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Obstructive Sleep Apnea and Risk For Incident Vertebral and Hip Fracture in Women

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Abstract

Background: Recent studies suggest a positive association between obstructive sleep apnea (OSA), a disorder associated with intermittent hypoxia and sleep fragmentation, and derangements in bone metabolism. However, no prospective study to date has investigated the association between OSA and fracture risk in women.

Methods: We conducted a prospective study examining the relation between OSA and risk of incident vertebral fracture (VF) and hip fracture (HF) in the Nurses' Health Study. History of physician-diagnosed OSA was assessed by self-reported questionnaires. A previous validation study demonstrated high concordance between self-reports and medical record identification of OSA. OSA severity was further categorized according to the presence or absence of self-reported sleepiness. Self-reports of VF were confirmed by medical record review. Self-reported HF was assessed by biennial questionnaires. Cox proportional-hazards models estimated the hazard ratio for fracture according to OSA status, adjusted for potential confounders, including BMI, physical activity, calcium intake, history of osteoporosis, and falls, and use of sleep medications.

Results: Among 55,264 women without prior history of fracture, physician-diagnosed OSA was self-reported in 1.3% in 2002 and increased to 3.3% by 2012. Between 2002 and 2014, 461 incident VF cases and 921 incident HF cases were documented. The multivariable-adjusted hazard ratio (HR) for confirmed VF for women with history of OSA was 2.00 (95%CI 1.29, 3.12) compared with no OSA history, with the strongest association observed for OSA with daytime

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sleepiness (HR 2.86; 95%CI 1.31, 6.21). No association was observed between OSA history and self-reported HF risk (HR 0.83; 95%CI 0.49, 1.43).

Conclusion: History of OSA is independently associated with higher risk of confirmed VF but did not have a statistically significant association with self-reported HF in women. Further research is warranted in understanding the role of OSA and intermittent hypoxia in bone metabolism and health that may differ by fracture site.

Keywords

Obstructive Sleep Apnea; Hip Fracture; Vertebral Fracture; Prospective Study; Nurses' Health Study

Introduction

Fractures are a major public health burden ⁽¹⁾ since they are associated with high cost ^(2,3), significant disability ^(4,5), increased morbidity ⁽⁶⁾ and mortality ⁽⁷⁾, and are predictive of future fracture risk ^(8,9). The incidence of vertebral fracture (VF) has been rising in recent years ⁽¹⁰⁾ and since 2013, hip fracture (HF) rates stopped declining and are now higher than expected ⁽¹¹⁾.

Obstructive sleep apnea (OSA), a serious respiratory sleep disorder, has been linked to increased cardiometabolic disease risk and premature death ^(12,13). While OSA is highly prevalent in the general population, a large proportion of OSA cases, particularly among women and those with mild or no symptoms, remain unrecognized and clinically underdiagnosed ⁽¹⁴⁾. Emerging research suggests a potential association between OSA and fracture risk through derangements in bone metabolism ⁽¹⁵⁾. Intermittent hypoxia (IH) in men with OSA was associated with lower bone mineral density (BMD)/osteoporosis ^(16–18), higher bone resorption markers ⁽¹⁹⁾ and increased risk of non-spine fracture ⁽²⁰⁾, although the evidence has not been consistent ⁽²¹⁾. Multiple mechanisms have been proposed. First, hypoxia can lead to vascular endothelial dysfunction and disrupted angiogenesis, resulting in decreased bone perfusion and bone loss ⁽²²⁾. Second, acidosis following IH can have detrimental effects on bone ^(23,24). Third, OSA is associated with sleep fragmentation, which can alter the immune system and amplify inflammatory pathways ⁽²⁵⁾, increasing bone resorption and suppressing bone formation ⁽²⁶⁾. Fourth, OSA and fracture risk could be modulated by sex hormones since factors associated with lower estrogen exposure (e.g., surgical versus natural menopause) have been associated with increased risk of OSA ⁽²⁷⁾, and lower estrogen level is associated with increased fracture risk ^(28–30). Finally, OSA may increase fracture risk due to higher likelihood of falls resulting from excessive daytime sleepiness (EDS), a key symptom of OSA.

While OSA may be less prevalent in women, its biological consequences and clinical sequelae may be more severe in women ^(31–33). However, no prospective study to date has investigated the association between OSA and fracture risk in women. We conducted this prospective analysis to examine the association between OSA and risk of incident VF and HF in the Nurses' Health Study (NHS). Built upon prior evidence, we hypothesized that a

history of OSA, particularly OSA concomitant with EDS representing more severe OSA and OSA-related inflammation⁽³⁴⁾, was associated with increased risk for VF and HF.

Methods

Study Population

The NHS is a prospective cohort study, enrolling 121,700 female nurses aged 30–55 years in 1976. Since then, biennial questionnaires have been mailed to participants querying lifestyle practices, medications, and newly diagnosed diseases with >90% follow-up of the eligible person-time. Most (97%) of the participants are white. This analysis included 55,264 participants (Supplemental Figure 1) with information on history of VF and HF and clinical diagnosis of OSA who did not have previous history of fracture at baseline (2002). The study was approved by the Institutional Review Board at Brigham and Women's Hospital (Boston, MA).

Assessment of OSA and Related Symptoms

Assessment of OSA and related symptoms was described previously^(27,35). The 2012 questionnaire asked participants, "Have you ever had sleep apnea diagnosed by clinicians or sleep study?" Those who answered affirmatively were then asked to report the diagnosis year as "before 2002", "2002–2005", "2006–2007", "2008–2009", "2010–2011", or "after 2012". A previous validation study demonstrated that self-reported OSA was highly reliable among nurses⁽³⁵⁾. All nurses with self-reported sleep apnea were confirmed by medical record review to have the diagnosis through at least one of the following objective diagnostic methods: 92% by in-lab polysomnography, 24% by overnight oximetry and 9% by home sleep apnea test. Almost all self-reported cases (98%) were classified as obstructive; 89% of cases were moderate-to-severe as defined by the Apnea-Hypopnea Index ≥ 15.

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". Habitual snoring was defined as snoring every night or most nights. Participants were queried about EDS in 2008 with the question, "On average, how often are your daily activities affected because you are sleepy during the day?" We defined EDS as ≥ 4 days/week of daytime sleepiness⁽²⁷⁾.

Our primary exposure definition was a history of clinician-diagnosed OSA. Consistent with our prior research⁽³⁶⁾, this binary OSA status was further combined with related symptoms to capture potential OSA severity, including no OSA without habitual snoring (reference group), no OSA with snoring, OSA without EDS, and OSA with EDS.

Assessment of Clinical Vertebral Fracture

Assessment of clinical VF in NHS was previously described by us^(37,38). Participants were asked on the 2012 questionnaire about lifetime history of a clinician-diagnosed "vertebral (spine) fracture, x-ray confirmed" as well as the year of first diagnosis. Participants were asked again about a VF diagnosis on the 2014 questionnaire. Participants who reported a VF in 2002 or afterwards were mailed a supplemental questionnaire. We requested permission

for participants' medical records which were related to the VF. We confirmed vertebral fracture cases by medical or radiology report among the participants who gave permission and for whom sufficient information was available in the records to make a diagnosis.

If the word "fracture" or language suggesting a VF (e.g., "vertebral collapse", "severe wedge compression", "acute compression") was in the medical record, then a self-reported VF was confirmed as a case. When a diagnosis of VF was less clear (e.g., "mild compression deformity"), participants were coded as "probable" cases and excluded from the analysis.

Our primary analysis included all VFs, including those related to low or moderate level trauma (e.g., tripping, slipping) as well as high-trauma or accidents, since OSA and EDS are associated with accidents ⁽³⁹⁾. We conducted a separate analysis that excluded VFs related to high-trauma or accidents. We excluded cervical or sacral fractures from the analysis. Only VF cases diagnosed between 2002 to May 31, 2014 and confirmed by record review were included in our analysis.

Assessment of Hip Fracture

Participants were initially asked on the 1982 questionnaire about previous HFs (date, bone site, and circumstances leading to the fracture). Incident HFs were reported on subsequent biennial questionnaires. Nurses who reported incident HFs were mailed supplemental questionnaires to obtain additional information regarding the fracture. Only fractures of the proximal femur were included as HF cases. Since a validation study found self-reported HFs to be highly reliable ⁽⁴⁰⁾, we used self-reported HFs in this cohort. Similar to the VF analysis, we included HFs related to low- or moderate-trauma as well as high-trauma or accidents, in the main analysis ^(41,42), and we conducted a separate analysis that excluded HFs related to high trauma or accidents.

Assessment of Covariates

Date of birth, height and race/ethnicity were self-reported. Every biennial questionnaire has queried participants on their weight, which was found to be highly reliable among a subset of participants who directly measured their weight ($r=0.97$) ⁽⁴³⁾. BMI (kg/m^2) was calculated from the weight and height information provided by participants. Information on waist circumference was collected in 1986, 1996, and 2000, which was found to be highly reliable among a subset of participants who directly measured their waist circumference ($r=0.88$) ⁽⁴³⁾. For participants without waist circumference data in 2000, we carried forward information collected on waist circumference in 1996 if available.

Information on postmenopausal hormone therapy (type and duration), sleep medications (nonbenzodiazepines or other prescription medications), and diuretics (thiazide or loop diuretics) was queried on biennial questionnaires. History of hypertension ⁽⁴⁴⁾ and diabetes ⁽⁴⁵⁾ were validated in this cohort. In a similar cohort, self-reported osteoporosis was recently validated ⁽⁴⁶⁾.

We used extensively validated ⁽⁴⁷⁾ semi-quantitative food-frequency questionnaires that were sent to participants in 2002, 2006, and 2010 to assess dietary intake. A number of dietary variables were considered in our models, including dietary and supplemental calcium intake,

and alcohol intake. Self-reported physical activity was validated previously in a similar cohort ($r=0.79$), and was assessed by metabolic equivalent task hours per week (MET-hours/week) ⁽⁴⁸⁾. Sleep duration was self-reported in 2000, 2002, 2008 and 2012 in the following categories: 5, 6, 7, 8, 9, 10, 11 hours.

Statistical Analyses

For the analysis of the association between OSA and VF, each participant's person-time of follow-up was counted from the return date of the 2002 questionnaire to 1) the date of VF diagnosis, 2) death, or 3) May 31, 2014, whichever occurred first. If participants reported a HF during the follow-up period, they were censored in the analysis. For the analysis of the association between OSA and HF, each participant's person-time of follow-up was counted from the return date of the 2002 questionnaire to 1) the date of HF diagnosis, 2) death, or 3) May 31, 2014, whichever occurred first. If participants reported a VF during the follow-up period, they were censored in the analysis.

We used Cox proportional-hazards models to estimate the hazard ratios and 95% confidence intervals (CI) for fracture according to OSA status. OSA was modeled as a time-dependent variable, allowing unexposed participants to become exposed at the time of OSA diagnosis. Except for race/ethnicity, all covariates were also modeled as time-varying in the analysis. The first multivariable model (Model 2) was stratified by age and calendar time, and adjusted for race/ethnicity, BMI, waist circumference, smoking, physical activity, alcohol intake, dietary and supplemental calcium intake, regular physical examination, sleep duration, duration of estrogen-only hormone therapy, duration of estrogen plus progestin hormone therapy, thiazide diuretic use, loop diuretic use, nonbenzodiazepine use, other sleep medication use, history of diabetes and hypertension. The next multivariable model (Model 3) further adjusted for number of falls and history of osteoporosis, which we hypothesized were potential mediators for the association between OSA and fracture risk. To test the proportional hazards assumption, we evaluated the interaction between OSA status and calendar time using a likelihood ratio test. The assumption was not violated (p for interaction=0.64 for HF and 0.69 for VF).

We further examined whether the associations between OSA and VF or HF risk differed by several pre-specified factors, including BMI, waist circumference, history of osteoporosis, and EDS. Differences in the associations were evaluated by likelihood ratio tests comparing the model with versus without the cross-product interaction terms between OSA and these factors. All P values are two-tailed. The analysis was performed using SAS 9.4 (SAS Institute, Cary, NC).

Results

Among 55,264 women (mean age 66.7 years, 99.3% postmenopausal), physician-diagnosed OSA was reported in 1.3% in 2002 and increased to 3.3% by 2012. At the mid-point of the follow-up in 2006, 1,111 of 54,268 (2.0%) women reported physician-diagnosed OSA (Table 1). Compared with women without OSA, women with OSA had higher BMI, larger waist circumference, lower physical activity, were more likely to have diabetes, hypertension, history of falls, and lower alcohol and caffeine intake, less likely to be a

current smoker, more likely to be using a sleep medication, and more likely to be using diuretics. Among participants with OSA, those with EDS had lower physical activity, were more likely to have diabetes, history of falls, and be using diuretics as well as other sleep medications.

Obstructive Sleep Apnea and Risk of Vertebral Fracture

During 545,111 person-years of follow-up over 12 years, there were 461 confirmed incident VF cases (Supplemental Figure 1). Among women with OSA, there were 23 incident VF cases. The cumulative incidence curve comparing participants with versus without OSA for VF are shown in Supplemental Figure 2. After adjusting for age and calendar time (Model 1), history of OSA was significantly associated with increased risk of VF (RR 2.22; 95%CI 1.45, 3.41) (Table 2). After multivariable adjustment (Model 2), the hazard ratio (HR) for VF was 2.00 (95%CI 1.29, 3.12) for women with history of OSA compared with women without history of OSA. This association was the strongest for women with OSA with concurrent EDS (HR 2.86; 95%CI 1.31, 6.21), although women with OSA without EDS were also at increased risk for VF (HR 1.80; 95%CI 1.07, 3.04). The association was moderately attenuated but remained statistically significant after further adjustment for history of osteoporosis and falls (Model 3) (HR 1.88; 95%CI 1.21, 2.93). When excluding high-trauma VF cases (n=21 exposed cases of 448 VF cases) in the analysis (Supplemental Table 1), the association was somewhat attenuated (fully-adjusted HR 1.77; 95%CI 1.11, 2.80). Inclusion of 24 additional probable VF cases after medical record review also resulted in similar positive associations between OSA and VF risk (Supplemental Table 2).

Obstructive Sleep Apnea and Risk of Hip Fracture

During 544,655 person-years of follow-up over 12 years, there were 921 incident HF cases. Among women with OSA, there were 14 incident HF cases. The cumulative incidence curve comparing participants with versus without OSA for HF are shown in Supplemental Figure 2. After adjusting for age and calendar time (Model 1), history of OSA was not significantly associated with risk of HF (HR 0.78; 95%CI 0.46, 1.32) (Table 3). The multivariable-adjusted results (Models 2 and 3) were materially unchanged (HR 0.83; 95%CI 0.49, 1.43 for Model 2, and HR 0.81; 95%CI 0.47, 1.40 for Model 3). There was no significant association among women with OSA with EDS (fully-adjusted HR 0.87; 95%CI 0.32, 2.36). Similarly, no association between OSA and HF risk was observed when high-trauma HF cases were excluded (Supplemental Table 1).

Additional Analyses

The results were materially unchanged when we included participants with prior history of vertebral or hip fracture. The associations between history of OSA and VF did not vary significantly by BMI, waist circumference, or EDS (Table 4; p for interaction>0.24), although the associations were suggestively stronger among women with BMI>30 kg/m², waist circumference<88cm or presence of EDS. There was a nominally statistically significant interaction with osteoporosis (p for interaction=0.03), with a stronger association observed for women who did not have a history of osteoporosis (HR 3.08; 95%CI 1.62, 5.84) versus those with a history of osteoporosis (HR 1.25; 95%CI 0.60, 2.59). OSA was not

associated with risk of HF in subgroups defined by BMI, waist circumference, history of osteoporosis and EDS.

Discussion

This is the first prospective study demonstrating an increased risk of VF in women with history of OSA. No prior prospective studies have examined the association between history of OSA and risk of incident VF or HF in women. We found an increased risk of VF among women with OSA but no statistically significant association between OSA and risk of HF. This study has several strengths including the prospective study design, large sample size, detailed, repeated assessments of covariates, large number of incident VF and HF events, and long follow-up period.

Prior studies have shown conflicting results for the association between OSA and BMD/osteoporosis^(16,17,21), bone resorption markers in men⁽¹⁹⁾ and non-spine fracture in men⁽²⁰⁾. Tomiyama et al.⁽¹⁹⁾ initially reported a link between OSA and bone metabolism when they reported that bone resorption markers were significantly higher in men with OSA compared with controls. Uzkeser et al.⁽¹⁷⁾ reported an increased risk of osteoporosis in a small cross-sectional study among men (n=21 men with OSA, 26 controls), but another cross-sectional study by Sforza et al.⁽²¹⁾ found that OSA was associated with higher BMD in older men and women (n=833). In a large insurance database study in Taiwan⁽¹⁶⁾, patients with OSA had 2.74 times (95%CI 1.69, 4.44) the risk of osteoporosis compared with patients without OSA. Among older men participating in the Study of Osteoporotic Fractures in Men Sleep Study (n=2,911), men with more sleep-related hypoxia during sleep had a 30% to 40% greater risk of non-spine fracture than those with normal nocturnal oxygen saturation⁽²⁰⁾.

Our finding of an increased risk of VF with OSA, but not with HF, suggests that risk factors may differ for fractures at different sites⁽⁴⁹⁾. The vertebra, site of the majority of osteoporotic fractures, is particularly susceptible to microdamage (e.g., diffuse damage and linear microcracks)⁽⁵⁰⁾ because of the vertebra's different biomechanics⁽⁵¹⁾, loading parameters⁽⁵²⁾, microarchitecture^(53,54), microvasculature⁽⁵⁵⁾, and structural integrity^(56,57) that accumulates with aging^(58,59). Compared with HFs, most VFs are not due to trauma, but precipitated by routine everyday activities⁽⁶⁰⁾.

Thus, the vertebra could be more sensitive than hip bone to the effects of IH, as seen with OSA, that results in altered endothelial cell function and vascular flow, acidosis, and a more inflammatory milieu. First, bone is highly vascularized tissue, but aging diminishes blood flow and perfusion⁽⁶¹⁾. OSA-related hypoxia can lead to altered hypoxia-inducible factor (HIF)- α signaling which could lead to endothelial dysfunction and disrupted angiogenesis, further decreasing bone perfusion and bone loss⁽²²⁾ as well as impairing bone remodeling⁽⁶²⁾. Second, bone cells are exquisitely sensitive to pH⁽²⁴⁾, and acidosis has direct effects on bone: it causes the release of calcium by direct dissolution of bone mineral⁽²³⁾, inhibits mineralization of bone matrix by osteoblasts⁽⁶³⁾, impairs osteoblast differentiation⁽⁶⁴⁾, suppresses collagen synthesis⁽⁶⁵⁾ and alkaline phosphatase activity⁽⁶⁶⁾, and stimulates osteoclasts to resorb bone⁽⁶⁷⁾, all of which could increase fracture risk⁽²³⁾. Acidosis can

have detrimental effects on bone microarchitecture⁽⁶⁸⁾ which is critical for maintaining bone integrity⁽⁵⁸⁾. Third, OSA is associated with sleep fragmentation, which can amplify a number of inflammatory pathways and alter innate immunity⁽²⁵⁾, thereby suppressing bone formation and increasing bone resorption⁽²⁶⁾. Altogether, the effects of IH can inhibit bone formation while promoting bone resorption and breakdown, thus impairing the vertebra's ability to repair microdamage that accumulates with aging^(58,59) and contributing to higher VF risk. We found the association between OSA and VF to be stronger among women with EDS, suggesting that more severe OSA may influence VF risk through greater hypoxic exposure, sleep fragmentation and inflammation⁽³⁴⁾. Whether OSA is a risk factor that may differ by fracture site requires further study.

In stratified analyses, we also found that the association between OSA and VF was stronger among women who were apparently at low risk for fracture based on traditional risk factors for fracture, including lack of history of osteoporosis, higher BMI, and lower central obesity, although these associations were not statistically significant. More studies are needed to confirm these findings and understand whether the impact of OSA on VF risk differs by other VF risk factor profiles.

There are several limitations to our observational study. First, we used self-reported OSA, HF and covariates in our analysis, and their impact on the association estimates should be noted. Although we previously showed that the BMI-specific prevalence of self-reported OSA in nurses (e.g., 2.5% in BMI<25 kg/m² and 30.8% in BMI>40 kg/m²)⁽³⁵⁾ was remarkably similar to that of moderate-to-severe OSA measured by polysomnography in U.S. women (e.g., 1.4% in BMI<25 kg/m² and 33.5% in BMI>40 kg/m²)⁽⁶⁹⁾, our reliance on self-reported OSA diagnosis may inadequately capture undiagnosed, mild-to-moderate cases. Such misclassification likely has attenuated the true association between OSA and fracture risk. Self-reported HF and covariates may also introduce measurement errors, but these errors were likely minimal given that the majority of self-reported data have been validated previously in our cohort with high reliability. There also remains the possibility of differential misclassification due to detection bias. However, it is less likely in this study population of nurses who are overall relatively health-conscious and educated, in which disparities in access to care is less of an issue than for the general population. Second, we did not have detailed information on OSA or fracture to provide a definitive mechanism for the observed associations. For example, we did not have information on BMD or morphometric fracture assessment. We also lacked information on OSA treatment, although prior research suggests that OSA treatment did not change bone turnover markers⁽⁷⁰⁾. Of note, despite lack of data on OSA severity or nocturnal hypoxia burden, the difference seen by OSA symptoms (e.g., EDS and snoring) suggest potential dose-response relationships between OSA severity and VF, providing additional biologic plausibility for this association. Third, our definition of clinical VF required coming to medical attention, which limited our ability to identify asymptomatic cases or confirm certain self-reported cases (e.g., we did not have permission, were unable to obtain the medical record, or there was insufficient evidence in the record to make a definitive VF diagnosis). We thus recognize that the observed VF incidence rate is lower because of our strict method of case ascertainment. There is also the possibility of an inaccurate recorded date of diagnosis since vertebral fractures could have been asymptomatic for awhile before coming to medical attention.

Fourth, although we adjusted for a wide range of important covariates in the analysis, residual or unmeasured confounding remains a possibility. Fifth, it should also be noted that the number of fracture cases with OSA or OSA-related symptoms was small (e.g., 21 VF cases among women with OSA and only 6 VF cases among women with OSA and EDS), thus we cannot rule out the possibility of chance findings. There were also a limited number of hip fracture cases among participants with OSA and thus our finding of a lack of a statistically significant association between OSA and HF could be related to the small number of HF cases. Finally, our findings are not necessarily generalizable to men or other races since our study population was female and almost entirely white.

In this large prospective cohort study, history of OSA was independently associated with increased risk of VF, but was not associated with risk of HF in women. Further research is warranted in understanding OSA as a risk factor for fracture that may differ by fracture site and the role that OSA and intermittent hypoxia may play in bone metabolism and health.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1.
Age-standardized characteristics of the study population at the mid-point of follow-up (2006)

	OSA status			
	No OSA+no snoring	No OSA+snoring	OSA+no EDS	OSA+EDS
N	44453	8704	853	258
Age, years*	70.8 (6.6)	69.8 (6.2)	69.7 (6.2)	69.3 (6.5)
Non-white, %	6	6	6	4
Body mass index (BMI), kg/m ²	26.2 (4.9)	28.7 (5.8)	31.9 (7.2)	32.1 (7.6)
Waist circumference, cm	85.7 (12.9)	92.0 (13.9)	97.1 (15.9)	97.8 (16.3)
History of hypertension, %	59	68	79	81
History of diabetes, %	8	13	23	27
History of osteoporosis, %	33	31	33	34
Any falls in the past, %	42	47	54	58
Number of falls in the past 2 years, %				
No fall	77	74	65	61
1–2 falls	20	22	28	30
3 falls	3	4	7	9
Physical activity, MET-hours/week	19.7 (17.6)	16.1 (15.2)	14.7 (12.7)	12.2 (11.5)
Physical exams in the past 2 years, %	95	95	97	95
Calcium intake from diet, mg/day	773.2 (217.0)	757.0 (211.5)	777.1 (204.3)	762.5 (205.4)
Calcium intake from supplement, mg/day	427.6 (331.2)	392.1 (320.2)	412.7 (324.5)	402.7 (325.7)
Alcohol use, g/day	5.7 (8.3)	5.4 (8.3)	4.1 (6.9)	3.6 (6.7)
Caffeine intake, mg/day	225.2 (160.6)	232.4 (162.5)	206.6 (155.3)	196.9 (149.9)
Current smokers, %	6	7	5	4
Self-reported sleep duration, hours	7.1 (1.1)	7.2 (1.2)	7.1 (1.3)	7.2 (1.4)
Ever estrogen HT, %	44	43	51	55
Duration of estrogen HT, months [/]	120.3 (98.0)	113.9 (96.3)	120.0 (105.8)	115.6 (94.8)
Ever estrogen-progestin HT, %	42	39	38	40
Duration of estrogen-progestin HT, months [/]	78.0 (55.5)	71.1 (54.3)	77.1 (56.9)	72.6 (52.5)
Nonbenzodiazepine sleep medication, %	7	6	10	11
Other sleep medication, %	4	4	8	11

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	OSA status			
	No OSA+no snoring	No OSA+snoring	OSA+no EDS	OSA+EDS
Thiazide diuretics, %	17	21	22	29
Loop diuretics, %	4	6	13	13
Bisphosphonate use, %	22	18	16	21

* Abbreviations: OSA: Obstructive sleep apnea. ESA: Excessive daytime sleepiness. HT: hormone therapy.
/ Among ever users.

Table 2.

Association of self-reported OSA status and related symptoms with vertebral fracture

	Cases	Person-years	Model 1	Model 2	Model 3
OSA diagnosis					
No	438	533994	1.00 (ref)	1.00 (ref)	1.00 (ref)
Yes	23	11117	2.22 (1.45, 3.41)	2.00 (1.29, 3.12)	1.88 (1.21, 2.93)
OSA status					
No OSA without snoring	364	444609	1.00 (ref)	1.00 (ref)	1.00 (ref)
No OSA with snoring	74	89385	1.07 (0.83, 1.38)	1.05 (0.81, 1.36)	1.02 (0.79, 1.32)
OSA without EDS	16	8492	1.98 (1.19, 3.29)	1.80 (1.07, 3.04)	1.70 (1.01, 2.87)
OSA with EDS	7	2625	3.24 (1.52, 6.91)	2.86 (1.31, 6.21)	2.56 (1.17, 5.59)

Model 1: Stratified by age and calendar time

Model 2: Model 1 + adjusted for race/ethnicity (white, non-white), BMI (<20.0, 20.0–24.9, 25.0–29.9, 30.0–34.9, 35.0–39.9, 40 kg/m²), waist circumference (<76.0, 76.0–87.9, 88.0–95.9, 96.0 cm, missing), smoking (never, past, current), alcohol intake (0, 0.1–4.9, 5.0–14.9, 15.0–29.9, 30.0 g/day), caffeine intake (in quintiles), physical activity, calcium intake from diet (in quintiles), calcium intake from supplements (in quintiles), regular physical examination (yes, no), sleep duration (<=5, 6, 7, 8, >=9 hours/day), duration of estrogen-only hormone therapy (no use, <5.0, 5.0–9.9, >=10 years), duration of estrogen plus progestin hormone therapy (no use, <5.0, 5.0–9.9, >=10 years), thiazide diuretic use (yes, no), loop diuretic use (yes, no), bisphosphonate use (yes, no), nonbenzodiazepine use (yes, no), other sleep medication use (yes, no), history of diabetes (yes, no), and history of hypertension (yes, no)

Model 3: Model 2 + number of falls (none, 1–2, 3 falls) and history of osteoporosis (yes, no)

Table 3.

Association of self-reported OSA status and related symptoms with hip fracture

	Cases	Person-years	Model 1	Model 2	Model 3
OSA diagnosis					
No	907	533528	1.00 (ref)	1.00 (ref)	1.00 (ref)
Yes	14	11127	0.78 (0.46, 1.32)	0.83 (0.49, 1.43)	0.81 (0.47, 1.40)
OSA status					
No OSA without snoring	784	444198	1.00 (ref)	1.00 (ref)	1.00 (ref)
No OSA with snoring	123	89330	0.91 (0.75, 1.10)	0.93 (0.77, 1.14)	0.92 (0.76, 1.12)
OSA without EDS	10	8500	0.73 (0.39, 1.37)	0.79 (0.42, 1.50)	0.77 (0.41, 1.46)
OSA with EDS	4	2627	0.87 (0.32, 2.34)	0.90 (0.33, 2.44)	0.87 (0.32, 2.36)

Model 1: Stratified by age and calendar time

Model 2: Model 1 + adjusted for race/ethnicity (white, non-white), BMI (<20.0, 20.0–24.9, 25.0–29.9, 30.0–34.9, 35.0–39.9, 40 kg/m²), waist circumference (<76.0, 76.0–87.9, 88.0–95.9, 96.0 cm, missing), smoking (never, past, current), alcohol intake (0, 0.1–4.9, 5.0–14.9, 15.0–29.9, 30.0 g/day), caffeine intake (in quintiles), physical activity, calcium intake from diet (in quintiles), calcium intake from supplements (in quintiles), regular physical examination (yes, no), sleep duration (<=5, 6, 7, 8, >=9 hours/day), duration of estrogen-only hormone therapy (no use, <5.0, 5.0–9.9, >=10 years), duration of estrogen plus progestin hormone therapy (no use, <5.0, 5.0–9.9, >=10 years), thiazide diuretic use (yes, no), loop diuretic use (yes, no), bisphosphonate use (yes, no), nonbenzodiazepine use (yes, no), other sleep medication use (yes, no), history of diabetes (yes, no), and history of hypertension (yes, no)

Model 3: Model 2 + number of falls (none, 1–2, 3 falls) and history of osteoporosis (yes, no)

Table 4.

Subgroup analysis of the associations between OSA and risk of vertebral and hip fractures¹

	Vertebral fracture			Hip fracture		
	Cases in OSA/ All cases	HR (95% CI)	P-interaction	Cases in OSA/ All cases	HR (95% CI)	P-interaction
BMI			0.26			0.25
<30 kg/m ²	9/366	1.42 (0.71, 2.84)		7/819	0.59 (0.27, 1.26)	
30 kg/m ²	14/95	2.41 (1.16, 5.02)		7/102	1.25 (0.54, 2.87)	
Waist circumference ²			0.71			0.04
<88 cm	5/194	2.21 (0.85, 5.75)		2/409	0.20 (0.03, 1.46)	
88 cm	12/201	1.23 (0.62, 2.44)		10/329	1.19 (0.60, 2.36)	
History of osteoporosis			0.03			0.83
No	14/174	3.08 (1.62, 5.84)		7/472	0.88 (0.41, 1.90)	
Yes	9/287	1.25 (0.60, 2.59)		7/449	0.70 (0.32, 1.52)	
Daytime sleepiness			0.23			0.82
No	16/417	1.82 (1.07, 3.09)		10/835	0.75 (0.40, 1.42)	
Yes	7/44	5.06 (0.94, 27.25)		4/86	0.99 (0.32, 3.09)	

¹ Stratified by age and calendar time, and adjusted for race/ethnicity (white, non-white), BMI (<20.0, 20.0–24.9, 25.0–29.9, 30.0–34.9, 35.0–39.9, 40 kg/m²), waist circumference (<76.0, 76.0–87.9, 88.0–95.9, 96.0 cm, missing), smoking (never, past, current), alcohol intake (0, 0.1–4.9, 5.0–14.9, 15.0–29.9, 30.0 g/day), caffeine intake (in quintiles), physical activity, calcium intake from diet (in quintiles), calcium intake from supplements (in quintiles), regular physical examination (yes, no), sleep duration (<5, 6, 7, 8, ≥9 hours/day), duration of estrogen-only hormone therapy (no use, <5.0, 5.0–9.9, ≥10 years), duration of estrogen plus progestin hormone therapy (no use, <5.0, 5.0–9.9, ≥10 years), thiazide diuretic use (yes, no), loop diuretic use (yes, no), bisphosphonate use (yes, no), nonbenzodiazepine use (yes, no), other sleep medication use (yes, no), history of diabetes (yes, no), and history of hypertension (yes, no), number of falls (none, 1–2, 3 falls) and history of osteoporosis (yes, no)

² Among a subset of participants with waist circumference measures