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# Sleep duration, baseline cardiovascular risk, inflammation and incident cardiovascular mortality in ambulatory U.S. Adults: National health and nutrition examination survey

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# Sleep duration, baseline cardiovascular risk, inflammation and incident cardiovascular mortality in ambulatory U.S. Adults: National health and nutrition examination survey

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ABSTRACT

*Introduction:* The interplay between sleep duration and inflammation on the baseline and incident cardiovascular (CV) risk is unknown. We sought to evaluate the association between sleep duration, C-reactive protein (CRP), baseline CV risk, and incident CV mortality.

*Methods:* We used data from the National Health and Nutrition Examination Survey 2005–2010 linked with the cause of death data from the National Center for Health Statistics for adults aged ≥18 years. The associations between self-reported sleep duration and CRP, 10-year atherosclerotic CV disease risk score (ASCVD) and CV mortality were assessed using Linear, Poisson and Cox proportional hazard modeling as appropriate.

*Results:* There were 17,635 eligible participants with a median age of 46 years (interquartile range [IQR] 31, 63). Among them, 51.3% were women and 46.9% were non-Hispanic Whites. Over a median follow-up of 7.5 years (IQR 6.0, 9.1), 350 CV deaths occurred at an incident rate of 2.7 per 1000-person years (IQR 2.4, 3.0). We observed a U–shaped associations between sleep duration and incident CV mortality rate (*P*-trend=0.011), sleep duration and 10-year ASCVD risk (*P*-trend <0.001), as well as sleep duration and CRP (*P*-trend <0.001). A self-reported sleep duration of 6-7 hours appeared most optimal. We observed that those participants who reported <6 or >7 hours of sleep had higher risk of CV death attributable to inflammation after accounting for confounders.

*Conclusions:* There was a U-shaped relationship of incident CV mortality, 10-year ASCVD risk, and CRP with sleep duration. These findings suggest an interplay between sleep duration, inflammation, and CV risk.

## 1. Introduction

Cardiovascular (CV) disease is the leading cause of mortality in the United States (US) [1,2]. Sleep duration is a risk factor for CV morbidity and mortality [3,4].

Current data suggest a high prevalence of sleep deficiency and sleep disorders in the US [5]. Studies have suggested an association of short and long sleep duration with higher CV mortality [6-8]. The exact pathophysiological basis behind this association is unknown. Inflammation has an independent association with worse CV prognosis and may be one of the factors mediating the association of sleep duration with CV mortality [9-11].

In this study, we investigate the associations of sleep duration with baseline CV risk, inflammation and their effect on incident CV mortality in a representative cohort of US adults. We hypothesize that both short and long sleep duration are associated are associated with higher inflammation and, therefore, higher CV risk.

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**Table 1**
Baseline characteristics of the study population.

| | Overall($n$ = 17,635) | Sleep Duration<br>< 6 hours<br>Short Sleep($n$ = 2,755) | 6-7 hours<br>Optimal Sleep($n$ = 8,714) | >7 hours<br>Long Sleep($n$ = 6,166) | p-value |
|---|---|---|---|---|---|
| Demographic Parameters | | | | | |
| Age (years) | 46 (31, 63) | 48 (34, 62) | 46 (31, 61) | 47 (29, 67) | <0.001 |
| Women | 9,052 (51.3%) | 1,390 (50.5%) | 4,380 (50.3%) | 3,282 (53.2%) | 0.001 |
| Race | | | | | |
| Non-Hispanic White | 8,268 (46.9%) | 1,020 (37.0%) | 4,193 (48.1%) | 3,055 (49.5%) | <0.001 |
| Non-Hispanic Black | 3,711 (21.0%) | 931 (33.8%) | 1,705 (19.6%) | 1,075 (17.4%) | |
| Mexican American | 3,357 (19.0%) | 406 (14.7%) | 1,630 (18.7%) | 1,321 (21.4%) | |
| Other Race - Including Multi-Racial | 815 (4.6%) | 142 (5.2%) | 430 (4.9%) | 243 (3.9%) | |
| Other Hispanic | 1,484 (8.4%) | 256 (9.3%) | 756 (8.7%) | 472 (7.7%) | |
| Anthropometry | | | | | |
| Body Mass Index (kg/m$^2$) | 27.8 (24.1, 32.1) | 28.8 (24.9, 33.5) | 27.7 (24.1, 32.0) | 27.3 (23.7, 31.7) | <0.001 |
| Comorbidities | | | | | |
| Diabetes Mellitus | 2,826 (16.8%) | 558 (21.4%) | 1,233 (14.9%) | 1,035 (17.6%) | <0.001 |
| Dyslipidemia | 12,107 (70.5%) | 1,870 (69.8%) | 5,996 (70.6%) | 4,241 (70.7%) | 0.640 |
| Hypertension | 9,536 (56.0%) | 1,648 (61.7%) | 4,552 (54.2%) | 3,336 (56.0%) | <0.001 |
| Systolic Blood Pressure (mmHg) | 120 (112, 134) | 122 (112, 136) | 120 (112, 132) | 122 (110, 136) | <0.001 |
| Diastolic Blood Pressure (mmHg) | 70 (62, 78) | 70 (62, 80) | 70 (62, 78) | 68 (60, 76) | <0.001 |
| Smoking | 7,715 (46.8%) | 1,379 (52.5%) | 3,750 (45.8%) | 2,586 (45.7%) | <0.001 |
| Chronic Obstructive Pulmonary Disease | 161 (1.0%) | 50 (1.9%) | 57 (0.7%) | 54 (1.0%) | <0.001 |
| Malignancy | 393 (8.3%) | 55 (7.6%) | 173 (7.4%) | 165 (9.8%) | 0.018 |
| Prevalent Cardiovascular Disease | 1,145 (7.0%) | 254 (9.7%) | 432 (5.3%) | 459 (8.2%) | <0.001 |
| 10-year ASCVD Risk[†] | 3.5 (0.5, 14.4) | 4.6 (0.9, 15.7) | 3.4 (0.6, 12.3) | 3.3 (0.4, 17.2) | <0.001 |
| On Psychotropic Medications | 2,111 (17.1%) | 413 (21.0%) | 860 (14.1%) | 838 (19.8%) | <0.001 |
| Laboratory Parameters | | | | | |
| Estimated GFR (mL/min/1.73m$^2$) | 98.7 (80.6, 121.4) | 98.4 (81.3, 118.7) | 98.5 (81.3, 120.4) | 99.3 (79.2, 123.1) | 0.510 |
| C-reactive Protein (mg/dL) | 0.19 (.07, .47) | 0.23 (0.09, 0.56) | 0.18 (0.07, 0.43) | 0.20 (0.08, 0.49) | <0.001 |
| Hemoglobin (g/dL) | 14.2 (13.1, 15.3) | 14.1 (13, 15.2) | 14.3 (13.3, 15.4) | 14.1 (13.1, 15.2) | <0.001 |
| Total Leukocyte Count (*10$^3$ cells/μL) | 7 (5.8, 8.4) | 7 (5.8, 8.5) | 6.9 (5.8, 8.4) | 7 (5.8, 8.4) | 0.190 |
| Sleep Duration (hours) | 7 (6, 8) | 5 (4, 5) | 7 (6, 7) | 8 (8, 8) | <0.001 |
| Sleep Disorder | 1,255 (7.1%) | 396 (14.4%) | 513 (5.9%) | 346 (5.6%) | <0.001 |

[†] In patients without prevalent cardiovascular disease ($n$ = 14,079). Data are represented as median (25th to 75th percentile), number (percentage). GFR estimated by the modification of diet in renal disease (MDRD) equation. Prevalent cardiovascular disease includes self-reported history of coronary artery disease, heart failure or stroke. Psychotropic medications include anticonvulsants, anxiolytics, sedatives, hypnotics, stimulants, antidepressants and antipsychotic medications. ASCVD, atherosclerotic cardiovascular disease, GFR, glomerular filtration rate; NHANES, National Health, and Nutrition Examination Survey; mmHg = millimeters of mercury; μl=microliter; kg/m$^2$= kilogram per-squared meter; g/dl=grams per deciliter; ml/min=milliliters per minute; mmol/L= millimoles per liter; mg/dl=milligrams per deciliter.

## 2. Methods

The study was conducted following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (eTable 1).

### 2.1. Study design and participants

The National Health and Nutrition Examination Survey (NHANES) collects data from a representative U.S. civilian non-institutionalized sample in a 2-year cycle. The NHANES uses a complex, four-stage, probability sampling design to select participants. Every participant gives informed consent and the institutional review board of the National Center for Health Statistics approves the protocol. The NHANES study design, operation, and contents have been published previously and are available online [12]. The sleep questionnaire was introduced in NHANES in 2005-06 for participants aged ≥16 years and consists of questions on sleep habits and disorders. We used data for adult participants aged ≥18 years from three NHANES cycles from 2005-2010 for the current analysis (Fig. 1), since data for both sleep habits and inflammatory markers were only available for these cycles. Our study used publicly available de-identified data hence it was exempt from the institutional review board approval.

### 2.2. Data synthesis

Data regarding sleep patterns were self-reported and collected during the home-interview phase of the NHANES. We combined the NHANES data with the cause of death from probabilistically linked death certificate records provided by the National Center of Health Statistics from the National Death Index [13].

### 2.3. Inclusion and exclusion criteria

We included participants aged ≥18 years for the current analysis. We excluded participants with missing data on sleep duration or follow-up. There were no exclusion criteria based on sleep duration or prevalent CV disease.

### 2.4. Study variables

Sleep duration was the independent variable of interest. For quantifying the sleep duration in hours, the participants were asked, “How much sleep you usually get at night on weekdays or workdays?” Participant’s responses were rounded in hours and recorded as a range of values from 1 to 12. A response of ≥12 h was recorded as 12 h or more. C-reactive protein (CRP) was the inflammatory marker in this investigation and was available from the blood samples collected at the time of the visit to the mobile examination center. Details of CRP measurement are given in the eMethods.

Data on demographic and clinical characteristics were collected either during the interview or visit to the mobile examination center. The variable codes and diagnostic criteria used to define co-morbidities are given in eMethods and eTable 2 in the supplement. Prevalent CV disease was defined as self-reported angina, heart attack, coronary artery disease, heart failure, or stroke. The 10-year atherosclerotic CV disease

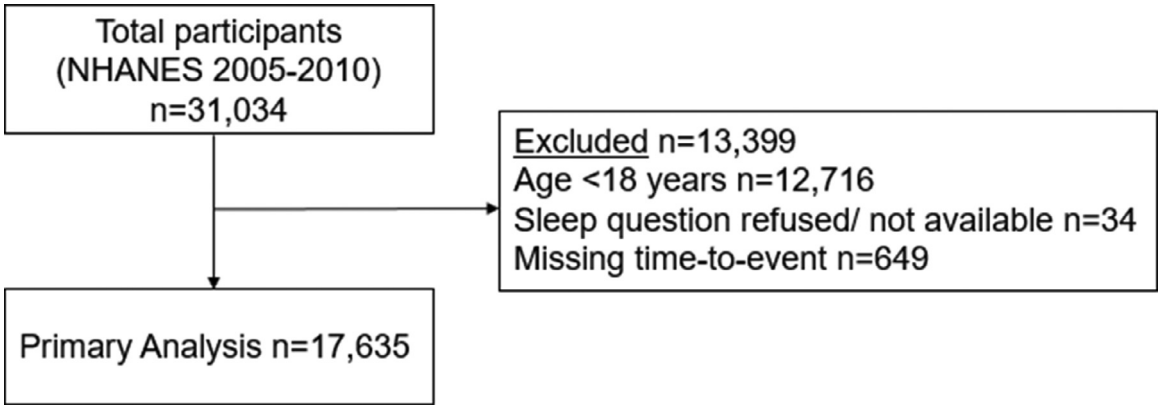



**Fig. 1.** Flow diagram for study selection. Cardiovascular disease is defined as self-reported coronary artery disease, heart failure, or stroke. TLC: Total Leukocyte Count, NHANES: National Health and Nutrition Examination Survey, μL: Microliter.

(ASCVD) risk was calculated using the pooled cohort-equations for participants without prevalent CV disease [14]. For estimation of ASCVD risk, participants aged <40 years or >79 years were considered as 40 and 79 years old, respectively. The class of prescription medication grouped as a psychotropic medication is given in eTable 2.

### 2.5. Study outcome

The outcome of our analysis was death due to cardiac causes (CV mortality) during follow-up. CV mortality was defined as a composite of death due to either disease of the heart (I00–I09, I11, I13, I20–I51) or cerebrovascular disease (I60–I69). Participants with CV mortality were censored at the date of death while those without CV mortality were censored either at the time of non-CV death or last date of follow-up. Follow-up time was defined as the time from the mobile examination center date to the date of death or end of mortality period.

### 2.6. Statistical analysis

Continuous variables were represented as medians with interquartile ranges (IQRs) and categorical variables were represented as counts with proportions. The Wilcoxon rank-sum test and Chi-squared tests were used to identify the differences in baseline characteristics in continuous and categorical variables, respectively. We used multivariate linear regression while accounting for non-linearity using restricted cubic spline models to ascertain the associations between sleep duration and CRP, as well as sleep duration and 10-year ASCVD risk. Multivariate Poisson regression models were used to ascertain the associations between sleep duration and incident rate of CV mortality.

The sleep duration with the lowest incidence rate of CV mortality was then defined as the optimal sleep duration. Sleep duration was classified as either less than optimal (short sleep), optimal, or more than optimal (long sleep). Hazard ratios (HRs) and 95% confidence intervals (CI) for sleep duration class and CV mortality were estimated in the unadjusted and adjusted Cox proportion hazard analyses. The proportionality assumption was verified using Schöenfeld residuals [15]. We also studied the association using four pre-defined self-reported sleep duration categories: <6 h, 6-<7 h, 7–8 h and >8 h.

The multivariable models consisted of the following covariates: age, gender, race, self-reported cardiovascular disease, hypertension, diabetes mellitus, glomerular filtration rate (estimated by the Modification of Diet in Renal Disease equation) [16], smoking status, body mass index, and dyslipidemia. Missing values of these covariates were imputed using age, gender, and race for the adjusted analysis [19]. There was no difference in the central tendency, spread, and predictive ability in the Cox model between imputed and the un-imputed variables (eTable 3). We also used competing risk regression analyses with non-CV mortality as a competing risk to estimate sub distributional hazard ratios for sleep categories according to the method described by Fine and Gray [17].

Further, we calculated the population attributable fraction of inflammation (defined as a CRP ≥0.3 mg/dL) across the sleep duration categories in the multivariable model to understand the proportional reduction in CV mortality with correction of inflammation across sleep categories [18].

K.G and N.S.B conceptualized and designed the study. K.G, S.N., R.K., and V.J. acquired the data. K.G., R.G., and N.S.B analyzed the data. K.G., S.N. and R.K drafted the manuscript. R.G, V.J., W.Z, S.D.P, and N.S.B revised the manuscript critically. All authors approved the final version of the manuscript. All statistical analyses were conducted in Stata version 14.2 (StataCorp, College Station, TX, U.S.A.). All p-values were 2-sided, with <0.05 considered statistically significant.

## 3. Results

### 3.1. Baseline characteristics

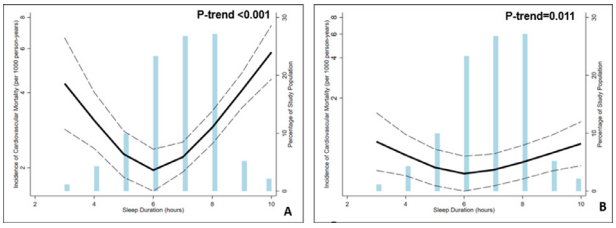
Out of 31,034 participants in the NHANES from 2005 and 2010, 17,635 participants met eligibility criteria (Fig. 1). The median age of the eligible participants was 46 years (IQR 31,63); women constituted 51.0% of the study population (Table 1). The majority of the population (46.9%) was non-Hispanic White. CRP concentration was available in 93.9% of the study participants and median CRP was 0.19 mg/dL (IQR 0.07, 0.47). The prevalence of diabetes mellitus, dyslipidemia, and hypertension was 17.0%, 71.0%, and 56.0%, respectively. Self-reported CV disease was found in 7% of participants. The 10-year ASCVD risk was computed in 80.0% of participants (the remaining 20.0% had missing variables or had prevalent CV disease) and the median risk was 3.5% (IQR 0.5, 14.4). Around 17.0% of participants were on some form of psychotropic medications. The median sleep duration was 7 hours (IQR 6, 8) and 7.0% of participants had a self-reported sleep disorder (Table 1).

Over a median follow-up of 7.5 years (IQR 6.0, 9.1), 350 CV deaths occurred at an incidence rate of 2.7 per 1000-person years (IQR 2.4, 3.0).

#### 3.1.1. Sleep duration and CV mortality

There was a U-shaped relationship between sleep duration and CV mortality with the lowest incidence rate associated with a sleep duration of 6–7 h (incidence rate 1.8 per 1000-person years, IQR 1.5, 2.2, *P*-trend<0.001) (Central Figure Panel A). This association remained robust after extensive adjustment in the multivariable model (Central Figure Panel B).

There were 2,755 (15.6%), 8,714 (49.4%), and 6,166 (35.0%) participants with less than optimal (<6 h, short sleep), optimal (6–7 h), and more than optimal sleep (>7 h, long sleep), respectively (Table 1). There




**Central Figure.** Relationship of cardiovascular mortality with sleep duration across the assembled cohort in the unadjusted (Panel A) and adjusted analyses (Panel B). Restricted cubic spline Poisson regression model estimates (solid black) are presented with 95% confidence intervals (dashed black). Blue bars represent the frequency histogram. The adjusted model included age, gender, race, self-reported cardiovascular disease, hypertension, diabetes mellitus, glomerular filtration rate estimated using Modification of Diet in Renal Disease equation, smoking status, body mass index, and dyslipidemia.

was no clinically significant difference in the age of participants across sleep categories. There was a significantly higher representation of non-Hispanic Blacks among short sleepers. There was a higher prevalence of diabetes mellitus, hypertension, and prevalent CV disease among those with short and long sleep compared to those with optimal sleep (Table 1).

The unadjusted risk of CV mortality among those with short and long sleep was 62% and 103% higher than those with optimal sleep (HR 1.62, 95% CI 1.19, 2.21, $p = 0.002$ for short sleep and HR 2.03, 95% CI 1.61, 2.57, $p < 0.001$ for long sleep). The elevated hazard remained significant after multivariate adjustment (HR 1.45, 95% CI 1.06, 1.99, $p = 0.019$ for short sleep and HR 1.45, 95% CI 1.14, 1.83, $p = 0.002$ for long sleep, Fig. 2 Panel A). This relationship was consistent among men and women (etable 4). Among the four pre-defined sleep categories, a self-reported sleep duration of 7–8 h was associated with a higher risk of CV mortality as compared with 6-<7 h (reference) in both unadjusted 1.88 (95% CI 1.37, 2.57) and unadjusted analysis 1.38 (1.01, 1.89) (eTable 5).

The association between sleep categories and CV mortality did not change in the competing risk regression model with death due to non-CV causes as a competing risk (standardized HR 1.42, 95% CI 1.04, 1.96, $p = 0.027$ for short sleep and standardized HR 1.41, 95% 1.11, 1.79, $p = 0.004$ for long sleep, Fig. 2 Panel B).

### 3.1.2. Sleep duration and 10-year ASCVD risk score

There was a U-shaped relationship with the median 10-year ASCVD risk score and the sleep duration such that participants with optimal sleep had the lowest risk ($P$-trend<0.001, Fig. 3).

### 3.1.3. Sleep duration and CRP

There was a U-shaped relationship between median CRP concentration and sleep duration such that patients with optimal sleep had the lowest CRP concentration (0.23 [IQR 0.09, 0.56] mg/dl for short sleep, and 0.20 [IQR 0.08, 0.49] mg/dl for long sleep versus 0.18 [IQR 0.07, 0.43] mg/dl optimal sleep, $p < 0.001$) both in the univariate and multivariable model (Fig. 4 Panel A and B).

The population attributable fraction of inflammation (CRP ≥0.3 mg/dL) for CV mortality was 14.1% (95% CI 4.4, 22.9, $p < 0.05$) for short sleep, and 12.8% (95% CI 4.0, 20.8, $p < 0.05$) for long sleep vs. 11.2 (95% CI 3.6, 18.2, $p < 0.05$) for optimal sleep in the multivariable model (Fig. 5)

## 4. Discussion

In this study of a large representative cohort of the U.S. population, we found a U-shaped relationship between self-reported sleep duration and CV mortality such that minimum risk was associated with a sleep duration of 6–7 h. Participants with less or more than 6–7 h of sleep had a higher CRP, 10-year ASCVD risk score, and CV mortality. These findings remained significant in the multivariable and competing risk regression models with non-CV mortality as a competing risk. Further, optimization of sleep is expected to reduce the population risk of CV mortality.

Previous studies and a meta-analysis of prospective cohort studies have suggested that both short and long sleep durations are associated with worse CV outcomes [4,6,7,20,21]. However, these studies used varying definitions of short and long sleep. Further, recommended sleep duration differs across age groups and there is no single cut-off for optimal sleep. To acknowledge this gap, we did not consider a priori definition of optimal sleep and found that the lowest CV risk is associated with a self-reported sleep duration of 6–7 h in US adults aged ≥18 years. These results are similar to other large-scale studies and are consistent with the recommendations of the American Academy of Sleep Medicine and Sleep Research Society [3,6,8,21–25].

There was a higher prevalence of established CV risk factors such as higher body mass index, diabetes mellitus, and hypertension among those with less-than-optimal sleep. This association has been consistently demonstrated in previous large studies [27–30]. Acute sleep de-

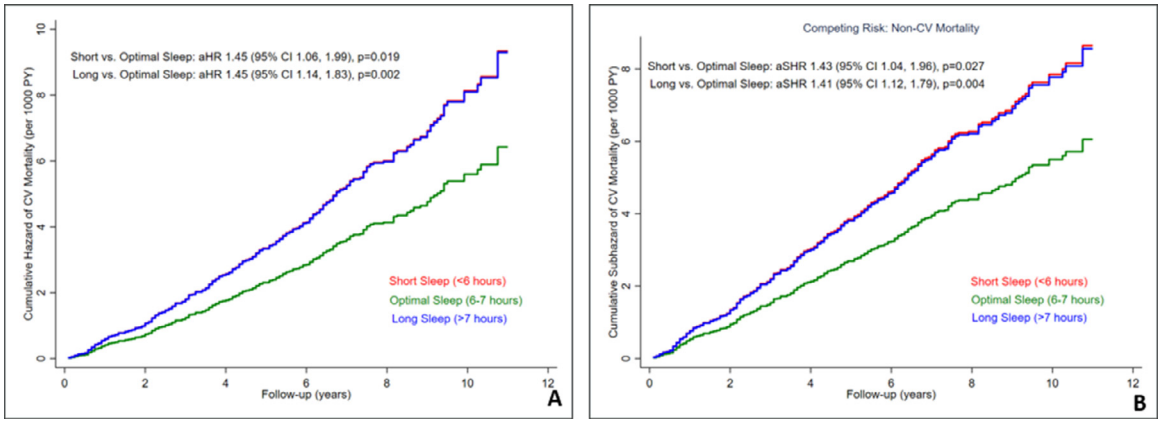



**Fig. 2.** Cumulative proportion (Panel A) and cumulative sub-hazard of CV mortality with non-CV mortality as a competing risk (Panel B) using Cox proportional hazard model. Red, green and blue line represent short (<6 hours), optimal (6-7 hours) and long sleep (>7 hours), respectively. The adjusted model in both analyses included age, gender, race, self-reported cardiovascular disease, hypertension, diabetes mellitus, glomerular filtration rate estimated using Modification of Diet in Renal Disease equation, smoking status, body mass index, and dyslipidemia. CV, cardiovascular, PY, person-years, aHR, adjusted hazard ratio, CI, confidence interval, aSHR, adjusted subhazard ratio.

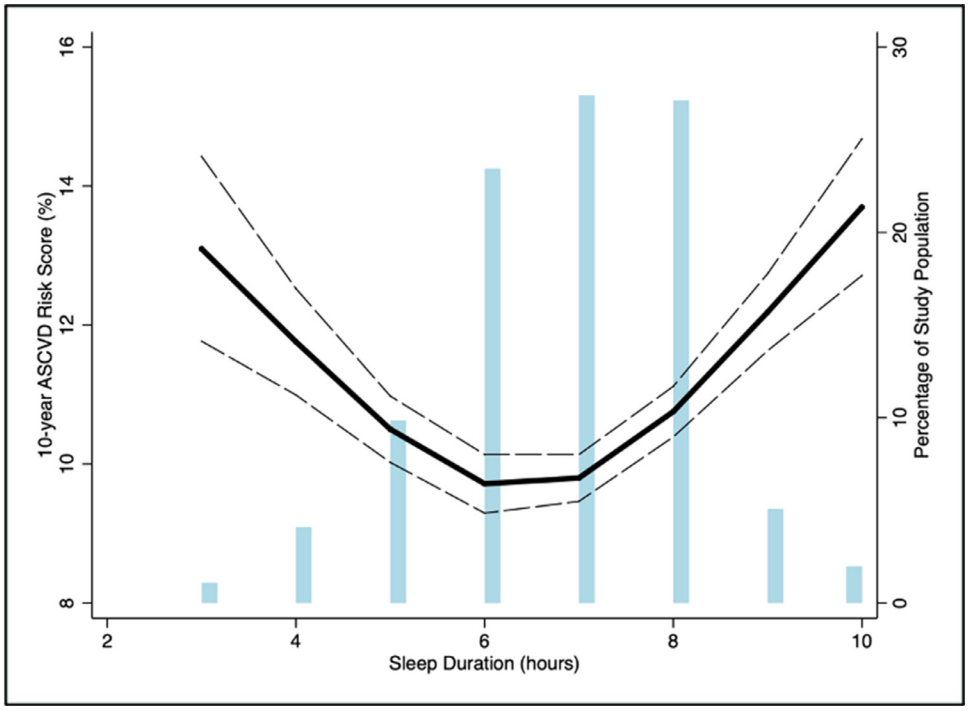



**Fig. 3.** Relationship of 10-year ASCVD risk score with sleep duration across the assembled cohort in participants without prevalent cardiovascular disease, defined self-reported history of coronary artery disease, heart failure or stroke. Restricted cubic spline Poisson regression model estimates (solid black) are presented with 95% confidence intervals (dashed black). Blue bars represent the frequency histogram (n=14,079). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

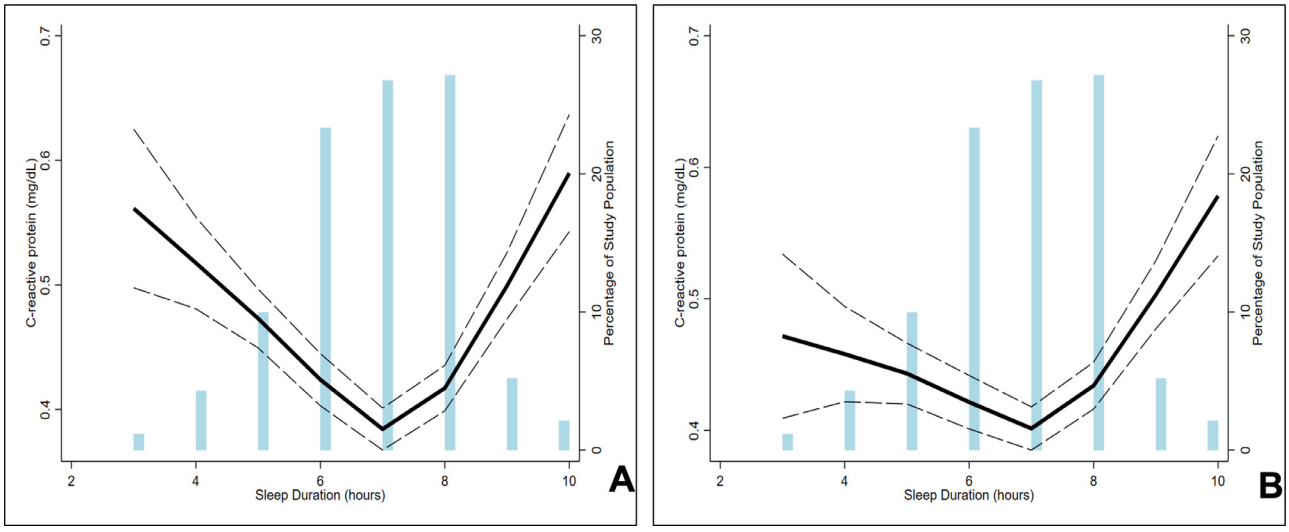



**Fig. 4.** Relationship of C-reactive protein with sleep duration across the assembled cohort in the unadjusted (Panel A) and unadjusted analyses (Panel B). Restricted cubic spline Poisson regression model estimates (solid black) are presented with 95% confidence intervals (dashed black). Blue bars represent the frequency histogram (n=16,560). The adjusted model included age, gender, race, self-reported cardiovascular disease, hypertension, diabetes mellitus, glomerular filtration rate estimated using Modification of Diet in Renal Disease equation, smoking status, body mass index, and dyslipidemia. Mg, milligram, dL, deciliter. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

privation leads to sympathetic activation and is associated with a rise in blood pressure, inflammation, and gluconeogenesis [30–34]. This "stress response" is associated with an increase in cortisol, CRP, and IL-6 [9,33,35]. This inflammatory milieu is associated with a higher risk of atherosclerotic events [10,11]. Thus, we hypothesize that sleep deprivation leads to higher CV mortality due to atherosclerotic events. Our results also suggest that both CRP and ASCVD risk are elevated among participants with <6 hours of sleep. The exact mechanisms behind adverse health events associated with chronic sleep deprivation are less precise but are likely due to the continuation of the same pathophysiological process [3].

The association of long sleep with increased CV mortality has been previously demonstrated [4,6,20]. Similar to previous studies, there was a higher prevalence of comorbidities such as diabetes mellitus and hypertension in this cohort [6,22]. These co-morbid conditions may cause the participant to sleep more [36,37]. But, the independent association of long sleep remained significant in the multivariable model. There was a higher prevalence of self-reported sleep disorders and the use of psychotropic medications in those with long sleep. There could be unmeasured confounding due to these factors. Data on type of sleep disorders were not collected as part of NHANES.

To the best of our knowledge, this is the first time that the association between short and long sleep, inflammation, cardiovascular risk, and CV mortality has been demonstrated in a large representative cohort of the US population. Through the U-shaped relationship between sleep duration and CRP, and sleep duration and ASCVD risk score, we hypothesize

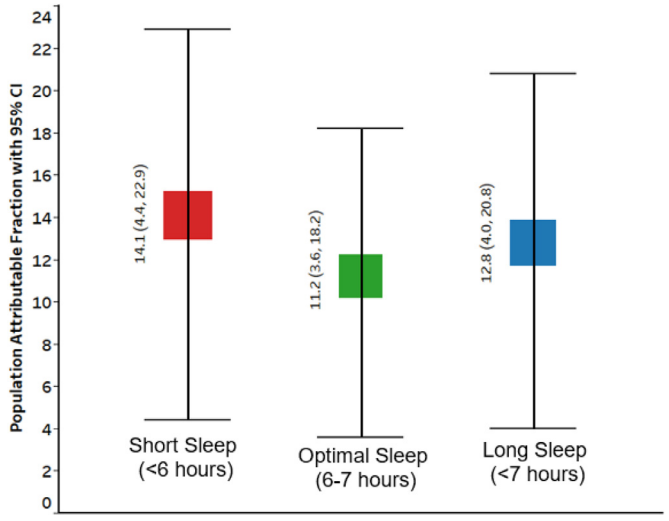



**Fig. 5.** Population attributable fraction(%) for sleep duration across sleep categories for cardiovascular mortality in the multivariable model. The square represents the population attributable fraction and dashed lines represent the 95% confidence interval(CI).

that patients with short or long sleep may have increased CV mortality due to atherosclerotic disease associated with inflammation. Previous findings also suggest a U-shaped relationship between coronary artery calcium score and sleep duration with a minimum score associated with a sleep duration of 7 hours [38]. Further, around 12–14% risk of CV mortality can be attributed to less or more than optimal sleep. This needs to be further investigated in large prospective studies. It is unknown if the correction of sleep pattern is associated with reduced inflammation, independent of other co-morbidities. Future studies should also investigate if immunomodulatory therapy in patients with short- or long sleep can alter CV outcomes.

There are several important limitations to our study. We used self-reported sleep duration. This may differ from the duration of sleep when measured by polysomnography. Previous studies suggest that self-report sleep times are generally overestimated [26,39]. Besides sleep duration, sleep quality and irregularity are important factors governing optimal sleep [40,41]. Data for these factors were not collected in the NHANES. Sleep duration and CRP were measured only during the initial visit. CRP measurement was done only at baseline and we could not correlate temporal trends due to lack of serial measurement. We also used imputed data for missing variables in the multivariable model. However, the association of unimputed and imputed variable was similar in the Cox model. We do not have the temporal trends of sleep duration and CRP to establish a causal relationship with CV mortality.

To conclude, the analysis of a large representative cohort of US adults suggests a U-shaped relationship of CV mortality, CRP, and 10-year ASCVD risk with sleep duration such that the minimum risk was associated with a sleep duration of 6–7 h. These hypothesis-generating findings suggest an association between sleep duration, inflammation, and CV mortality.

## Declaration of Competing Interest

None of the authors had any conflicts of interest or financial disclosures to declare directly related to this investigation.

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## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ajpc.2021.100246.

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