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# Prediagnosis Sleep Duration, Napping, and Mortality Among Colorectal Cancer Survivors in a Large US Cohort

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**Study Objectives:** Prediagnosis lifestyle factors can influence colorectal cancer (CRC) survival. Sleep deficiency is linked to metabolic dysfunction and chronic inflammation, which may contribute to higher mortality from cardiometabolic conditions and promote tumor progression. We hypothesized that prediagnosis sleep deficiency would be associated with poor CRC survival. No previous study has examined either nighttime sleep or daytime napping in relation to survival among men and women diagnosed with CRC.

**Methods:** We examined self-reported sleep duration and napping prior to diagnosis in relation to mortality among 4869 CRC survivors in the NIH-AARP Diet and Health Study. Vital status was ascertained by linkage to the Social Security Administration Death Master File and the National Death Index. We examined the associations of sleep and napping with mortality using traditional Cox regression (total mortality) and Compositing Risk Regression (cardiovascular disease [CVD] and CRC mortality). Models were adjusted for confounders (demographics, cancer stage, grade and treatment, smoking, physical activity, and sedentary behavior) as well as possible mediators (body mass index and health status) in separate models.

**Results:** Compared to participants reporting 7–8 hours of sleep per day, those who reported <5 hr had a 36% higher all-cause mortality risk (Hazard Ratio (95% Confidence Interval), 1.36 (1.08–1.72)). Short sleep (<5 hr) was also associated with a 54% increase in CRC mortality (Substitution Hazard Ratio (95% Confidence Interval), 1.54 (1.11–2.14)) after adjusting for confounders and accounting for competing causes of death. Compared to no napping, napping 1 hr or more per day was associated with significantly higher total and CVD mortality but not CRC mortality.

**Conclusion:** Prediagnosis short sleep and long napping were associated with higher mortality among CRC survivors.

**Keywords:** sleep, napping, colorectal cancer, mortality.

**Statement of Significance**

Prediagnosis sleep duration may impact metabolic health and immune function and therefore influence colorectal cancer survival. However, little is known about prediagnosis sleep and napping habits in relation to total and cause-specific mortality among colorectal cancer patients. We investigated the associations between self-reported sleep and napping duration well before cancer diagnosis and total, cardiovascular and colorectal cancer mortality in almost 5000 colorectal cancer patients. We found that both very short sleep and extended napping were associated with poor survival in our survivor population. Very short sleep was associated with higher colorectal cancer-specific mortality while, extended napping was associated with higher cardiovascular mortality. More studies are needed to confirm our findings, evaluate the effect of sleep deficiency on different subtypes of colorectal cancer, and examine the health impacts of postdiagnosis sleep among cancer patients.

## INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer diagnosed in the United States, with over 130 thousand new cases diagnosed in 2015.[1] In the past two decades, the survival rate for CRC patients has continued to improve due to advances in early detection and treatment. It is estimated that there are now over 1 million CRC survivors in the United States.[1] It is thus important to understand the factors that influence survival among CRC patients. Disease progression and survival among CRC patients are determined by both tumor characteristics and patient characteristics. Several lifestyle factors, including body-mass index (BMI),[2] physical activity,[3] sedentary behavior,[4,5] and diet[6] measured prediagnosis, have been shown to influence total and CRC-specific mortality. It has been hypothesized that obesity, a sedentary lifestyle, and poor diet can lead to hyperinsulinemia and chronic inflammation, which is not only associated with higher mortality from cardiometabolic conditions but also creates a systemic milieu that favors tumor progression.[7,8]

Sleep and circadian rhythms play a critical role in regulating human metabolism and the immune response.[9,10] Sleep deficiency has been linked to higher adiposity,[11] metabolic syndrome,[12] insulin resistance,[13] and elevated levels of inflammatory markers[14] and therefore could impact tumor development and recurrence. Several studies have linked both short (≤5 hr per day) and long (≥9 hr) sleep with elevated risk of colorectal cancer, supporting a role of sleep in colorectal carcinogenesis.[15,16] Moreover, there is also a well-established, U-shaped association between sleep duration and total and cardiovascular mortality in the general population.[17,18] However, no study has examined the relationship between prediagnosis sleep duration and mortality among CRC patients.

We studied prediagnosis sleep duration and daytime napping in relation to total, cardiovascular, and CRC mortality among CRC survivors. Understanding the relationship between sleep and mortality among cancer patients could provide clues about novel factors that could influence disease prognosis and predict survival.

## METHODS

### Study Population

The NIH-AARP Diet and Health Study was established in 1995–1996. A baseline questionnaire was mailed to AARP members who were 50 to 71 years old and resided in six US states (California, Florida, Louisiana, New Jersey, North Carolina, and Pennsylvania) and two metropolitan areas (Atlanta, Georgia, and Detroit, Michigan). In total, 566 399 people satisfactorily completed the baseline questionnaire.

Within 6 months of the baseline, a second questionnaire, the risk factor questionnaire including questions on habitual sleep duration and napping, was mailed to participants who did not report a history of cancer diagnosis at baseline. Details of this study have been previously reported.[19] The study was approved by the National Cancer Institute Special Studies Institutional Review Board.

Incident cancer cases were identified through linkage to eight original and three additional (Arizona, Nevada, and Texas) state cancer registry databases through December 31, 2006. A previous validation study found that approximately 90% of cancers were identified through registry linkage.[20] Cancer registry data included cancer diagnosed, diagnosis date, morphology code, grade, stage, and first course of treatment within 1 year of diagnosis. Of the 334 905 participants who completed both the baseline and the risk factor questionnaire, we identified 5295 patients with primary CRC using *the International Classification of Diseases for Oncology*, Third Edition (ICD-O-3, codes C180-189, C199 and C209).[21] Of these, we excluded participants without information on sleep ($N = 31$) or napping ($N = 10$) and those diagnosed with in situ (stage 0, $N = 385$). Our final analytic cohort included 4869 patients.

### Assessment of Sleep Duration and Napping

In the risk factor questionnaire, participants were asked to report "the amount of time they slept at night" in a typical 24-hr period over the past 12 months. They were asked to choose from "less than 5 hours," "5–6 hr," "7–8 hr," and "9 or more hours" or leave the answer blank. They were also asked to report their napping duration in this period by choosing from "none," "less than 1 hour," "1–2 hr,", "3–4 hr," and "5 or more hours". We combined the highest three categories of napping into one group (1+ hour) to preserve statistical power. The median lag time between sleep assessment and cancer diagnosis was 4.3 years.

### Covariate Assessment

The baseline and risk factor questionnaire also collected information on a broad range of covariates, including demographic characteristics, such as age, race and ethnicity, and education; lifestyle factors, such as smoking history, physical activity, sedentary behavior, and BMI; medical history such as hypertension, hypercholesterolemia, and diabetes; dietary intake, including total calorie, total fat, fruits and vegetables, meat, whole grain, coffee, and alcohol; and the use of dietary supplement, nonsteroidal anti-inflammatory drug, and menopausal hormone therapy in women.

### Mortality Ascertainment

The vital status of study participants was ascertained by annual linkage to the Social Security Administration Death Master File and the National Death Index (NDI) Plus through December 31, 2011. A previous study found that our ascertainment method yielded 95% accurate results.[22] The end points of our analysis were total mortality, cardiovascular disease (CVD) mortality (*International Classification of Diseases, 10th Revision* [*ICD-10*] codes I00-I78), and CRC cancer mortality (*ICD-10* code C18 to C20).

### Statistical Analysis

We used IVEware 2.0 (http://iveware.org) to impute missing values, using 10 iterations and 5 imputations. The highest percentages of missing values were observed for tumor stage (34.5%) and tumor grade (15.4%). The percentages of missing values for all other variables were 3% or lower. We compared the distribution of study characteristics among participants with and without missing information on tumor characteristics and found that although the two groups were largely comparable, there were statistically significant differences by cancer site, treatment, and education (Supplementary Table 1). We used traditional Cox regression to estimate the hazard ratios and two-sided 95% confidence intervals (CIs) for total mortality. For cause-specific mortality, because multiple causes of death are in competition for patients with CRC, we used the competing risk regression model developed by Fine and Grey[23] to estimate subdistribution hazard ratios (SHRs) accounting for the presence of competing risks (eg, for analysis on CRC deaths, any non-CRC deaths would be modeled as a competing outcome). Person-years of follow-up time were calculated as the time between cancer diagnosis and death or the end of follow-up (December 31, 2011), whichever came sooner. We examined all potential confounders (Table 1) in regression models and retained those that had a substantial impact on the results (≥5% change in effect estimates). We considered a series of multivariate regression models: The base model was adjusted for age at diagnosis (continuous) and sex (male, female); a second model further included clinical information about CRC and treatment (cancer site (colon, rectum), tumor stage (localized or regional), tumor grade (well differentiated, moderately differentiated, poorly differentiated, undifferentiated, or distant metastases/systemic disease), surgery (yes or no), chemotherapy (yes or no), and radiation (yes or no); a third model was additionally adjusted for potential confounders education (<12 years, high school, some college, college, and post college), smoking (current, former, or never smoker), TV viewing (≤2, 3–4, 5–6, 7+ hr/d), and physical activity (never or rarely, 1–3 hr/wk, 4+ hr/wk), and we consider the association estimated from this model to be the main results of the study. In a fourth model, we additionally examined the effects of potential mediators, including BMI (continuous), self-reported health (excellent, very good, good, fair, and poor), and history (yes, no) of heart disease, stroke, and diabetes. Finally, in a fifth model, we mutually adjusted for sleep and napping, in addition to all the covariates included in Model 4. All regression analysis was conducted using PROC PHREG in SAS 9.4 (SAS Institute, Cary, North Carolina).

## RESULTS

Study characteristics by categories of sleep duration and napping are presented in Tables 1 and 2, respectively. Sleep duration and napping were associated with multiple demographic, lifestyle factors, and health conditions. However, they were not associated with cancer site, stage, grade, or treatment. Both short (<5 hr) and long (9+ hour) sleep were associated with higher prevalence of extended daytime napping (1+ hour).

During a median of 7.8 years of follow-up, we identified 2336 deaths (295 CVD deaths and 1250 CRC deaths). We found a higher all-cause mortality risk among CRC survivors

**Table 1—**Study characteristics by prediagnosis sleep duration among colorectal cancer patients in the NIH-AARP Diet and Health Study (1995–1996).

| | Sleep duration | | | | *p* value |
|---|---|---|---|---|---|
| | <5 hr (*N* = 150) | 5–6 hr (*N* = 1519) | 7–8 hr (*N* = 2984) | 9+ hr (*N* = 216) | |
| Colorectal cancer diagnosis, % | | | | | .40[a] |
| Colon | 74.0 | 71.8 | 74.1 | 73.1 | |
| Rectum | 26.0 | 28.2 | 25.9 | 26.9 | |
| Tumor summary stage, % | | | | | .65[a] |
| Localized | 31.3 | 27.0 | 27.8 | 28.7 | |
| Regional | 26.7 | 29.2 | 26.3 | 28.2 | |
| Metastatic | 8.0 | 10.5 | 10.7 | 8.8 | |
| Unknown | 34.0 | 33.3 | 35.2 | 34.3 | |
| Tumor grade at diagnosis, % | | | | | .68[a] |
| Well differentiated | 14.0 | 11.1 | 10.8 | 11.1 | |
| Moderately differentiated | 55.3 | 57.9 | 57.9 | 59.3 | |
| Poorly differentiated | 14.7 | 13.8 | 15.7 | 13.9 | |
| Undifferentiated | 0.0 | 0.5 | 0.8 | 0.5 | |
| Unknown | 16.0 | 16.7 | 14.8 | 15.3 | |
| First course of cancer treatment, % | | | | | |
| Chemotherapy | 31.8 | 32.1 | 34.2 | 29.5 | .37[a] |
| Surgery | 72.5 | 80.3 | 79.7 | 81.8 | .22[a] |
| Radiation | 11.1 | 11.8 | 10.9 | 6.5 | .20[a] |
| Age at cancer diagnosis, years, mean (SD) | 67.4 (5.5) | 68.3 (5.6) | 68.6 (5.4) | 68.9 (5.2) | .03[b] |
| Age at sleep assessment, years, mean (SD) | 63.9 (4.5) | 64.4 (4.9) | 64.7 (4.7) | 65.1 (4.4) | .04[b] |
| Women, % | 40.0 | 36.5 | 32.3 | 32.4 | .01[a] |
| College or graduate degree, % | 18.9 | 33.5 | 40.5 | 33.2 | <.0001[a] |
| Non-Hispanic white, % | 89.3 | 92.2 | 95.5 | 97.2 | <.0001[a] |
| Napping, % | | | | | <.0001[a] |
| None | 38.7 | 41.5 | 47.0 | 45.4 | |
| <1 hr/day | 40.0 | 44.0 | 43.4 | 35.7 | |
| 1+ hr/day | 21.3 | 14.5 | 9.6 | 19.0 | |
| Smoking at baseline, % | | | | | .17[a] |
| Current smoker | 15.8 | 12.3 | 10.9 | 10.2 | |
| Former smoker | 51.8 | 55.5 | 57.3 | 63.4 | |
| Never smoke | 32.4 | 32.2 | 31.8 | 26.3 | |
| BMI at baseline, kg/m2, mean (SD) | 29.1 (6.1) | 27.8 (5.2) | 27.1 (4.8) | 27.8 (5.4) | <.0001[b] |
| Watching TV at baseline, 5+ hours/day, % | 30.8 | 25.0 | 23.8 | 25.6 | <.0001[a] |
| Baseline MVPA, >4 hr/week, % | 37.8 | 45.1 | 47.1 | 47.4 | 0.0002[a] |
| Total drinks of alcohol at baseline, mean (SD) | 1.1 (3.9) | 1.1 (3.2) | 1.2 (3.0) | 2.2 (4.6) | <.0001[c] |
| Red meat intake at baseline, g/kcal, mean (SD) | 35.8 (23.1) | 37.2 (23.0) | 36.4 (21.4) | 37.2 (24.0) | .86[c] |
| Self-reported diseases at baseline, % | | | | | |
| Diabetes | 18.0 | 13.5 | 10.3 | 13.9 | .0005[a] |
| Heart disease | 18.7 | 16.0 | 15.9 | 18.5 | .61 |
| Stroke | 2.0 | 2.7 | 2.6 | 3.7 | .75 |
| Self-reported health at baseline, poor or fair, % | 26.7 | 13.8 | 10.9 | 18.5 | <.0001[a] |

[a] *p* value was derived from Chi-square test.
[b] *p* value was derived from one-way ANOVA.
[c] *p* value was derived from Kruskal–Wallis test.
Abbreviation: BMI, bodymass index; hr, hour; MVPA, moderate-to-vigorous physical activity; SD, standard deviation.

**Table 2—**Study characteristics by prediagnosis napping among colorectal cancer patients in the NIH-AARP Diet and Health Study (1995–1996).

| | Napping | | | *p value* |
|---|---|---|---|---|
| | **None (*N* = 2188)** | **<1 hr (*N* = 2101)** | **1+ hr (*N* = 580)** | |
| Colorectal cancer diagnosis, % | | | | *.99*[a] |
| Colon | 73.3 | 73.3 | 73.6 | |
| Rectum | 26.7 | 26.7 | 26.4 | |
| Tumor summary stage, % | | | | *.68*[a] |
| Localized | 27.5 | 27.7 | 28.5 | |
| Regional | 27.4 | 28.1 | 24.3 | |
| Metastatic | 10.9 | 10.0 | 10.5 | |
| Unknown | 34.2 | 34.3 | 36.7 | |
| Tumor grade at diagnosis, % | | | | *.46*[a] |
| Well differentiated | 11.6 | 10.3 | 11.2 | |
| Moderately differentiated | 56.4 | 58.9 | 60.2 | |
| Poorly differentiated | 15.7 | 14.8 | 12.8 | |
| Undifferentiated | 0.6 | 0.9 | 0.5 | |
| Unknown | 15.7 | 15.1 | 15.3 | |
| First course of cancer treatment, % | | | | |
| Chemotherapy | 34.0 | 33.0 | 31.5 | *.56*[a] |
| Surgery | 81.0 | 78.8 | 78.9 | *.18*[a] |
| Radiation | 10.8 | 10.7 | 12.6 | *.50*[a] |
| Age at cancer diagnosis, years, mean (SD) | 68.0 (5.6) | 69.0 (5.4) | 68.8 (5.3) | *<.0001*[b] |
| Age at sleep assessment, years, mean (SD) | 63.8 (4.9) | 65.2 (4.5) | 65.3 (4.5) | *<.0001*[b] |
| Women, % | 40.5 | 29.3 | 25.0 | *<.0001*[a] |
| College or graduate degree, % | 38.0 | 38.7 | 30.4 | *<.0001*[a] |
| Non-Hispanic white, % | 95.2 | 94.6 | 90.2 | *<.0001*[a] |
| Sleep duration at baseline, % | | | | *<.0001*[a] |
| <5 hr | 2.7 | 2.9 | 5.5 | |
| 5–6 hr | 28.8 | 31.8 | 37.9 | |
| 7–8 hr | 64.1 | 61.6 | 49.5 | |
| 9+ hr | 4.5 | 3.7 | 7.1 | |
| Smoking at baseline, % | | | | *<.0001*[a] |
| Current smoker | 11.2 | 10.5 | 15.4 | |
| Former smoker | 54.5 | 58.6 | 59.5 | |
| Never smoke | 34.2 | 30.9 | 25.1 | |
| BMI at baseline, kg/m2, mean (SD) | 26.9 (4.7) | 27.7 (5.1) | 28.7 (5.7) | *<.0001*[b] |
| Watching TV at baseline, 5+ hours/day, % | 19.1 | 26.8 | 36.1 | *<.0001*[a] |
| Baseline MVPA, >4 hr/week, % | 46.0 | 48.1 | 40.0 | *<.0001*[a] |
| Total drinks of alcohol at baseline, mean (SD) | 1.3 (3.2) | 1.2 (3.2) | 1.1 (3.2) | *<.0001*[c] |
| Red meat intake at baseline, g/kcal, mean (SD) | 36.1 (22.1) | 36.7 (21.9) | 39.0 (22.8) | *.01*[c] |

who reported the shortest sleep duration ($HR_{<5\ hr\ vs\ 7–8\ hour}$ (95% CI), 1.36 (1.08–1.72); Table 3), and the association remained after adjusting for potential confounders. Compared to those reporting 7–8 hr of sleep, people reporting less than 5 hr of sleep also had 54% increase in CRC mortality (SHR (95% CI), 1.54 (1.11–2.14)), accounting for competing risk of dying from non-CRC causes. Although there was a suggestion of an increase in CVD mortality (SHR (95% CI), 1.41, (0.80–2.48)

**Table 2**—*Continued*

| | | | | |
|---|---|---|---|---|
| Self-reported diseases at baseline, % | | | | |
| Diabetes | 7.8 | 13.6 | 19.1 | .0007[a] |
| Heart disease | 12.1 | 17.7 | 25.5 | <.0001[a] |
| Stroke | 2.0 | 2.8 | 4.7 | .002 |
| Self-reported health at baseline, poor or fair, % | 8.1 | 14.1 | 24.0 | <.0001[a] |

[a]*p* value was derived from Chi-square test.
[b]*p* value was derived from one way ANOVA.
[c]*p* value was derived from Kruskal–Wallis test.
Abbreviation: BMI, body-mass index; hr, hour; MVPA, moderate-to-vigorous physical activity; SD, standard deviation; ANOVA, analysis of variance.

among the shortest sleep category, the association was not statistically significant, perhaps due to few CVD deaths. Adjusting for potential mediators (BMI and health status) attenuated the association for total mortality but had little impact on CRC mortality (Table 3, Model 4). Controlling for napping did not change the results substantially. When we stratified by lag time (time between the completion of risk factor questionnaire and cancer diagnosis, median, 4.5 years), we found that the association between short sleep duration (<5 hr) and CRC deaths appeared stronger among those with a lag time≥4.5 years (Supplementary Table 2).

Napping was associated with higher total mortality risk (Table 4). Compared to no napping, moderate napping (<1 hr/day) and extended napping (1+ hr/day) were associated with 10% and 35% higher mortality risks (1.10 (1.00–1.21) for <1 hr/day and 1.35 (1.18, 1.54) for 1+ hr/day), respectively. The association was reduced but remained statistically significant after adjusting for BMI and health status. The association between extended napping and mortality was particularly strong for cardiovascular deaths ($SHR_{1+\text{ hr vs none}}$ (95% CI),1.62 (1.18–2.24)). Adjusting for sleep duration had little impact on the association with napping. In the lag time analysis, the association between 1+ hr napping and higher risk of all-cause mortality appeared to be stronger among participants with less than 4.5 years between reporting sleep patterns and cancer diagnosis; however, the association with cardiovascular death was stronger among those who developed CRC 4.5 years or more after reporting sleep patterns (Supplementary Table 3).

## DISCUSSION

In this group of individuals with CRC, we found that both very short sleep and extended napping were associated with higher total mortality. We also found evidence suggesting an association between short sleep and higher CRC-specific mortality. The association between extended napping and mortality appeared to be driven largely by CVD deaths.

The result suggesting higher CRC mortality among short sleepers is intriguing and consistent with our hypothesis that prediagnosis sleep deficiency may have an adverse effect on CRC prognosis. Several lines of evidence suggest such a link is plausible. In population studies, research has also repeatedly linked insufficient sleep and sleep disorders to obesity,[11] insulin resistance,[12,13] and chronic inflammation,[24,25] all of which have been associated with more rapid cancer progression among CRC patients.[2,7,8,26]

Although ours is the first study that examined the role of habitual sleep before diagnosis in CRC-specific mortality among CRC survivors, several previous studies examined the relationship between sleep duration and CRC incidence and they reported mixed findings. For example, a study in the Women's Health Initiative reported a 32% increase in risk of developing CRC among those who reported ≤5 hr of sleep,[15] suggesting a role of short sleep in colorectal carcinogenesis. However, this finding was not replicated in the male participants in the Health Professionals Follow-up Study.[16] More importantly, a recent study that included the entire cohort of the NIH-AARP study did not find an association between short sleep duration and CRC risk.[27] The different findings for CRC risk and mortality in the same study could be potentially explained by several factors: First, it has been reported that there are several subtypes of CRC with different etiology, prognosis, and response to treatments.[28,29] For example, it has been noted that inflammation-associated CRC has a distinct molecular feature and poor outcomes.[30] It is possible that the association between sleep and CRC varies by subtype, and if sleep deficiency has a particularly strong link with those subtypes with poor prognosis, such as the inflammation subtype, then it would be reasonable to expect that sleep duration may have a smaller impact on overall CRC risk but a larger effect on CRC mortality. Moreover, a limitation of some of the earlier studies on sleep duration and CRC risk, including the in the NIH-AARP study, was that they failed to control for CRC screening. It is well established that CRC screening has a large impact on CRC incidence. On the other hand, it is possible that cancer screening behavior is also associated with sleep duration—for example, people with short sleep tend to exhibit an overall pattern of poor health lifestyle and may be also less likely to receive health services such as cancer screening. As a result, the lack of relationship between sleep duration and CRC risk could be due to the confounding effect of CRC screening. Taken together, we believe more research is needed to understand the relationship between sleep and CRC. Studies that examine the effect of sleep deficiency on subtypes of CRC and evaluate the interaction between sleep and other health behaviors could be particularly beneficial for the field.

Earlier studies on sleep duration and mortality in the general population showed an association between short sleep and higher CVD mortality. Although the number of CVD deaths among very

**Table 3—**Associations between prediagnosis sleep duration and mortality among colorectal cancer patients in the NIH-AARP Diet and Health Study.

| | Sleep duration | | | |
|---|---|---|---|---|
| | **<5 hr** | **5–6 hr** | **7–8 hr** | **9+ hr** |
| All-cause death | | | | |
| No. death | 84 | 710 | 1441 | 101 |
| HR (95% CI) | | | | |
| Model 1 | 1.28 (1.03–1.60) | 0.98 (0.90–1.08) | ref | 0.99 (0.81–1.21) |
| Model 2 | 1.49 (1.18–1.89) | 0.98 (0.89–1.08) | ref | 1.10 (0.89–1.37) |
| Model 3 | 1.36 (1.08–1.72) | 0.96 (0.87–1.05) | ref | 1.08 (0.86–1.34) |
| Model 4 | 1.25 (0.98–1.58) | 0.94 (0.85–1.03) | ref | 1.04 (0.83–1.30) |
| Model 5 | 1.22 (0.96–1.56) | 0.93 (0.84–1.02) | ref | 1.02 (0.81–1.28) |
| Colorectal cancer death | | | | |
| No. death | 45 | 368 | 782 | 55 |
| SHR (95% CI) | | | | |
| Model 1 | 1.21 (0.89–1.64) | 0.93 (0.82–1.05) | ref | 0.98 (0.74–1.29) |
| Model 2 | 1.61 (1.15–2.25) | 0.95 (0.82–1.08) | ref | 1.08 (0.79–1.49) |
| Model 3 | 1.54 (1.11–2.14) | 0.93 (0.81–1.07) | ref | 1.07 (0.78–1.47) |
| Model 4 | 1.52 (1.10–2.11) | 0.93 (0.81–1.06) | ref | 1.08 (0.79–1.47) |
| Model 5 | 1.53 (1.10–2.12) | 0.93 (0.81–1.07) | ref | 1.08 (0.79–1.48) |
| Cardiovascular disease death | | | | |
| No. death | 13 | 95 | 179 | 8 |
| SHR (95% CI) | | | | |
| Model 1 | 1.60 (0.91–2.80) | 1.10 (0.85–1.41) | ref | 0.60 (0.29–1.22) |
| Model 2 | 1.56 (0.89–2.74) | 1.07 (0.83–1.37) | ref | 0.58 (0.28–1.18) |
| Model 3 | 1.41 (0.80–2.48) | 1.02 (0.79–1.31) | ref | 0.52 (0.26–1.07) |
| Model 4 | 1.23 (0.69–2.21) | 0.98 (0.76–1.27) | ref | 0.47 (0.23–0.96) |
| Model 5 | 1.19 (0.66–2.14) | 0.99 (0.76–1.28) | ref | 0.46 (0.23–0.95) |

Model 1: Adjusted for age at diagnosis (continuous) and sex (male, female).
Model 2: Adjusted for covariates in Model 1 and cancer site (colon, rectum), tumor stage (localized, regional), tumor grade (well differentiated, moderately differentiated, poorly differentiated, undifferentiated), surgery (yes, no), chemotherapy (yes, no), and radiation (yes, no).
Model 3: Adjusted for covariates in Model 2 and education (<12 years, high school, some college, college and post college), smoking (current, former, never smoker), TV viewing (≤2, 3–4, 5–6, 7+ hr/d), and MVPA (never or rarely, 1–3 hr/wk, 4+ hr/wk).
Model 4: Adjusted for covariates in Model 3, BMI (continuous), self-reported health (excellent, very good, good, fair, poor), and history (yes, no) of heart disease, stroke and diabetes.
Model 5: Adjusted for covariates in Model 4 and napping (none, <1 hr/d, 1+ hr/d).
Abbreviations: BMI, bodymass index; CI, confidence interval; HR, hazard ratio; hr, hour; MVPA, moderate-to-vigorous physical activity; SHR, subdistribution hazard ratio.

short sleepers were small in our population, we observed a suggestive trend of increase in CVD risk among those who reported <5 hr of sleep. Larger studies are needed to clarify the relationship between short sleep and CVD mortality among CRC patients.

We observed no association between ≥9 hr sleep and mortality in our study. The lack of association between long sleep duration and total and CVD mortality is in contrast to previous findings. Two meta-analyses reported that long sleep duration was associated with 30% increase in total mortality and 41% increase in developing or dying from CVD,[17,18] while our previous investigation also showed an 11% increase in total mortality in the NIH-AARP Health and Diet Study.[31] Although the exact mechanism linking long sleep with higher mortality in the general population is still unclear, it has been postulated that this association may be at least partially explained by the fact that long sleep is a marker of fatigue due to underlying diseases, failing health, and sleep disturbances, all of which may contribute to higher mortality.[32] However, it is unclear whether long sleep among cancer patients can serve as a similar marker for these conditions. In addition, physiological or pathological changes in the bodily environment associated with CRC progression and treatment might

**Table 4**—Associations between prediagnosis napping and mortality among colorectal cancer patients in the NIH-AARP Diet and Health Study.

| | Napping | | |
|---|---|---|---|
| | None | <1 hr | 1+ hr |
| All-cause death | | | |
| No. death | 940 | 1044 | 352 |
| HR (95% CI) | | | |
| Model 1 | ref | 1.11 (1.01–1.21) | 1.44 (1.27–1.63) |
| Model 2 | ref | 1.13 (1.02–1.24) | 1.49 (1.31–1.69) |
| Model 3 | ref | 1.10 (1.00–1.21) | 1.35 (1.18–1.54) |
| Model 4 | ref | 1.05 (0.95–1.16) | 1.21 (1.05–1.39) |
| Model 5 | ref | 1.05 (0.96–1.16) | 1.21 (1.06–1.40) |
| Colorectal cancer death | | | |
| No. death | 561 | 543 | 146 |
| SHR (95% CI) | | | |
| Model 1 | ref | 0.98 (0.87–1.11) | 0.96 (0.80–1.15) |
| Model 2 | ref | 1.00 (0.87–1.14) | 0.98 (0.80–1.19) |
| Model 3 | ref | 1.00 (0.88–1.14) | 0.96 (0.78–1.18) |
| Model 4 | ref | 1.00 (0.87–1.14) | 0.95 (0.78–1.17) |
| Model 5 | ref | 1.00 (0.87–1.15) | 0.96 (0.78–1.18) |
| Cardiovascular disease death | | | |
| No. death | 109 | 122 | 64 |
| SHR (95% CI) | | | |
| Model 1 | ref | 1.03 (0.79–1.33) | 1.94 (1.42–2.66) |
| Model 2 | ref | 1.00 (0.77–1.31) | 1.98 (1.44–2.71) |
| Model 3 | ref | 0.95 (0.73–1.24) | 1.62 (1.18–2.24) |
| Model 4 | ref | 0.85 (0.65–1.12) | 1.28 (0.92–1.79) |
| Model 5 | ref | 0.84 (0.64–1.11) | 1.78 (0.91–1.78) |

Model 1: Adjusted for age at diagnosis (continuous) and sex (male, female).
Model 2: Adjusted for covariates in Model 1 and cancer site (colon, rectum), tumor stage (localized, regional), tumor grade (well differentiated, moderately differentiated, poorly differentiated, undifferentiated), surgery (yes, no), chemotherapy (yes, no), and radiation (yes, no).
Model 3: Adjusted for covariates in Model 2 and education (<12 years, high school, some college, college and post college), smoking (current, former, never smoker), TV viewing (≤2, 3–4, 5–6, 7+ hr/d), and MVPA (never or rarely, 1–3 hr/wk, 4+ hr/wk).
Model 4: Adjusted for covariates in Model 3, BMI (continuous), self-reported health (excellent, very good, good, fair, poor), and history (yes, no) of heart disease, stroke and diabetes.
Model 5: adjusted for covariates in Model 4 and napping (none, <1 hr/d, 1+ hr/d)
Abbreviations: BMI, bodymass index; CI, confidence interval; HR, hazard ratio; hr, hour; MVPA, moderate-to-vigorous physical activity; SHR, subdistribution hazard ratio.

also alter the sleep–mortality relationship. Future studies are needed to understand the health implication of long sleep among cancer survivors.

We found a strong link between napping and total and CVD mortality, and the association was most pronounced among individuals reporting napping for more than 1 hr per day. Both the association and the dose–response effect have been reported before. Several recent meta-analyses consistently showed higher all-cause mortality and higher risk of CVD among people with a nap duration of more than 1 hr.[33–35] Like long sleep, napping has also been recognized as a marker for health problems, including fatigue, depression, and poor nighttime sleep quality, particularly in countries where napping is not part of the cultural norm.[36] Therefore, the higher mortality associated with extended napping among cancer patients may be due to underlying health conditions that cause both daytime sleepiness and later death. Interestingly, adjusting for nighttime sleep had little impact on the effects of napping, suggesting that the association could not be explained by insufficient sleep at night alone.

A strength of our study is that we assessed sleep duration before cancer diagnosis and with a relatively long lag time (median 4.3 years), making reverse causation less likely. Also, we collected information on a large number of covariates, which allowed us to examine their roles as potential confounders in our analysis. Our study also has several limitations. First, only a small portion of the participants reported <5 hr (3%) and ≥9 hr sleep (5%); therefore, our analysis may be underpowered to detect statistically significant associations, particularly for CVD mortality. Second, sleep duration and napping were self-reported and are subject to error and misclassification. Previous studies have shown that self-reported and measured sleep duration are only moderately correlated,[37] which may result in misclassification of exposure. Particularly, people with short sleep are more likely to overreport their sleep duration than are people with longer sleep, which may lead to differential bias in observed associations. Third, because the sleep categories provided in the questionnaire were broad, we were not able to evaluate the effect of more refined sleep categories or for more extreme sleep durations. Fourth, sleep duration and napping habits may change following diagnosis. Unfortunately, we did not have adequate information on postdiagnosis sleep and napping and therefore were not able to examine postdiagnosis sleep and napping in relation to mortality. Fifth, a substantial portion of participants had missing information for tumor stage, grade, and treatment, and we had to impute the missing values. Sixth, the stratified analysis by lag time showed possible interaction with lag time, suggesting that the results may be influenced by differences in timing of data collection. Finally, we did not have information on sleep quality, sleep disorders such as insomnia, sleep apnea, and simple snoring, and history of shift work, all of which are important aspects of sleep and circadian rhythms and may influence CRC survival.

In conclusion, we found prediagnosis short sleep and extended napping were associated with higher mortality in CRC survivors. More studies on lifestyle factors such as sleep and napping in relation to cancer prognosis are needed particularly in the postdiagnosis period, as they might help clinicians to better understand the factors that affect health outcomes of cancer patients. Moreover, sleep disturbances are prevalent among cancer survivors,[38] and effective interventions have been developed to address these challenges faced by patients.[39] It would be important for future studies to examine whether these interventions could not only improve

sleep outcomes but also affect cancer prognosis and overall survival.

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## SUPPLEMENTARY MATERIAL

Supplementary data are available at *SLEEPJ* online.

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## DISCLOSURE STATEMENT

None declared.