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Self-reported sleep characteristics and risk for incident vertebral and hip fracture in women

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ABSTRACT

Objective: To examine the relationships between self-reported sleep characteristics and risk of incident vertebral fracture and hip fracture in women.
Design: Longitudinal cohort study.
Setting: Nurses' Health Studies (NHS: 2002-2014, NHSII: 2001-2015).
Participants: Total 122,254 female registered nurses (46,129 NHS, 76,125 NHSII) without prior history of fracture.
Exposure: Sleep was characterized by 4 sleep-related domains—sleep duration, sleep difficulty, snoring, and excessive daytime sleepiness—assessed by self-reported questionnaires.
Outcomes: Self-reports of vertebral fracture were confirmed by medical record review and hip fracture was assessed by biennial questionnaires.
Results: Over 12-14 years of follow-up, 569 incident vertebral fracture cases (408 in NHS, 161 in NHSII) and 1,881 hip fracture cases (1,490 in NHS, 391 in NHSII) were documented. In the pooled analysis, the multivariable-adjusted HR (95% CI) for vertebral fracture was 1.20 (0.86, 1.66) for sleep duration ≤5 hours vs. 7 hours and 0.82 (0.60, 1.12) for ≥9 vs. 7 hours; 1.63 (0.93, 2.87) for sleep difficulties all-the-time vs. none/little-of-the-time (p-trend = 0.005); 1.47 (1.05, 2.05) for snoring every night/week vs. never/occasionally (p-trend = 0.03), and 2.20 (1.49, 3.25) for excessive daytime sleepiness daily vs. never (p-trend < 0.001). In contrast, associations were not observed with hip fracture risk.
Conclusion: Poorer sleep characteristics were associated with risk of vertebral fracture. Our study highlights the importance of multiple dimensions of sleep in the development of vertebral fractures. Further research is warranted to understand the role of sleep in bone health that may differ by fracture site, as well as sleep interventions that may reduce the risk of fracture.

Introduction

Emerging research suggests that alterations in sleep and circadian rhythmicity can have detrimental effects on bone metabolism and health.[1] Almost one-third of American adults report sleeping less than 7 hours per night.[2] Insufficient sleep can undermine bone remodeling activity, which increases overnight and is critical for repairing microdamage from daily wear and tear.[3] Poor sleep quality, as reflected by long sleep latency and sleep fragmentation, may dampen the restorative functions of sleep and lead to abnormal bone metabolism. Intermittent nocturnal hypoxemia, which is characteristic of sleep apnea, has also been associated with abnormal bone metabolism and increased fracture risk.[4]

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Further, circadian rhythmicity plays an important role in bone metabolism and homeostasis.[1,5-7] Circadian disruption resulting from sleep disturbances can inhibit osteoblast function and bone formation while promoting bone resorption and breakdown, thus impairing the bone's ability to repair the microdamage[8] that accumulates with aging[9] and potentially contributing to higher fracture risk. Given the rise in vertebral fracture (VF) incidence[10] and halt in the decline in hip fracture (HF) rates leading to higher than expected levels in recent years,[11] as well as the significant morbidity, mortality,[12] and high costs[13] associated with fractures, identifying modifiable risk factors, such as sleep, is crucial for fracture prevention.

There has been growing interest in measuring multiple complementary sleep dimensions.[14] While several prior studies reported no statistically significant to modestly significant associations between sleep and hip fracture risk in women,[15-18] few longitudinal studies have simultaneously examined multiple sleep dimensions and fracture risk.[4,15-18] We investigated the association between 4 key sleep characteristics—sleep duration, sleep difficulty, snoring, and excessive daytime sleepiness (EDS)—and incident VF and HF risk in Nurses' Health Studies (NHS and NHSII) participants. We hypothesized that poorer sleep characteristics are prospectively associated with increased fracture risk.

Methods

Study population

NHS and NHSII are 2 ongoing, large-scale prospective cohort studies. NHS enrolled 121,700 female nurses aged 30-55 years in 1976. NHSII enrolled 116,429 female nurses aged 25-42 years in 1989. Since then, biennial questionnaires have been mailed to participants with comprehensive questions on newly diagnosed diseases, medications, and lifestyle practices with >90% follow-up of the eligible person-time. The vast majority (97%) of the participants are white. This current analysis included women with information on both fracture history and self-reported sleep who did not have prior history of fracture at baseline (NHS: 2002; NHSII: 2001). The study was approved by the Institutional Review Board at Brigham and Women's Hospital (Boston, MA). Return of a completed questionnaire was accepted as implied informed consent by the Institutional Review Board.

Assessment of self-reported sleep characteristics

Assessment of self-reported sleep characteristics—sleep duration, sleep difficulty, snoring and EDS—was described previously.[19-21] For sleep duration, NHS participants were asked about total hours of actual sleep (≤5, 6, 7, 8, 9, 10, and ≥ 11 hours) in a 24-hour period on the 2000, 2002, 2008, and 2012 questionnaires. NHSII participants were asked about average sleep duration in a 24-hour period (<5, 5, 6, 7, 8, 9, and 10+ hours) on the 2001, 2009, and 2013 questionnaires. Response categories were harmonized between the 2 cohorts as ≤5, 6, 7, 8 and ≥9 hours. Sleep duration assessed by a single question was found to correlate highly with sleep duration in daily sleep diaries over a one-week period in the NHS cohort (r=0.79), with high reproducibility over 2 years (Cohen's κ statistic = 0.81).[22] Sleep difficulty was assessed in 2000: "How much of the time during the past 4 weeks have you had difficulty falling asleep or staying asleep?" Possible responses were "all of the time," "most of the time," "a good bit of the time," "some of the time," "a little of the time," and "none of the time." For snoring, participants were asked on the 2002, 2008 and 2012 questionnaires whether they snore "every night," "most nights," "a few nights a week," "occasionally," or "almost never." Participants were queried about EDS in 2008: "On average, how often are your daily activities affected because you are sleepy during the day?" Possible responses included "almost every day," "4-6 days/week," "1-3 days/week," "rarely," and "never." Sleep difficulty, snoring and EDS were assessed by similar questions in NHSII on the 2001 and 2013 questionnaires.

Ascertainment of clinical vertebral fracture

Ascertainment of clinical VF was described previously.[23] In brief, participants were asked about lifetime history of a clinician-diagnosed "vertebral (spine) fracture, x-ray confirmed" and the year of first diagnosis in 2012 (NHS) and 2013 (NHSII). Participants were again asked about a VF diagnosis in 2014 (NHS) and 2015 (NHSII). A supplemental questionnaire was mailed to participants who reported a VF in 2001 or afterwards. Permission was requested to obtain participants' medical records related to the VF. Among the participants who gave consent and for whom sufficient information was available to make a diagnosis, we confirmed VF cases by radiology or medical report. Our primary analysis included VFs associated with low or moderate level trauma (eg, slipping, tripping). Only confirmed cases of VF were included in the analysis.

Ascertainment of hip fracture

Participants were asked to report all previous HFs (date, bone site, and circumstances leading to the fracture) on the 1982 questionnaire in NHS and incident HFs were reported biennially. In NHSII, participants were asked about HF on the 2005, 2009, 2013 and subsequent biennial questionnaires. Supplemental questionnaires were mailed to nurses who reported an incident HF. Because of their frequent association with falls, only fractures of the proximal femur were included in the definition of a HF. We relied on self-reported HF in these cohorts since in a prior validation study, self-reported HFs were found to be highly reliable.[24] Similar to the VF analysis, only HFs that were due to low- or moderate-trauma were considered in the main analysis.

Assessment of covariates

Date of birth, height and race/ethnicity were self-reported. Weight has been queried on every biennial questionnaire in NHS and NHSII. Among a subset of participants who directly measured their weight, self-reported weight was highly reliable (r = 0.97).[25] BMI (kg/m^2) was calculated from the information provided by participants on weight and height. Waist circumference was queried among NHS participants in 1986, 1996, and 2000 and NHSII participants in 1993 and 2005. Among a subset of NHS participants, self-reported waist circumference using a tape measure was highly reliable when compared with technician-measured waist circumferences (r = 0.88).[25] For participants who did not provide waist circumference information on a questionnaire, we carried forward information from a prior questionnaire if available.

Information on postmenopausal hormone therapy (HT; type and duration) and diuretics (thiazide or loop diuretics) was queried on biennial questionnaires. Clinical history of hypertension,[24] diabetes,[26] osteoporosis,[27] and obstructive sleep apnea (OSA)[21] was validated previously in the cohort. Clinical depression was defined by either anti-depressant use or physician-diagnosed depression.[28]

Extensively validated[29] semiquantitative food-frequency questionnaires were used to assess dietary intake, which were completed every 4 years since 1986 in NHS and 1991 in NHSII. The dietary factors considered in our models included dietary and supplemental intake of calcium and vitamin D, alcohol intake, caffeine intake and protein intake. Self-reported physical activity was validated previously against physical activity diaries (r = 0.79) in NHSII, and was assessed by metabolic equivalent task hours per week (MET-hours/week).[30]

Statistical analyses

For the analysis of VF, person-time of follow-up for each participant was counted from the date on which the baseline questionnaire was returned (2002 for NHS, 2001 for NHSII) to (1) the date of VF diagnosis, (2) death, or (3) end of follow-up (May 31, 2014 for NHS, May 31, 2015 for NHSII), whichever occurred first. Participants were censored if they reported a HF during the follow-up period. For the analysis of HF, person-time of follow-up for each participant was counted from the date on which the baseline questionnaire was returned (2002 for NHS, 2001 for NHSII) to (1) the date of HF diagnosis, (2) death, or (3) end of follow-up (May 31, 2014 for NHS, May 31, 2015 for NHSII), whichever occurred first. Participants were censored if they reported a VF during the follow-up period.

Multivariable Cox proportional-hazards models were used to estimate the hazard ratios (HR) and 95% CI for fracture risk according to categories of sleep characteristics as described above. The primary multivariable model was stratified by calendar time and age, and adjusted for race/ethnicity, BMI, waist circumference, physical activity, smoking status, menopausal status and postmenopausal hormone use, use of thiazide diuretics, furosemide and bisphosphonates, clinical diagnosis of hypertension, diabetes, OSA and depression, recent physical exam, and multiple dietary factors. Except for race/ethnicity, all covariates were modeled as time-varying in the analysis. We conducted the analyses first in each cohort separately, and then combined the data for pooled analyses with test of potential between-cohort heterogeneity using the random-effects meta-analysis approach. While we treated OSA as a confounder, we also evaluated models in which OSA was not included as a variable. We considered 2 additional multivariable models as sensitivity analyses. While we considered osteoporosis and falls to be mediators and thus did not include these variables in the models of our primary analyses, in sensitivity analysis, we further adjusted for them in a separate model to assess their potential impact on the associations. The second model further mutually adjusted for the 4 sleep characteristics in the same model.

Based on the dose-response relationships observed in the primary analysis, we collapsed exposure groups into broader categories to provide a simpler summary of the associations that could be used in subgroup analyses. The categories included ≤6, 7-8 and ≥9 hours for sleep duration, most/all of the time versus none/some of the time for sleep difficulty, most/every night versus a few nights/never for snoring, ≥4 days/week versus ≤3 days/week for EDS. Using these broader sleep characteristic categories, we examined the associations with VF or HF risk overall and by 3 prespecified factors, history of osteoporosis (yes, no), BMI (<30 kg/m^2, ≥30 kg/m^2), and history of rotating shiftwork (ever/never). Likelihood ratio tests comparing the model with versus without the cross-product interaction terms were used to assess the statistical significance of the subgroup heterogeneity.

Finally, given the cumulative evidence supporting insomnia with short sleep duration as a biologically severe sleep phenotype,[31] we examined the joint associations of sleep difficulty and sleep duration with fracture risk based on 4 mutually exclusive categories (no sleep difficulty and >6 hours of sleep [reference], no sleep difficulty and ≤6 hours, sleep difficulty and >6 hours, and sleep difficulty and ≤6 hours). Similarly, we evaluated the joint associations of 2 hallmark symptoms related to OSA, snoring and EDS, with VF and HF risk. All P values are 2-tailed. The analysis was performed using SAS 9.4 (SAS Institute, Cary, NC).

Results

Among 46,129 NHS and 76,125 NHSII participants, the mean baseline age was 66 years and 46 years, respectively. Women who had shorter sleep duration were more likely to be non-white, a current smoker, and a never or past user of postmenopausal hormone therapy (Table 1). Women in NHS had a higher prevalence of osteoporosis at baseline compared to NHSII participants.

Self-reported sleep characteristics and risk of vertebral fracture

During 12-14 years of follow-up, there were 569 incident cases of VF (408 in NHS and 161 in NHSII). We observed similar associations between NHS and NHSII (p-heterogeneity >0.12). After multivariable adjustment in the pooled analysis, there was a moderate inverse association between sleep duration and VF risk (p-trend = 0.03; Table 2). Compared with 7 hours of sleep, the HR (95%CI) was 0.96 (0.77, 1.21) for 6 hours, 1.20 (0.86, 1.66) for ≤5 hours, 0.84 (0.68,

Table 1
Baseline characteristics by self-reported sleep duration in the Nurses' Health Study (2002) and Nurses' Health Study II (2001)[1].

	NHS			NHSII		
	≤5 hours	7 hours	9+ hours	≤5 hours	7 hours	9+ hours
	2,463	17,954	3,408	4,251	32,197	3,977
Age, years[2]	66.8 (6.9)	65.8 (6.5)	67.2 (6.5)	46.9 (4.6)	46.3 (4.7)	46 (4.7)
Non-white race, %	11	5	4	12	4	5
Body mass index, kg/m^2	27.4 (5.9)	26.6 (5)	27.5 (5.5)	28.3 (7.1)	26.4 (6.0)	27.4 (6.8)
Waist circumference, cm	86.7 (14.3)	86.0 (12.9)	89.3 (13.5)	79.6 (14.5)	77.6 (12.2)	79.4 (13.2)
Physical activity (MET-hours/week)	18.4 (23.4)	19.1 (22.4)	16.3 (25.9)	22.2 (35.1)	20.6 (24.8)	18.3 (25.3)
Current smoker, %	8	7	7	13	7	7
Clinical diagnoses						
Diabetes, %	10	7	10	10	6	8
Hypertension, %	53	49	56	23	16	20
Osteoporosis, %	24	23	24	6	6	6
Depression, %	3	4	12	6	6	17
Recent physical exams, %	93	95	95	86	86	88
Dietary calcium (mg/day)	831.3 (323.3)	861.0 (319.7)	850.1 (325.6)	860.2 (354.5)	892.5 (319.3)	878.5 (329.3)
Calcium supplement (mg/day)	589.1 (530.2)	640.7 (519.5)	588.1 (527.4)	332.4 (448.2)	350.7 (437.2)	340.4 (438.6)
Alcohol intake (g/day)	4.9 (9.5)	6.2 (10.2)	7.2 (13.0)	3.3 (7.3)	4.0 (6.9)	4.4 (8.5)
Caffeine intake (mg/day)	136.4 (146.3)	140.9 (135.8)	132.7 (128.7)	241.9 (238.5)	224.2 (203.0)	213.6 (203.5)
Bisphosphonate use, %	12	13	11	7	8	8
Thiazide use, %	13	15	17	7	5	5
Lasix use, %	4	2	4	2	1	1

NHS, Nurses' Health Study; NHSII, Nurses' Health Study II; MET, metabolic equivalent of task.
[1] Baseline characteristics of participants who reported 6 hours and 8 hours of sleep are not shown in the table.
[2] Value is not age-adjusted.

Table 2
Risk of vertebral fracture associated with self-reported sleep characteristics in the Nurses' Health Study and Nurses' Health Study II.

	NHS			NHSII			Pooled
	Cases	P-Y	HR (95% CI)[1]	Cases	P-Y	HR (95% CI)[1]	HR (95% CI)[2]
Sleep duration							
5 hours or less	28	31,143	1.02 (0.67, 1.54)	17	55,485	1.57(0.91, 2.70)	1.20 (0.86, 1.66)
6 hours	83	101,676	1.10 (0.84, 1.45)	29	231,846	0.71 (0.46, 1.09)	0.96 (0.77, 1.21)
7 hours	144	201,254	Reference	73	410,688	Reference	Reference
8 hours	107	158,078	0.92 (0.71, 1.18)	37	277,475	0.71 (0.47, 1.05)	0.84 (0.68, 1.04)
9 hours or more	46	50,465	0.91 (0.64, 1.28)	5	49,423	0.47 (0.19, 1.18)	0.82 (0.60, 1.12)
Sleep difficulty							
None or a little	261	365,910	Reference	96	704,567	Reference	Reference
Some of the time	77	113,877	0.91 (0.70, 1.17)	37	180,442	1.37 (0.93, 2.01)	1.02 (0.82, 1.26)
Most of the time	62	56,420	1.53 (1.15, 2.03)	23	124,339	1.19 (0.75, 1.90)	1.41 (1.11, 1.80)
All the time	8	6,409	1.56 (0.76, 3.22)	5	15,569	1.74 (0.69, 4.37)	1.63 (0.93, 2.87)
p-trend			0.02			0.09	0.005
Snoring							
Never or occasionally	213	314,235	Reference	93	669,900	Reference	Reference
A few nights per week	15	33,720	0.73 (0.43, 1.24)	9	56,336	0.95 (0.47, 1.94)	0.81 (0.53, 1.23)
Most nights	37	53,915	1.14 (0.80, 1.64)	22	95,589	1.50 (0.92, 2.45)	1.25 (0.93, 1.66)
Every night	25	28,820	1.35 (0.88, 2.09)	19	73,590	1.54 (0.90, 2.63)	1.47 (1.05, 2.05)
Don't know	118	111,925	1.12 (0.89, 1.42)	18	129,502	0.89 (0.53, 1.48)	1.08 (0.88, 1.33)
p-trend[3]			0.24			0.05	0.03
Excessive daytime sleepiness							
Never	113	167,900	Reference	11	109,626	Reference	Reference
Rarely	236	308,392	1.07 (0.85, 1.35)	86	569,869	1.51 (0.80, 2.84)	1.09 (0.88, 1.34)
1-3 days/week	32	47,121	0.94 (0.63, 1.40)	27	224,748	1.16 (0.57, 2.37)	0.92 (0.67, 1.28)
4-6 days/week	13	7,925	2.26 (1.24, 4.09)	14	68,684	1.95 (0.87, 4.36)	1.78 (1.15, 2.76)
Daily	14	11,277	1.52 (0.85, 2.72)	23	51,990	4.06 (1.93, 8.53)	2.20 (1.49, 3.25)
p-trend			0.02			0.07	<.001

NHS, Nurses' Health Study; NHSII, Nurses' Health Study II; P-Y, Person-years; HR, Hazard ratio; CI, Confidence interval.
[1] Stratified by age and calendar time, and adjusted for race/ethnicity, BMI, waist circumference, physical activity, smoking status, menopausal status and postmenopausal hormone use, use of thiazide diuretics, furosemide (Lasix) and bisphosphonates, clinical diagnosis of hypertension, diabetes, obstructive sleep apnea and depression, recent physical exam, and dietary factors (all in quintiles, including alcohol intake, caffeine intake, protein intake, dietary and supplementary calcium intake, and dietary and supplementary vitamin D intake).
[2] Additionally stratified by cohort in the pooled analysis.
[3] The 'don't know' category was excluded when calculating the p-trend.

1.04) for 8 hours and 0.82 (0.60, 1.12) for ≥9 hours. Sleep difficulty, snoring and EDS were all associated with increased risk of VF. The multivariable-adjusted HR (95%CI) was 1.63 (0.93, 2.87) comparing women who reported sleep difficulty all the time versus none/a little (p-trend = 0.005), 1.47 (1.05, 2.05) comparing women who reported snoring every night versus never/occasionally, and 2.20 (1.49, 3.25) comparing women who reported daily EDS versus never (p-trend < 0.001). These associations were essentially unchanged when we removed OSA from the models (data not shown). These associations were slightly attenuated with additional adjustment for osteoporosis and falls. Mutual adjustment for these 4 sleep characteristics in the same model attenuated these associations further (Supplemental Table 1).

Self-reported sleep characteristics and risk of hip fracture

We documented 1,881 incident cases of HF (1,490 in NHS and 391 in NHSII) during 12-14 years of follow-up. The associations between sleep characteristics and HF risk did not differ significantly between NHS and NHSII (p-heterogeneity > 0.08). After adjusting for potential confounders (Table 3), there were slight increases in HF risk associated with longer sleep duration (HR for ≥9 hours versus 7 hours: 1.15; 95% CI: 0.98, 1.34), sleep difficulty (HR for all the time versus none/a little: 1.45; 95% CI: 1.04, 2.00) and EDS (HR for daily versus never: 1.24; 95% CI: 0.97, 1.59). However, we observed no significant trends across categories of these sleep characteristics (p-trend ≥ 0.08). Frequency of habitual snoring was not associated with HF risk (p-trend = 0.29). These associations were essentially unchanged when we removed OSA from the models (data not shown). Sensitivity analyses additionally adjusting for history of osteoporosis, falls or simultaneously adjusting for sleep characteristics resulted in similar associations (Supplemental Table 1).

Subgroup analyses

When grouping sleep characteristics into broader categories (Table 4), the HR (95%CI) for VF was 0.88 (0.65, 1.19) comparing ≥9 versus 7-8 hours of sleep, 1.43 (1.15, 1.79) comparing sleep difficulty most/all of the time versus none/some of the time, 1.36 (1.07, 1.71) comparing snoring most/every night versus never/a few nights and 1.93 (1.46, 2.54) comparing EDS ≥4 versus ≤3 days/week. These associations did not vary significantly by history of osteoporosis (p-interaction ≥ 0.12; Table 4) or BMI (p-interaction ≥ 0.14; Supplemental Table 2), except that the positive association between snoring and VF risk was only observed among women without osteoporosis (HR: 1.82; 95% CI: 1.34, 2.48) but not observed among women with osteoporosis (HR: 0.91; 95% CI: 0.62, 1.33; p-interaction = 0.01). Overall, these associations did not differ significantly by shift work status, although the patterns observed in the primary analyses tended to be more apparent among women who had ever worked shift work schedules, especially for the positive associations of sleep difficulty with HF and VF risk. For example, the HR (95% CI) for HF comparing sleep difficulty most/all of the time versus none/some of the time was 1.81 (1.08, 3.04) among ever shift workers and 1.22 (0.90, 1.66) among never shift workers.

The comparable HR (95%CI) for HF after regrouping sleep characteristics was 1.15 (0.99, 1.33) for sleep duration, 1.12 (0.98, 1.28) for sleep difficulty, 0.91 (0.78, 1.05) for snoring, and 1.21 (1.01, 1.44) for

Table 3
Risk of hip fracture associated with self-reported sleep characteristics in NHS and NHSII.

	NHS			NHSII			Pooled
	Cases	P-Y	HR (95% CI)[1]	Cases	P-Y	HR (95% CI)[1]	HR (95% CI)[2]
Sleep duration							
5 hours or less	108	31,077	1.02 (0.82, 1.26)	34	55,459	1.55 (1.05, 2.28)	1.12 (0.93, 1.34)
6 hours	237	101,582	0.78 (0.67, 0.92)	90	231,771	1.12 (0.86, 1.47)	0.86 (0.75, 0.98)
7 hours	524	200,946	Reference	133	410,577	Reference	Reference
8 hours	418	157,830	0.96 (0.84, 1.09)	111	277,391	1.15 (0.89, 1.48)	1.00 (0.89, 1.12)
9 hours or more	203	50,340	1.13 (0.96, 1.34)	23	49,400	1.10 (0.70, 1.72)	1.15 (0.98, 1.34)
Sleep difficulty							
None or a little	978	365,322	Reference	239	704,380	Reference	Reference
Some of the time	322	113,708	0.95 (0.84, 1.08)	73	180,385	1.09 (0.84, 1.42)	0.98 (0.87, 1.10)
Most of the time	163	56,351	0.99 (0.84, 1.18)	67	124,277	1.31 (0.99, 1.73)	1.07 (0.93, 1.24)
All the time	27	6,394	1.40 (0.95, 2.07)	12	15,557	1.45 (0.80, 2.63)	1.45 (1.04, 2.00)
p-trend			0.75			0.03	0.14
Snoring							
Never or occasionally	843	313,769	Reference	230	669,706	Reference	Reference
A few nights per week	62	33,687	0.87 (0.67, 1.13)	25	56,312	1.22 (0.80, 1.85)	0.94 (0.76, 1.18)
Most nights	118	53,854	0.94 (0.77, 1.15)	33	95,571	0.86 (0.59, 1.25)	0.92 (0.77, 1.10)
Every night	51	28,801	0.78 (0.58, 1.04)	33	73,567	1.01 (0.68, 1.49)	0.86 (0.69, 1.09)
Don't know	416	111,664	0.90 (0.80, 1.02)	70	129,443	1.33 (1.01, 1.75)	0.96 (0.86, 1.07)
p-trend[3]			0.14			0.87	0.29
Excessive daytime sleepiness							
Never	422	167,654	Reference	45	109,592	Reference	Reference
Rarely	872	307,894	1.08 (0.96, 1.22)	191	569,713	0.82 (0.59, 1.14)	1.04 (0.93, 1.16)
1-3 days/week	122	47,057	0.90 (0.73, 1.11)	88	224,662	0.92 (0.64, 1.32)	0.95 (0.80, 1.12)
4-6 days/week	32	7,910	1.24 (0.86, 1.80)	29	68,664	0.98 (0.61, 1.58)	1.19 (0.90, 1.57)
Daily	42	11,259	1.03 (0.74, 1.43)	38	51,968	1.36 (0.87, 2.13)	1.24 (0.97, 1.59)
p-trend			0.73			0.03	0.08

NHS, Nurses' Health Study; NHSII, Nurses' Health Study II; P-Y, Person-years; HR, Hazard ratio; CI, Confidence Interval.
[1] Stratified by age and calendar time, and adjusted for race/ethnicity, BMI, waist circumference, physical activity, smoking status, menopausal status and postmenopausal hormone use, use of thiazide diuretics, furosemide (Lasix) and bisphosphonates, clinical diagnosis of hypertension, diabetes, obstructive sleep apnea and depression, recent physical exam, and dietary factors (all in quintiles, including alcohol intake, caffeine intake, protein intake, dietary and supplementary calcium intake, and dietary and supplementary vitamin D intake).
[2] Additionally stratified by cohort in the pooled analysis.
[3] The 'don't know' category was excluded when calculating the p-trend.

EDS. No significant differences in these associations were observed by history of osteoporosis (p-interaction ≥ 0.14; Table 4), BMI (p-interaction ≥ 0.15; Supplemental Table 2).

Additional analyses

Compared with those who reported no sleep difficulty and >6 hours of sleep (Table 5), women who reported sleep difficulty with short sleep duration (≤6 hours) had the highest VF risk (HR: 1.51; 95% CI: 1.11, 2.07). Sleep difficulty with >6 hours of sleep was also associated with increased VF risk (HR: 1.40; 95% CI: 1.04, 1.88), whereas short sleep duration without sleep difficulty was not associated with VF risk. By contrast, only sleep difficulty with >6 hours of sleep was modestly associated with HF risk (HR: 1.22; 95% CI: 1.03, 1.44). When examining snoring and EDS jointly, women who reported both had an almost 2.5-fold increased risk of VF compared

Table 4
Pooled associations of vertebral and hip fracture with self-reported sleep characteristics by history of osteoporosis[1].

	Vertebral fracture				Hip fracture			
	Overall	No osteoporosis	Osteoporosis	*p* int	Overall	No osteoporosis	Osteoporosis	*p* int
Sleep duration				.38				0.56
Short (6 hours or less)	1.10 (0.91, 1.33)	1.18 (0.90, 1.56)	0.99 (0.76, 1.30)		0.93 (0.83, 1.03)	1.02 (0.88, 1.18)	0.83 (0.70, 0.98)	
Medium (7-8 hours)	Reference	Reference	Reference		Reference	Reference	Reference	
Long (9 hours or more)	0.88 (0.65, 1.19)	1.10 (0.73, 1.67)	0.60 (0.37, 0.95)		1.15 (0.99, 1.33)	1.27 (1.03, 1.57)	1.03 (0.83, 1.27)	
Sleep difficulty				.77				0.14
None or some of the time	Reference	Reference	Reference		Reference	Reference	Reference	
Most or all of the time	1.43 (1.15, 1.79)	1.49 (1.07, 2.06)	1.37 (1.00, 1.87)		1.12 (0.98, 1.28)	1.21 (1.01, 1.45)	1.00 (0.82, 1.22)	
Snoring[2]				.01				0.17
Never or a few nights	Reference	Reference	Reference		Reference	Reference	Reference	
Most or every night	1.36 (1.07, 1.71)	1.82 (1.34, 2.48)	0.91 (0.62, 1.33)		0.91 (0.78, 1.05)	0.81 (0.67, 1.00)	1.04 (0.84, 1.29)	
Excessive daytime sleepiness			.12				0.86	
≤3 days/week	Reference	Reference	Reference		Reference	Reference	Reference	
≥4 days/week	1.93 (1.46, 2.54)	1.45 (0.93, 2.26)	2.23 (1.54, 3.23)		1.21 (1.01, 1.44)	1.20 (0.93, 1.53)	1.15 (0.88, 1.49)	

p int, *p* value for interaction.
[1] Adjusted for the same covariates in Table 2.
[2] The "don't know" category was excluded in the analysis.

Table 5
Associations of joint sleep characteristics with risk of vertebral and hip fracture

	Vertebral fracture		Hip fracture	
	Cases	HR (95% CI)[1]	Cases	HR (95% CI)[1]
Sleep duration + sleep difficulty				
No sleep difficulty and >6 hours	360	Reference	1,255	Reference
No sleep difficulty and ≤6 hours	111	1.05 (0.85, 1.31)	357	0.91 (0.81, 1.03)
Sleep difficulty and >6 hours	52	1.40 (1.04, 1.88)	157	1.22 (1.03, 1.44)
Sleep difficulty and ≤6 hours	46	1.51 (1.11, 2.07)	112	0.96 (0.79, 1.17)
Snoring + EDS[2]				
No snoring and no EDS	300	Reference	1,083	Reference
Snoring only	85	1.30 (1.01, 1.68)	211	0.95 (0.81, 1.11)
EDS only	30	1.69 (1.14, 2.51)	77	1.20 (0.95, 1.53)
Both snoring and EDS	18	2.44 (1.46, 4.07)	24	0.91 (0.60, 1.38)

EDS, Excessive daytime sleepiness; HR, Hazard ratio; CI, Confidence interval.
[1] Adjusted for the same covariates in Table 2.
[2] The "don't know" category was excluded in the analysis.

with those who reported neither (HR: 2.44; 95% CI: 1.46, 4.07). Presence of either of these 2 symptoms was also associated with increased VF risk, with HR (95% CI) of 1.30 (1.01, 1.68) for snoring only and 1.69 (1.14, 2.51) for EDS only. However, snoring and EDS, either individually or in combination, was not significantly associated with HF risk.

Discussion

In this longitudinal cohort study of women, we found that multiple characteristics of poor sleep—shorter sleep duration, sleep difficulty, snoring and EDS—were associated with increased VF risk. Overall, the results did not support an association with risk of HF. Our findings are consistent with emerging theories of multiple dimensions of sleep health[14] and support investigating these multiple dimensions as a risk factor for vertebral fracture. This study has several strengths including the longitudinal study design, large number of incident VF and HF events, long follow-up, and detailed, repeated assessments of covariates. Although NHS and NHSII differed in many aspects, such as age, menopausal status and fracture incidence, similar signals were observed between the 2 cohorts, providing additional credibility to our findings.

Of the 4 sleep characteristics, more studies have examined the association between sleep duration and bone health. Prior studies on sleep duration and bone mineral density have all been cross-sectional and had conflicting results,[32,33] with some finding an association with shorter sleep duration,[34,35] longer sleep duration,[36] both,[37] or no significant association in women.[38] Several prospective studies (2 in men[4,17,18] and 3 in women[15–18]) examined the associations of fracture risk with one or 2 dimensions of sleep. Our study is consistent with other prospective studies in women which did not report a statistically significant increased risk of HF.[15–18] In men, the MrOS Sleep Study (n = 2911) reported an increased risk of non-spine fracture among those with versus without greater nocturnal hypoxia attributed to sleep disordered breathing (SDB).[4] An increased HF risk was found among men who reported premature awakening in the Malmo Preventive Project; however, the association was not statistically significant in women.[17,18]

Other prospective studies in women did not examine the association with VF[15,16] or were not powered to detect an association.[18] In the Study of Osteoporotic Fractures (n = 8101 postmenopausal women),[16] women with longer sleep duration (≥10 hours) had a higher risk of non-spine fracture (HR: 1.26; 95% CI: 1.00, 1.58) and a similar but non-significant increased risk of HF (HR: 1.43; 95% CI: 0.95, 2.15) compared with women who slept 8-9 hours per 24 hours. In the Women's Health Initiative (WHI) (n=157,206),[15] short sleep duration (≤5 hours/night) was associated with a significantly increased risk of all fractures, including VF (HR: 1.12; 95% CI: 1.05, 1.20), but not HF alone (HR: 0.82; 95% CI: 0.61, 1.09). There was no statistically significant association between the other sleep characteristics and fracture. Vertebral fractures were included in a composite outcome of central body fractures (hip, pelvis, spine), but was not examined as a separate outcome. A prior validation study in WHI had noted a relatively lower rate of agreement between self-report and medical records for clinical VF (51%), compared with 78% for hip and 81% for forearm/wrist fractures.[39]

To our knowledge, no prior studies investigated snoring and EDS or their joint association, which are key features of SDB, with fracture risk. Other than the Malmo Preventive Project,[18] our study is the only one which has investigated the association between multiple sleep domains and VF risk in women. We found substantially higher VF risk among women with both snoring and EDS, suggesting that more severe SDB could influence VF risk through greater hypoxic exposure, sleep fragmentation and inflammation.[40] Further, given that snoring and EDS are 2 key symptoms for OSA, these findings were also consistent with our prior findings of a strong association between OSA and VF risk, particularly among women with EDS.[20] As we adjusted for clinically-diagnosed OSA in the analyses, our current findings suggest that independent of a clinical diagnosis of OSA, the symptoms of snoring and EDS were associated with increased VF risk.

In subgroup analyses, we also observed a positive association between snoring and VF risk among women without osteoporosis, but this association was not observed among women with osteoporosis. Since osteoporosis is known to be one of the strongest risk factors for fracture, the potent effects of osteoporosis on fracture risk likely override those from snoring among those with osteoporosis, thus masking the association between snoring and VF risk among those with osteoporosis. A potential clinical implication of this is that asking about snoring or EDS could possibly help identify patients at increased risk of VF, even without a clinical diagnosis of OSA, or without traditional risk factors for fracture such as osteoporosis.

Our results did not support an association between sleep characteristics and HF risk which is consistent with the limited number of prior studies that demonstrated no statistically significant to modestly significant associations with HF risk in women. Our finding of differing risk by fracture site underscores the importance of studying risk factors for fracture sites separately. In a previous study, we also found that the association between OSA and risk for VF and HF differed by site.[20] The vertebra, site of the majority of fractures, is more trabecular-rich and metabolically active, compared to the hip which contains more dense, less metabolically active cortical bone. The vertebra's different microarchitecture and structural integrity[41] make it particularly vulnerable to microdamage (eg, linear microcracks and diffuse damage).[8] Thus, the vertebra could be more sensitive to disruptions in the tightly regulated homeostatic mechanisms for bone remodeling and repair that are necessary to maintain healthy vertebra.

Direct disruption of the molecular machinery generating circadian rhythms using clock gene knockout mouse models resulted in altered osteoclast[5] and osteoblast function,[6] thus affecting bone formation[7] and resorption,[5,6] altering bone microstructure and creating a low bone mass phenotype. Altogether, the effects of poorer sleep and potentially associated disturbances in circadian rhythmicity could have more pronounced effects on the vertebra by inhibiting bone formation while promoting bone resorption and breakdown, thus impairing the vertebra's ability to repair microdamage that accumulates with aging[9] and contributing to higher VF risk.

There are several limitations to our observational study. There is the possibility of residual or unmeasured confounding, such as cognitive function and use of narcotics or sedatives, which we did not have information on during the study period. Misclassification of sleep characteristics or fractures was also possible. Our assessment of the 4 sleep-related domains were based on self-reports, which could be subject to measurement errors.[42] Our definition of clinical VF required coming to medical attention, which limited our ability to identify asymptomatic cases (eg, those that may be discovered incidentally by radiographic studies) or confirm certain self-reported cases (eg, we did not have permission, were not able to obtain, or there was insufficient evidence in the medical record to make a definitive VF diagnosis). There is also the possibility of a chance finding due to multiple statistical comparisons. Finally, since our study population was female and almost entirely white, our findings are not necessarily generalizable to men or other races.

In this longitudinal cohort study, poorer sleep as defined by 4 sleep-related characteristics—sleep duration, sleep difficulty, snoring, and EDS—was independently and significantly associated with increased risk of clinical VF. Our results did not support an association between these sleep characteristics and risk of HF. This suggests that risk factors for fractures can differ by fracture site. Further research is warranted in understanding the multiple sleep dimensions as a risk factor for fracture and the role that sleep may play in bone metabolism and health.

Declaration of conflict of interest

The authors report no conflicts of interest.

Disclosures

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Author contributions

All authors contributed significantly to the manuscript. Study design: TH, JMP. Acquisition and data analysis: TH, JMP. Data interpretation: All authors. Manuscript drafting: TH, JMP. Critical revision of the manuscript for important intellectual content: All authors. Responsibility for the data integrity and accuracy of the data analysis: TH, JMP.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.sleh.2021.11.011.

References

1. Swanson CM, Kohrt WM, Buxton OM, et al. The Importance of the circadian system & sleep for bone health. *Metabolism*. 2018;84:28–43. https://doi.org/10.1016/j.metabol.2017.12.002.
2. Okunowo O, Orimoloye HT, Bakre SA, Njesada NS, Solomon A. Age- and body weight-dependent association between sleep duration and hypertension in US adults: findings from the 2014-2017 National Health Interview Survey. *Sleep Health*. 2019;5(5):509–513. https://doi.org/10.1016/j.sleh.2019.05.003.
3. Swanson CM, Shea SA, Wolfe P, et al. Bone turnover markers after sleep restriction and circadian disruption: a mechanism for sleep-related bone loss in humans. *J Clin Endocrinol Metab*. 2017;102(10):3722–3730. https://doi.org/10.1210/jc.2017-01147.
4. Cauley JA, Blackwell TL, Redline S, et al. Hypoxia during sleep and the risk of falls and fractures in older men: the Osteoporotic Fractures in Men Sleep Study. *J Am Geriatr Soc*. 2014;62(10):1853–1859. https://doi.org/10.1111/jgs.13069.
5. Xu C, Ochi H, Fukuda T, et al. Circadian clock regulates bone resorption in mice. *J Bone Miner Res*. 2016;31(7):1344–1355. https://doi.org/10.1002/jbmr.2803.
6. Takarada T, Xu C, Ochi H, et al. Bone resorption is regulated by circadian clock in osteoblasts. *J Bone Miner Res*. 2017;32(4):872–881. https://doi.org/10.1002/jbmr.3053.
7. Yuan G, Hua B, Yang Y, et al. The circadian gene clock regulates bone formation via PDIA3. *J Bone Miner Res*. 2017;32(4):861–871. https://doi.org/10.1002/jbmr.3046.
8. Seref-Ferlengez Z, Kennedy OD, Schaffler MB. Bone microdamage, remodeling and bone fragility: how much damage is too much damage? *BoneKEy Rep*. 2015;4:644. https://doi.org/10.1038/bonekey.2015.11.
9. Green JO, Wang J, Diab T, Vidakovic B, Guldberg RE. Age-related differences in the morphology of microdamage propagation in trabecular bone. *J Biomech*. 2011;44(15):2659–2666. https://doi.org/10.1016/j.jbiomech.2011.08.006.
10. Amin S, Achenbach SJ, Atkinson EJ, Khosla S, Melton 3rd. LJ. Trends in fracture incidence: a population-based study over 20 years. *J Bone Miner Res*. 2014;29(3):581–589. https://doi.org/10.1002/jbmr.2072.
11. Lewiecki EM, Wright NC, Curtis JR, et al. Hip fracture trends in the United States, 2002 to 2015. *Osteoporos Int*. 2018;29(3):717–722. https://doi.org/10.1007/s00198-017-4345-0.
12. Melton 3rd LJ, Achenbach SJ, Atkinson EJ, Therneau TM, Amin S. Long-term mortality following fractures at different skeletal sites: a population-based cohort study. *Osteoporos Int*. 2013;24(5):1689–1696. https://doi.org/10.1007/s00198-012-2225-1.
13. Pike CT, Birnbaum HG, Schiller M, Swallow E, Burge RT, Edgell ET. Prevalence and costs of osteoporotic patients with subsequent non-vertebral fractures in the US. *Osteoporos Int*. 2011;22(10):2611–2621. https://doi.org/10.1007/s00198-010-1494-9.
14. Buysse DJ. Sleep health: can we define it? Does it matter? *Sleep*. 2014;37(1):9–17. https://doi.org/10.5665/sleep.3298.
15. Cauley JA, Hovey KM, Stone KL, et al. Characteristics of self-reported sleep and the risk of falls and fractures: the Women's Health Initiative (WHI). *J Bone Miner Res*. 2019;34(3):464–474. https://doi.org/10.1002/jbmr.3619.
16. Stone KL, Ewing SK, Lui LY, et al. Self-reported sleep and nap habits and risk of falls and fractures in older women: the study of osteoporotic fractures. *J Am Geriatr Soc*. 2006;54(8):1177–1183. https://doi.org/10.1111/j.1532-5415.2006.00818.x.
17. Holmberg AH, Johnell O, Nilsson PM, Nilsson JA, Berglund G, Akesson K. Risk factors for hip fractures in a middle-aged population: a study of 33,000 men and women. *Osteoporos Int*. 2005;16(12):2185–2194. https://doi.org/10.1007/s00198-005-2006-1.
18. Holmberg AH, Johnell O, Nilsson PM, Nilsson J, Berglund G, Akesson K. Risk factors for fragility fracture in middle age. A prospective population-based study of 33,000 men and women. *Osteoporos Int*. 2006;17(7):1065–1077. https://doi.org/10.1007/s00198-006-0137-7.
19. Baden MY, Hu FB, Vetter C, Schernhammer E, Redline S, Huang T. Sleep duration patterns in early to middle adulthood and subsequent risk of type 2 diabetes in women. *Diabetes Care*. 2020;43(6):1219–1226. https://doi.org/10.2337/dc19-2371.
20. Huang T, Tworoger SS, Redline S, Curhan GC, Paik JM. Obstructive sleep apnea and risk for incident vertebral and hip fracture in women. *J Bone Miner Res*. 2020;35(11):2143–2150. https://doi.org/10.1002/jbmr.4127.
21. Huang T, Lin BM, Markt SC, et al. Sex differences in the associations of obstructive sleep apnoea with epidemiological factors. *Eur Respir J*. 2018;51(3). https://doi.org/10.1183/13993003.02421-2017.
22. Patel SR, Ayas NT, Malhotra MR, et al. A prospective study of sleep duration and mortality risk in women. *Sleep*. 2004;27(3):440–444.
23. Paik JM, Rosen HN, Gordon CM, Curhan GC. Diuretic use and risk of vertebral fracture in women. *Am J Med*. 2016;129(12):1299–1306. https://doi.org/10.1016/j.amjmed.2016.07.013.
24. Colditz GA, Martin P, Stampfer MJ, et al. Validation of questionnaire information on risk factors and disease outcomes in a prospective cohort study of women. Research Support, U.S. Gov't, P.H.S. *Am J Epidemiol*. 1986;123(5):894–900.
25. Rimm E, Stampfer M, Colditz GA, Chute C, Litin L, Willett W. Validity of self-reported waist and hip circumference in men and women. *Epidemiology*. 1990;1(6):466–473.
26. Manson JE, Colditz GA, Stampfer MJ, et al. A prospective study of maturity-onset diabetes mellitus and risk of coronary heart disease and stroke in women. *Arch Intern Med*. 1991;151(6):1141–1147.
27. Prochaska M, Taylor E, Vaidya A, Curhan G. Low bone density and bisphosphonate use and the risk of kidney stones. *Clin J Am Soc Nephrol*. 2017;12(8):1284–1290. https://doi.org/10.2215/CJN.01420217.
28. Huang T, Balasubramanian R, Yao Y, et al. Associations of depression status with plasma levels of candidate lipid and amino acid metabolites: a meta-analysis of individual data from three independent samples of US postmenopausal women. *Mol Psychiatry*. 2021;26(7):3315–3327. https://doi.org/10.1038/s41380-020-00870-9.

29. Yuan C, Spiegelman D, Rimm EB, et al. Validity of a dietary questionnaire assessed by comparison with multiple weighed dietary records or 24-hour recalls. *Am J Epidemiol*. 2017;185(7):570–584. https://doi.org/10.1093/aje/kww104.
30. Wolf A, Hunter D, Colditz G, et al. Reproducibility and validity of a self-administered physical activity questionnaire. *Int J Epidemiol*. 1994;23(5):991–999.
31. Vgontzas AN, Fernandez-Mendoza J, Liao D, Bixler EO. Insomnia with objective short sleep duration: the most biologically severe phenotype of the disorder. *Sleep Med Rev*. 2013;17(4):241–254. https://doi.org/10.1016/j.smrv.2012.09.005.
32. Moradi S, Shab-Bidar S, Alizadeh S, Djafarian K. Association between sleep duration and osteoporosis risk in middle-aged and elderly women: a systematic review and meta-analysis of observational studies. *Metabolism*. 2017;69:199–206. https://doi.org/10.1016/j.metabol.2017.01.027.
33. Swanson CM, Blatchford PJ, Stone KL, et al. Sleep duration and bone health measures in older men. *Osteop Int*. 2021;32(3):515–527. https://doi.org/10.1007/s00198-020-05619-2.
34. Cunningham TD, Di Pace BS. Is self-reported sleep duration associated with osteoporosis? Data from a 4-year aggregated analysis from the National Health and Nutrition Examination Survey. *J Am Geriatr Soc*. 2015;63(7):1401–1406. https://doi.org/10.1111/jgs.13477.
35. Ochs-Balcom HM, Hovey KM, Andrews C, et al. Short sleep is associated with low bone mineral density and osteoporosis in the women's health initiative. *J Bone Miner Res*. 2020;35(2):261–268. https://doi.org/10.1002/jbmr.3879.
36. Saint Martin M, Labeix P, Garet M, et al. Does subjective sleep affect bone mineral density in older people with minimal health disorders? The PROOF cohort. *J Clin Sleep Med*. 2016;12(11):1461–1469. https://doi.org/10.5664/jcsm.6266.
37. Chen G, Chen L, Wen J, et al. Associations between sleep duration, daytime nap duration, and osteoporosis vary by sex, menopause, and sleep quality. *J Clin Endocrinol Metab*. 2014;99(8):2869–2877. https://doi.org/10.1210/jc.2013-3629.
38. Swanson CM, Blatchford PJ, Orwoll ES, et al. Association between objective sleep duration and bone mineral density in older postmenopausal women from the Study of Osteoporotic Fractures (SOF). *Osteoporos Int*. 2019;30(10):2087–2098. https://doi.org/10.1007/s00198-019-05007-5.
39. Chen Z, Kooperberg C, Pettinger MB, et al. Validity of self-report for fractures among a multiethnic cohort of postmenopausal women: results from the Women's Health Initiative observational study and clinical trials. *Menopause*. 2004;11(3):264–274.
40. Vgontzas AN, Papanicolaou DA, Bixler EO, et al. Sleep apnea and daytime sleepiness and fatigue: relation to visceral obesity, insulin resistance, and hypercytokinemia. *J Clin Endocrinol Metab*. 2000;85(3):1151–1158. https://doi.org/10.1210/jcem.85.3.6484.
41. Lambers FM, Bouman AR, Tkachenko EV, Keaveny TM, Hernandez CJ. The effects of tensile-compressive loading mode and microarchitecture on microdamage in human vertebral cancellous bone. *J Biomech*. 2014;47(15):3605–3612. https://doi.org/10.1016/j.jbiomech.2014.10.011.
42. Jackson CL, Patel SR, Jackson 2nd WB, Lutsey PL, Redline S. Agreement between self-reported and objectively measured sleep duration among white, black, Hispanic, and Chinese adults in the United States: Multi-Ethnic Study of Atherosclerosis. *Sleep*. 2018;41(6). https://doi.org/10.1093/sleep/zsy057.