stages, which may underlie the apparent association between duration and calcification. Sleep quality is multidimensional, and there is no perfect metric for measuring it; the apnea-hypopnea index from polysomnography is probably the closest to a criterion standard. Actigraphy-measured fragmentation has not been widely used in research, although 1 recent study did find a significant correlation between it and obesity in the elderly.[33] How actigraphic fragmentation relates to other measures of sleep quality remains unclear.

However, actigraphy provides several advantages compared with self-reported sleep. Previous data indicate that self-reported sleep is only weakly correlated with total sleep time from polysomnography (r=0.16)[12] but that actigraphy is highly correlated with polysomnography total sleep time (r>0.90).[19,20] Actigraphy-measured sleep has been shown to be relatively stable year to year in this cohort,[34] indicating that our measure likely represents sleep duration throughout the study. Actigraphy avoids potential biases in self-reported sleep duration caused by the perception of fatigue in states of poor health.[14]

While some participants at risk do not have follow-up data (Table 1), we do not see evidence that omitting them is likely to affect our conclusions. There were a few significant differences between those with follow-up scans and those without, but we adjusted for these factors in regression analysis. Importantly, the mean measured and self-reported sleep levels were similar between those with and without follow-up data.

Because of the well-established association between apnea and cardiac outcomes,[35-37] our lack of a clinical apnea diagnosis is the study's main limitation. We used the Berlin Questionnaire to identify high-risk individuals. For apnea to bias our results away from the null hypothesis, apnea must be more prevalent among individuals with short sleep duration, and the Berlin Questionnaire must be so inaccurate as to leave significant residual confounding. Different studies have reported both longer and shorter sleep durations for apnea patients.[38-42] The Berlin Questionnaire has been found to have high sensitivity (0.86) and moderate specificity (0.77),[23] meaning our high-risk group should include almost all of the persons with apnea and a moderate number without. If we stratify by apnea risk, however, the sleep effect among those with low apnea risk is quite similar to the effect in the whole sample (OR, 0.72 [95% CI, 0.20-1.01]), suggesting that residual apnea confounding is not likely to be responsible for our positive results. The small effect of apnea risk on incidence in Table 2 is likely a result both of the inclusion of persons without apnea in the high-risk group and also the large effect on baseline prevalence; that is, persons with apnea were not in our at-risk cohort because they had already developed calcification before baseline.

Figure 2. Coronary Calcification Incidence by Mean Sleep Duration



Error bars indicate 95% confidence intervals, which are 95% binomial intervals. Three self-reports were missing. P<.001 for trend for actigraphy and P=.12 for trend for self-report.

Table 3. Logistic Regression of Incident Coronary Calcification

Covariate	OR (95% CI)	*P* Value
Actigraphy-measured sleep per hour		
Unadjusted model (n = 495)	0.57 (0.44-73.0)	<.001
Model adjusted for for race, sex, age, smoking, education, and apnea risk (n = 494)	0.67 (0.49-0.91)	.01
Model additionally adjusted for BMI, HDL-C, LDL-C, blood pressure, and diabetes (n = 478)	0.66 (0.48-0.92)	.01
Self-reported sleep per hour[a]	0.87 (0.67-1.13)	.30
Fragmentation index per SD of 7.7 points[a]	1.07 (0.80-1.42)	.66
PSQI score per SD of 2.9 points[a]	1.21 (0.88-1.65)	.24
Epworth score per SD of 4.0 points[a]	1.26 (0.96-1.66)	.10

Abbreviations: BMI, body mass index, CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; OR, odds ratio; PSQI, Pittsburgh Sleep Quality Index.
[a] Adjusted for race, sex, age, smoking, education, and apnea risk.

Calcification as an end point also has strengths and weaknesses. Calcification tends to increase over time[32] and is a potent risk factor for coronary events.[2,3] By observing persons in early middle age, we have reduced the possibility that unmeasured health problems confound the association.[14] However, early calcification is not a clinical outcome and coronary events may not necessarily follow.

We have not been able to find previous literature directly relating sleep with calcification. However, we note that previous studies have established a relationship between self-reported sleep duration and related outcomes, such as hypertension[8,43] and coronary events.[44] Sleep apnea has been linked to calcification in a clinical population[35] as well as to heart disease in population-based cohorts.[36,37] Contrary to others,[43,44] we find no evidence of a U-shaped relationship. However, such a relationship might be impossible to find in this study population because so few had more than 8 hours of measured sleep. Also, our sleep measurement avoided the potential problem that self-reports of long sleep are confounded by health factors.[14] Finally, the association between long sleep duration and cardiac outcome could be a feature that emerges at older ages.

We highlight 3 possible mechanisms to explain this association. First, the determinants of sleep duration are poorly understood, although socioeconomic correlations[10] exist. There may be unknown common factors predicting both sleep and calcification. Second, we may have been unable to adequately assess mediating mechanisms. Our inflammatory marker data are incomplete; fibrinogen and interleukin 6 were available only at follow-up. Cortisol profiles, which have been correlated with both calcification[45] and sleep,[46] were not investigated. More frequent measurements may be needed to capture the activity of hypothesized mediators. For example, transient decreases in glucose tolerance following evenings of short sleep duration[47] might not be detected at either examination. Third, unmeasured diurnal variation of calcification pathways may be at work. For example, blood pressure declines during sleep[48] and significantly predicts[4] calcification incidence.

In summary, this study demonstrates that objectively measured sleep is inversely associated with coronary artery calcification. This study further demonstrates the utility of a simple objective measure of sleep that can be used at home. Future studies will be needed for crucial extensions to these results. First, these results need confirmation in other cohorts. Second, does sleep moderate the rate at which calcification accumulates? Third, will objective sleep tie to coronary disease event outcomes over the long term? While calcification predicts such outcomes, it is difficult to know how and if the predictors of calcification themselves will determine outcomes, or if their impact will be purely mediated by their effect on calcification. Finally, if this association is born out, interventional studies will be needed to guide clinical advice.

Author Contributions: Dr Lauderdale had full access to all of 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: King, Knutson, Rathouz, Sidney, Liu, Lauderdale.
Acquisition of data: Knutson, Sidney, Liu.
Analysis and interpretation of data: King, Rathouz, Lauderdale.
Drafting of the manuscript: King, Lauderdale.
Critical revision of the manuscript for important intellectual content: Knutson, Rathouz, Sidney, Liu.
Statistical analysis: King, Rathouz, Lauderdale.
Obtained funding: Sidney, Liu, Lauderdale.
Administrative, technical, or material support: Knutson, Liu, Lauderdale.
Study supervision: Liu, Lauderdale.
Financial Disclosures: None reported.
Funding/Support: Research for this study was supported by grant AG 11412 from the National Institute on Aging and the Medical Scientist National Research Service Award T 32 GM07281. The Coronary Artery Risk Development in Young Adults (CARDIA) study is supported by US Public Health Service contracts NO1-HC-48047, NO1-HC-48048, NO1-HC-48049, NO1-HC-48050, and NO1-HC-95095 from the National Heart, Lung, and Blood Institute.
Role of the Sponsor: No funding organization or sponsor aside from the National Heart, Lung, and Blood Institute played a role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

REFERENCES

1. Rumberger JA, Simons DB, Fitzpatrick LA, Sheedy PF, Schwartz RS. Coronary artery calcium area by electron-beam computed tomography and coronary atherosclerotic plaque area: a histopathologic correlative study. *Circulation*. 1995;92(8):2157-2162.
2. Detrano R, Guerci AD, Carr JJ, et al. Coronary calcium as a predictor of coronary events in four racial or ethnic groups. *N Engl J Med*. 2008;358(13):1336-1345.
3. Greenland P, Bonow RO, Brundage RH, et al. ACCF/AHA 2007 clinical expert consensus document on coronary artery calcium scoring by computed tomography in global cardiovascular risk assessment and in evaluation of patients with chest pain. *J Am Coll Cardiol*. 2007;49(3):378-402.
4. Kronmal RA, McClelland RL, Detrano R, et al. Risk factors for the progression of coronary artery calcification in asymptomatic subjects: results from the Multi-Ethnic Study of Atherosclerosis (MESA). *Circulation*. 2007;115(21):2722-2730.
5. Loria CM, Liu K, Lewis CE, et al. Early adult risk factor levels and subsequent coronary artery calcification: the CARDIA Study. *J Am Coll Cardiol*. 2007;49(20):2013-2020.
6. Yan LL, Liu K, Daviglus ML, et al. Education, 15-year risk factor progression, and coronary artery calcium in young adulthood and early middle age: the Coronary Artery Risk Development in Young Adults study. *JAMA*. 2006;295(15):1793-1800.
7. Knutson KL, Spiegel K, Penev P, Van Cauter E. The metabolic consequences of sleep deprivation. *Sleep Med Rev*. 2007;11(3):163-178.
8. Gangwisch JE, Heymsfield SB, Boden-Albala B, et al. Short sleep duration as a risk factor for hypertension: analysis of the First National Health and Nutrition Examination Survey. *Hypertension*. 2006;47(5):833-839.
9. Zisapel N. Sleep and sleep disturbances: biological basis and clinical implications. *Cell Mol Life Sci*. 2007;64(10):1174-1186.
10. Lauderdale DS, Knutson K, Yan L, et al. Objectively measured sleep characteristics among early middle-aged adults: the CARDIA Study. *Am J Epidemiol*. 2006;164(1):5-16.
11. Gangwisch JE, Malaspina D, Boden-Albala B, Heymsfield SB. Inadequate sleep as a risk factor for obesity: analysis of the NHANES I. *Sleep*. 2005;28:1289-1296.
12. Silva GE, Goodwin JL, Sherrill DL, et al. Relationship between reported and measured sleep times: the Sleep Heart Health Study (SHHS). *J Clin Sleep Med*. 2007;3(6):622-630.
13. Lauderdale DS, Knutson KL, Yan LJ, Liu K, Rathouz PJ. Self-reported and measured sleep duration: how similar are they? *Epidemiology*. 2008;19(6):838-845.
14. Knutson KL, Turek FW. The U-shaped association between sleep and health: the 2 peaks do not mean the same thing. *Sleep*. 2006;29(7):878-879.
15. Friedman GD, Cutter GR, Donahue RP, et al. CARDIA: study design, recruitment, and some characteristics of the examined subjects. *J Clin Epidemiol*. 1988;41(11):1105-1116.
16. Carr JJ, Nelson JC, Wong ND, et al. Calcified coronary artery plaque measurement with cardiac CT in population-based studies: standardized protocol of Multi-Ethnic Study of Atherosclerosis (MESA) and Coronary Artery Risk Development in Young Adults (CARDIA) study. *Radiology*. 2005;234(1):35-43.
17. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M Jr, Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol*. 1990;15(4):827-832.
18. Jean-Louis G, von Gizycki H, Zizi F, Spielman A, Hauri P, Taub H. The actigraph data analysis software, I: a novel approach to scoring and interpreting sleep-wake activity. *Percept Mot Skills*. 1997;85(1):207-216.
19. Tryon WW. Issues of validity in actigraphic sleep assessment. *Sleep*. 2004;27(1):158-165.
20. Ancoli-Israel S, Cole R, Alessi C, Chambers M, Moorcroft W, Pollak CP. The role of actigraphy in the study of sleep and circadian rhythms. *Sleep*. 2003;26(3):342-392.

21. Buysse DJ, Reynolds CF III, Monk TH, et al. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res*. 1989; 28(2):193-213.
22. Johns MW. A new method for measuring daytime sleepiness: the Epworth Sleepiness Scale. *Sleep*. 1991;14(6):540-545.
23. Netzer NC, Stoohs R, Netzer C, et al. Using the Berlin Questionnaire to identify patients at risk for the sleep apnea syndrome. *Ann Intern Med*. 1999; 131(7):485-491.
24. Hann D, Winter K, Jacobsen P. Measurement of depressive symptoms in cancer patients: evaluation of the Center for Epidemiological Studies Depression Scale (CES-D). *J Psychosom Res*. 1999;46(5):437-443.
25. Cook W, Medley D. Proposed hostility and pharisaic-virtue scales for the MMPI. *J Appl Psychol*. 1954; 238:414-418.
26. Evans PD, Moran P. The Framingham type A scale, vigilant coping, and heart-rate reactivity. *J Behav Med*. 1987;10(3):311-321.
27. Jacobs DR Jr, Ainsworth BE, Hartman TJ, Leon AS. A simultaneous evaluation of 10 commonly used physical activity questionnaires. *Med Sci Sports Exerc*. 1993;25(1):81-91.
28. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem*. 1972;18(6):499-502.
29. Sloan RP, McCreath H, Tracey KJ, Sidney S, Liu K, Seeman T. RR interval variability is inversely related to inflammatory markers: the CARDIA study. *Mol Med*. 2007;13(3-4):178-184.
30. Reiner AP, Carty CL, Carlson CS, et al. Association between patterns of nucleotide variation across the three fibrinogen genes and plasma fibrinogen levels: the Coronary Artery Risk Development in Young Adults (CARDIA) study. *J Thromb Haemost*. 2006; 4(6):1279-1287.
31. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA*. 2001;285(19):2486-2497.
32. Yoon HC, Emerick AM, Hill JA, Gjertson DW, Goldin JG. Calcium begets calcium: progression of coronary artery calcification in symptomatic subjects. *Radiology*. 2002;224(1):236-241.
33. van den Berg JF, Knvistingh Neven A, Tulen JH, et al. Actigraphic sleep duration and fragmentation are related to obesity in the elderly: the Rotterdam Study. *Int J Obes (Lond)*. 2008;32(7):1083-1090.
34. Knutson KL, Rathouz PJ, Yan LL, Liu K, Lauderdale DS. Intra-individual daily and yearly variability in actigraphically recorded sleep measures: the CARDIA study. *Sleep*. 2007;30(6):793-796.
35. Jung HH, Han H, Lee JH. Sleep apnea, coronary artery disease, and antioxidant status in hemodialysis patients. *Am J Kidney Dis*. 2005;45(5):875-882.
36. Marin JM, Carrizo SJ, Vicente E, Augusti AG. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. *Lancet*. 2005;365(9464): 1046-1053.
37. Drager LF, Bortolotto LA, Lorenzi MC, Figueiredo AC, Krieger EM, Lorenzi-Filho G. Early signs of atherosclerosis in obstructive sleep apnea. *Am J Respir Crit Care Med*. 2005;172(5):613-618.
38. Hedner J, Pillar G, Pittman SD, Zou D, Grote L, White DP. A novel adaptive wrist actigraphy algorithm for sleep-wake assessment in sleep apnea patients. *Sleep*. 2004;27(8):1560-1566.
39. Hastings PC, Vazir A, O'Driscoll DM, Morrell MJ, Simonds AK. Symptom burden of sleep disordered breathing in mild-to-moderate congestive heart failure patients. *Eur Respir J*. 2006;27(4): 748-755.
40. García-Díaz E, Quintana-Gallego E, Ruiz A, et al. Respiratory polygraphy with actigraphy in the diagnosis of sleep apnea-hypopnea syndrome. *Chest*. 2007; 131(3):725-732.
41. Zou D, Grote L, Peker Y, Lindblad U, Hedner J. Validation a portable monitoring device for sleep apnea diagnosis in a population based cohort using synchronized home polysomnography. *Sleep*. 2006; 29(3):367-374.
42. Patel SR, Blackwell T, Redline S, et al. The association between sleep duration and obesity in older adults [published ahead of print on October 21, 2008]. *Int J Obes (Lond)*. In press.
43. Gottlieb DJ, Redline S, Nieto FJ, et al. Association of usual sleep duration with hypertension: the Sleep Heart Health Study. *Sleep*. 2006;29(8):1009-1014.
44. Ayas NT, White DP, Manson JE, et al. A prospective study of sleep duration and coronary heart disease in women. *Arch Intern Med*. 2003;163(2): 205-209.
45. Matthews K, Schwartz J, Cohen S, Seeman T. Diurnal cortisol decline is related to coronary calcification: CARDIA study. *Psychosom Med*. 2006;68 (5):657-661.
46. Leproult R, Copinschi G, Buxton O, Van Cauter E. Sleep loss results in an elevation of cortisol levels the next evening. *Sleep*. 1997;20(10):865-870.
47. Spiegel K, Leproult R, Van Cauter E. Impact of sleep debt on metabolic and endocrine function. *Lancet*. 1999;354(9188):1435-1439.
48. Staessen J, Bulpitt CJ, O'Brien E, et al. The diurnal blood pressure profile: a population study. *Am J Hypertens*. 1992;5(6 pt 1):386-392.

