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Hypoxia During Sleep and the Risk of Falls and Fractures in Older Men: The Osteoporotic Fracture in Men Sleep Study

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Abstract

Objectives—Sleep disturbances are common and have been linked to a greater risk of fractures and falls but whether nocturnal hypoxia contributes is unknown.

Design, Setting, Participants—To test the hypothesis that low arterial oxygen saturation during sleep is associated with a greater risk of falls and fractures, we studied 2911 men age 67 or older.

Measurements—The primary exposure measure was percentage of sleep time with arterial oxygen saturation <90% measured by polysomnography. The main outcome measures were

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Conflict of Interest:

Jane A Cauley, Susan Redline, Howard A Fink, Eric S Orwoll, Katie L Stone and Terri L Blackwell have no conflicts to reports. Kristine E Ensrud serves as a consultant on a Data Monitoring Committee for Merck Sharpe & Dohme. Sonia Ancoli-Israel serves as consultant for Astra Zeneca, Ferring Pharmaceuticals Inc., GlaxoSmithKline, Hypnocore, Johnson & Johnson, Merck, NeuroVigil, Inc., Orphagen Pharmaceuticals, Pfizer, Philips, Purdue Pharma LP and Sanofi-Aventis.

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Study concept and design: Jane A Cauley, Susan Redline, Sonia Ancoli-Israel. Acquisition of data: Jane A Cauley, Susan Redline, Kristine E Ensrud, Eris S Orwoll, Katie L Stone. Analysis and interpretation of data: Jane A Cauley, Susan Redline and Terri L Blackwell. Drafting of the manuscript: Jane A Cauley. Critical revision of the manuscript for important intellectual content: Terri L Blackwell, Susan Redline, Kristine E Ensrud, Sonia Ancoli-Israel, Howard A Fink, Eris S Orwoll and Katie L Stone. Takes responsibility for the integrity of the data analysis. Jane A Cauley, Terri L Blackwell. Approving final version of manuscript: Jane A Cauley, Terri L Blackwell, Susan Redline, Kristine E Ensrud, Sonia Ancoli-Israel, Howard A Fink, Eric S Orwoll and Katie L Stone.

incident falls within 1 year and incident non-spine fractures over an average follow-up of 6.8 years.

Results—Men with 10% sleep time at arterial oxygen saturation <90% were older, reported more comorbidities, had poorer physical function and were more likely to have sleep disordered breathing than men with <10% sleep time at arterial oxygen saturation <90%. After multivariate adjustment, men with 10% of sleep time with arterial oxygen saturation <90% had an increased risk of having 1 and 2 falls compared to those with <1% of sleep time with <90% arterial oxygen saturation (relative risk = 1.25; 95% confidence interval = 1.04, 1.51) and (relative risk = 1.43; 95% CI = 1.06, 1.92), respectively. Men with an increasing percentage of sleep time with arterial oxygen saturation <90% had a 30-40% increased risk of non-spine fracture compared to those with normal nocturnal hypoxia in models adjusting for sleep disorder breathing.

Conclusion—Increasing hypoxia during sleep may represent a novel risk factor for falls and fractures in older men. Interventions aimed at decreasing nocturnal hypoxia may decrease falls and fractures.

Keywords

nocturnal hypoxia; fractures; falls; mortality; older men

INTRODUCTION

Sleep disordered breathing (SDB) is a common disorder among older adults, affecting up to 60%.¹ Intermittent hypoxia is the hallmark of obstructive sleep apnea (OSA) and has been linked to a number of adverse cardiovascular consequences.²⁻⁴ Hypoxia has also been linked to poor physical function.⁵ To our knowledge, no previous study has linked nocturnal hypoxia to the risk of fractures and falls. A central question is the role of overnight hypoxemia as opposed to SDB in falls and fractures. Hypoxic stress could influence bone formation⁶ by itself above and beyond an effect of SDB.

The objective of the current analysis was to test the pre-specified hypothesis that nocturnal hypoxia increases the risk of falls and fractures and that these associations would be independent of SDB. We tested these hypotheses in a multicenter cohort of older men (Outcomes of Sleep Disorders in Older Men: Study of Osteoporotic Fractures in Men (MrOS) Sleep Study).

METHODS

Participants

From 2000 through 2002, 5,994 men at least 65 years of age were recruited from population based listings in: Birmingham, Alabama; Minneapolis, Minnesota; Palo Alto, California; the Monongahela Valley near Pittsburgh, Pennsylvania, Pennsylvania; Portland, Oregon; and San Diego, California.^{7, 8} Men with a history of bilateral hip replacement and men who were unable to walk without the assistance of another person were excluded.

From 2003 through 2005, the MrOS Sleep Study recruited 3,135 (105% of recruitment goal) participants for a comprehensive sleep assessment. Of the 2860 who did not participate in

the MrOS sleep examination, 1997 declined participation, 150 were ineligible, 349 died, 39 terminated prior to the visit, and 324 were not contacted because recruitment goals had been achieved. Of the 3,135 who completed the MrOS sleep examination, 2,911 (93%) had technically adequate in-home polysomnography (PSG) data and are included in these analyses.

All men provided written informed consent, and the study was approved by the Institutional Review Board at each site.

Outcomes

Information on falls and fractures that occurred after the sleep visit was obtained by our postcard follow-up system. Postcards were mailed every four months; >97% of these contacts were complete. We included all falls that occurred within one year of the sleep examination. All fractures were confirmed by radiographic report. All fractures that occurred after the sleep examination up to August 2012 were included in this analysis, with an average follow-up of 6.8 $\pm$ 1.7 years (range 9 days to 8.4 years).

Collection of Polysomnography Data—In home sleep studies were completed using unattended, portable PSG (Safiro model, Compumedics, Inc®, Melbourne, Australia). The recording montage was as follows: C₃/A₂ and C₄/A₁ electroencephalograms, bilateral electrooculograms and a bipolar sub mental electromyogram to determine sleep stages; thoracic and abdominal respiratory inductance plethysmography to determine respiratory effort; airflow (by nasal-oral thermocouple and nasal pressure cannula); finger pulse oximetry (Nonin pulse oximeter, Nonin, MN); lead I EKG; body position (mercury switch sensor); and bilateral leg movements (piezoelectric sensors). Centrally-trained and certified staff performed home visits to set up the unit, verify the values of the impedances for each channel, confirm calibration of position sensors and note any problems encountered during set up, similar to the protocol used in the Sleep Heart Health Study.⁹ Staff returned the next morning to collect the equipment and download the data to the Central Sleep Reading Center (Cleveland, OH) for scoring by a trained technician using standard criteria.^{10, 11}

Wake after sleep onset (WASO), a measure of sleep fragmentation, was defined as the minutes scored awake during the sleep period after sleep onset. Resting arterial oxygen saturation (SaO₂) level was determined just prior to sleep using the PSG recorder's oximeter finger pulse. The percent of sleep time with SaO₂ <90% was calculated after periods of artifact were manually deleted. Any saturations <90% are considered clinically abnormal but to allow for some misclassification, we considered subjects with 0 to <1% SaO₂ <90% as normal; these men formed the referent group. The remaining men were further divided a priori into three groups based on clinical judgment: percent of sleep time <90%, 1 to <3.5%; 3.5 to <10%; 10 to 97%.

Hypopneas were scored using criteria developed for the Sleep Heart Health Study⁹ and are consistent with current recommendations.¹² Briefly, the hypopnea definition requires a 30% greater drop in flow for 10 seconds or longer association with greater than 3% oxygen desaturation. The apnea hypopnea index (AHI) was calculated by dividing the average number of apneas and hypopneas by the total sleep time. SDB was defined as AHI $\geq$ 15.¹³

Other Measurements

Questionnaire data included information on demographic factors, lifestyle habits, self-reported health, race/ethnicity and fall and medical history. Physical activity was assessed by the Physical Activity Scale in the Elderly (PASE).¹⁴ Functional status was measured with information on five Instrumental Activities of Daily Living (IADL).^{15, 16} The occurrence of non-spine fracture after the age of 50 was calculated by combining self-reported fracture data for the time period up to the start of the MrOS baseline visit and adjudicated fracture data from the time between the baseline visit and the sleep examination.

Participants were asked to complete the Epworth Sleepiness Scale (ESS) to classify subjective daytime sleepiness among people with sleeping disorders. Scores ranged from 0–24, with a standard cutoff over 10 indicating excessive daytime sleepiness.¹⁷

At the clinic visit body weight (kg) was measured in light indoor clothing on a standard balance beam or digital scale. Participants were asked to rise from a chair without using their arms and complete five chair stands. To test balance, men were asked to stay within a narrow walking path (20 cm) over 6m. If a participant had three or more deviations from the path or no successful attempts, the trial was considered unsuccessful. Participants were asked to bring all current prescription and nonprescription medications used within the last 30 days. All medications recorded by the clinics were stored in an electronic medications inventory database (San Francisco Coordinating Center, San Francisco, CA). Each medication was matched to its Ingredient(s) based on the Iowa Drug Information Service Drug Vocabulary (College of Pharmacy, University of Iowa, Iowa City, IA).¹⁸

BMD (g/cm^2) of the total hip was measured using dual-energy x-ray absorptiometry (QDR 4500W, Hologic Inc., Waltham MA). Standardized procedures for participant positioning and scan analysis were executed for all scans. Cross-calibration studies performed found no linear differences across scanners.⁸

Statistical Analyses

Characteristics of men across categories of nocturnal hypoxia were compared using analysis of variance, Kruskal-Wallis tests or chi-square tests, Table 1. Loss to follow-up for fracture outcomes was addressed by censoring follow-up time to the last contact in proportional hazards models. The 22 men with missing follow-up for the falls outcomes were not included in the analysis. Modified Poisson regression with a robust error variance was used to calculate the relative risk (RR) and 95% CI intervals of experiencing at least 1 fall and 2 or greater falls one year after the sleep assessments, Table 2.¹⁹ Cox proportional hazards models were used to calculate the relative hazard (RH) of fracture and 95% CIs, Table 3. Base models included adjustments for age, clinic and race. In multivariate models (MV) we additionally adjusted for weight, comorbidities, self-reported health status, number of IADL impairments, neuromuscular function, lifestyle, total sleep time and WASO. MV models for fracture were also adjusted for BMD, fall history and corticosteroid use. Multivariable models for falls also adjusted for benzodiazepine use. To test whether the associations between nocturnal hypoxia and outcomes were mediated by SDB, we adjusted for the AHI. In a sensitivity analysis, we also excluded men with low daytime resting at SaO_2 92% and

reran the falls and fracture analyses. Secondary analyses were performed truncating follow-up for an individual to the start of CPAP or oxygen therapy for SDB. For all analyses, categorical variables were used as described and quantitative characteristics, as continuous variables.

All significance levels reported were two-sided and all analyses were conducted using SAS version 9.2 (SAS Institute Inc, Cary, NC). No imputations were done for missing values.

RESULTS

A total of 360 (12.4%) men spent 10% or more of their total sleep time at $\text{SaO}_2 < 90\%$, Table 1. Men with the nocturnal hypoxia during sleep were also more likely to have abnormal resting SaO_2 and an AHI indicating SDB. These men were older, more likely to be Caucasian, to smoke, to use their arms to stand and to be unable to complete the narrow walk compared to men with normal SaO_2 during sleep. These men also had lower levels of alcohol consumption and physical activity, were less likely to report good to excellent health and had higher levels of IADL impairments. Compared to men with normal SaO_2 levels during sleep, those with the greatest nocturnal hypoxia weighed on average about 10 kg more, were more likely to report diabetes, chronic obstructive pulmonary disease (COPD), congestive heart failure (CHF), and a fall in the past 12 months but there was no difference in overall cardiovascular disease (CVD), stroke, Parkinson's disease or fracture history. Use of osteoporosis medications was generally low but was more prevalent in men with normal SaO_2 during sleep. Current use of corticosteroids was greater in men with greatest nocturnal hypoxia. Use of sleep medications did not differ across nocturnal SaO_2 . There was no difference in antipsychotic medication use or opioid use across nocturnal SaO_2 but men with the greatest nocturnal hypoxia were more likely to report benzodiazepine use. Total sleep time was lower and sleep fragmentation was higher for those men with the worst SaO_2 levels during sleep.

Twenty four (0.8%) men reported continuous positive airway pressure (CPAP) and 8 (0.3%) oxygen therapy at the sleep visit. A total of 272 (9.3%) started CPAP and 127 (4.3%) oxygen therapy over the follow-up period.

Falls—A total of 820 (28.4%) men reported at least one fall one year after the sleep visit; 396 (13.8%) reported 2 or more falls. After minimal adjustment, compared to the referent group, men with $\text{SaO}_2 < 90\%$ for 10% of their sleep time were more likely to experience a fall (RR=1.42; 1.21–1.67, p trend=0.0001) and 2 falls (RR=1.62; 1.25–2.10, p trend=0.0003), Table 2. In the fully adjusted model, men with the greatest nocturnal hypoxia had 25% significant increased odds of experiencing a fall and 43% significant increased odds of experiencing 2 or more falls. A significant graded response was evident between increasing nocturnal hypoxia and fall risk. These associations were independent of resting SaO_2 . In models adjusted for AHI or excluding men who started CPAP or oxygen, the associations were similar in magnitude.

Fractures

After an average of almost 7 years, 362 (12.4%) men experienced a confirmed incident non-spine fracture. After minimal adjustment, there was a trend whereby increasing nocturnal hypoxia with $\text{SaO}_2 < 90\%$ was associated with an increased risk of fracture, but it was not significant ($p=0.12$), Table 3. Results were similar after further MV adjustment (p trend=0.08). After adjustment for AHI, there was a significant trend of increasing fracture risk with increasing nocturnal hypoxia, $p=0.047$. Exclusion of men with low resting SaO_2 yielded similar results. In models truncating to start of CPAP or oxygen treatment, increasing sleep time with $\text{SaO}_2 < 90\%$ was associated with a 30 to 40% increased risk of fracture (p trend=0.049).

DISCUSSION

Among a large population of community-dwelling older men, greater sleep time with $\text{SaO}_2 < 90\%$ was associated with an increased risk of falls and fractures. These results were independent of age, obesity, physical function and important comorbidities. The associations between nocturnal hypoxia and falls and fractures were also independent of AHI suggesting that overnight intermittent hypoxia alone increases the risk of falls and fractures. Nocturnal hypoxia and the AHI were correlated ($r=0.59$) but not perfectly suggesting that biological effects of hypoxia could be distinct from SDB. Our results suggest that greater sleep time at lower oxygen saturation maybe a likely mechanism linking sleep disorders to falls and fractures. Our results extend the deleterious effects of various sleep disorders on CVD to include falls and fractures.

Poor respiratory function and COPD have been linked to lower BMD and an increased risk of osteoporosis.^{20–22} Airflow obstruction was also shown to be a risk factor for osteoporosis.²³ Long-term fracture risk was elevated in those with adult onset asthma.²⁴ It is not known if these associations are direct but our results suggest that intermittent hypoxia during sleep may contribute.

Men with greater sleep time at low oxygen saturation were older, more likely to smoke (although overall smoking prevalence was quite low) and reported more diabetes, COPD and CHF, all of which could have contributed to an increased risk of falls and fractures. These men also reported more impairments and poorer health status. Sleep disturbances including poor sleep quality, lower sleep efficiency, prolonged sleep latency and SDB have been shown to be independently associated with frailty.²⁵ Hypoxia during sleep and SDB were also associated with poor functional recovery after a stroke.^{26, 27} Thus, poor neuromuscular function and comorbidities may have contributed to our findings but our results were independent of these factors. Nevertheless, it is possible that prospective declines in physical function could have contributed to the increased risk of fractures. We limited our fall follow-up to one year and it is unlikely that declines in physical function could have contributed to our findings with respect to falls.

We previously reported that daytime napping was associated with an increased risk of falls.²⁸ It is possible that individuals with low SaO_2 during sleep may nap more which may

have contributed to their increased risk of falls. However, we found no difference in excessive daytime sleepiness by nocturnal hypoxia.

Testosterone levels have been linked with less healthy sleep in older men. Lower levels of testosterone were associated with more sleep time with $\text{SaO}_2 < 90\%$.²⁹ Although this association was largely explained by obesity, body weight may act directly or indirectly via low testosterone. Low testosterone has also been linked to an increased risk of falls³⁰ and poor physical function.³¹ Hypogonadal men also have an increased risk of falls³² and fracture.³³ Thus, sex steroid hormones may underlie the associations with falls and fractures that we observed.

There may be several additional mechanisms linking lower $\text{SaO}_2 < 90\%$ during sleep to fractures. Experimental evidence suggests that hypoxemia may promote osteoblastic differentiation and subsequent transformation to osteocytes.³⁴ These in-vitro findings suggest that oxygen tension could be an important regulator of osteoblasts. But, it is currently unknown if hypoxia influences the lifespan and apoptosis of osteocytes. Osteoblasts are sensitive to oxygenation and respond to hypoxia by activating the hypoxia-inducible factor pathway.³⁵ Hypoxia has also been linked to oxidative stress³⁶ which in turn could increase the accumulation of advanced glycation end products in bone, further altering the structure of collagen.³⁷ SDB has also been associated with increases in inflammation.³⁸ A recent meta-analysis demonstrated that treatment for sleep apnea with CPAP improved levels of inflammatory markers.³⁹ Inflammation has also been linked to fractures^{40, 41} and could also contribute to the observation that greater sleep time with $\text{SaO}_2 < 90\%$ influences the risk of fractures.⁵

This study has a number of strengths, including large sample size, enrollment of community-dwelling older men not selected on the basis of sleep disorders, objective sleep parameters and prospective design. Analyses were adjusted for multiple potential confounders. Fracture outcomes were confirmed by review of medical records.

However, this study has several limitations. Participants were predominantly Caucasian men, and findings might not apply to other groups. Analyses were adjusted for several factors, but the possibility of residual confounding cannot be eliminated. Participants did not have a clinical evaluation for primary sleep disorders such as restless leg syndrome or objective measures of obstructive lung disease.

In conclusion, increasing sleep time at $\text{SaO}_2 < 90\%$ was associated with an increased risk of falls and fractures independent of physical function, comorbidities and AHI. Nocturnal hypoxia may represent a novel risk factor for falls and fractures. The increasing trends observed with increasing nocturnal hypoxia suggest that interventions aimed at decreasing nocturnal hypoxia may decrease falls and fractures.

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Table 1

Baseline characteristics across oxygen saturation during sleep: Percent of sleep time with $\text{SaO}_2 < 90\%$ ^a.

Characteristics	Oxygen saturation levels				P-value
	0 - <1%	1 - <3.5%	3.5 - <10%	10 - 97%	
N (%)	(1410)	(767)	(374)	(360)	---
Age (yr)	76.1 ± 5.6	76.5 ± 5.5	76.7 ± 5.6	76.9 ± 5.4	0.035
Non-Caucasian	150 (10.6)	68 (8.9)	24 (6.4)	28 (7.8)	0.049
Weight (kg)	79.0 ± 11.7	82.8 ± 12.7	85.6 ± 13.7	89.9 ± 14.5	<0.0001
Smoking					
Current	27 (1.9)	14 (1.8)	5 (1.3)	12 (3.3)	0.011
Past	788 (55.9)	457 (59.6)	225 (60.2)	233 (64.7)	
Physical activity ^b	148.3 ± 71.3	148.1 ± 71.4	140.3 ± 72.4	135.8 ± 69.3	0.002
Alcohol use (drinks/wk)	3.5 ± 4.1	3.5 ± 4.4	3.3 ± 4.3	2.9 ± 4.2	0.002
Uses arms to stand	63 (4.5)	44 (5.7)	33 (8.8)	39 (10.9)	<0.0001
Unable to complete narrow walk	157 (11.5)	103 (14.2)	65 (20.2)	67 (20.0)	<0.0001
Total Hip BMD (g/cm ²)	0.94 ± 0.14	0.97 ± 0.14	0.96 ± 0.14	0.96 ± 0.14	0.002
Medical history					
CVD ^c	452 (32.2)	254 (33.2)	130 (34.9)	132 (36.8)	0.36
Diabetes	155 (11.0)	123 (16.0)	48 (12.9)	61 (16.9)	0.001
COPD	55 (3.9)	29 (3.8)	21 (5.6)	46 (12.8)	<0.0001
CHF	66 (4.7)	49 (6.4)	25 (6.7)	34 (9.4)	0.006
Stroke	55 (3.9)	31 (4.0)	15 (4.0)	10 (2.8)	0.75
Parkinson's disease	24 (1.7)	7 (0.9)	1 (0.3)	4 (1.1)	0.11
Fell past 12 months	413 (29.3)	208 (27.1)	122 (32.7)	139 (38.6)	0.0007
Non-spine fracture since age 50	345 (24.5)	202 (26.3)	98 (26.2)	96 (26.7)	0.72
Medications					
Osteoporosis ^d	63 (4.5)	25 (3.3)	24 (6.4)	11 (3.1)	0.054
Sleep ^e	30 (2.1)	16 (2.1)	5 (1.3)	8 (2.2)	0.79
Corticosteroids ^f	130 (9.3)	63 (8.4)	28 (7.6)	48 (13.4)	0.02
Benzodiazepine use ^g	53 (3.8)	37 (4.8)	17 (4.6)	26 (7.2)	0.045

Characteristics	Oxygen saturation levels				P-value
	0 - <1%	1 - <3.5%	3.5 - <10%	10 - 97%	
Antipsychotic medication use ^h	12 (0.9)	9 (1.2)	2 (0.5)	4 (1.1)	0.72
Opioid use ⁱ	53 (3.8)	40 (5.2)	13 (3.5)	19 (5.3)	0.26
Number of IADL impairments (0-5)	0.3 ± 0.8	0.4 ± 0.8	0.4 ± 0.9	0.6 ± 1.1	<0.0001
Good to excellent health	1238 (87.8)	682 (88.9)	314 (84.2)	290 (80.6)	0.0003
Resting SaO ₂ level 92%	24 (1.7)	36 (4.7)	22 (5.9)	79 (21.9)	<0.0001
Sleep					
Excessive daytime sleepiness	177 (12.6)	91 (11.9)	53 (14.2)	59 (16.4)	0.16
AHI ≥15	265 (18.8)	432 (56.3)	287 (76.7)	280 (77.8)	<0.0001
Total sleep time, min	357.3 ± 69.7	358.3 ± 67.9	351.1 ± 71.1	347.2 ± 69.2	0.032
Sleep fragmentation (WASO), min	109.8 ± 64.3	117.6 ± 66.8	119.0 ± 67.8	130.0 ± 72.2	<0.0001

Mean ± SD or n (%).

^aNumber of men with missing data: weight, (2); physical activity, (1); alcohol use, (15); users arms to stand, (3); unable to do narrow walk, (150); total hip BMD, (28); history of CVD, (7); history of diabetes, COPD, CHF, stroke, Parkinson's disease, falls, (1); non-spine fracture after age 50, (4); corticosteroid use, (12); good to excellent health status, (2).

^bPhysical activity in the elderly scale (PASE).

^cCVD: history of MI, angina, CHF, cardiac bypass surgery, angioplasty, pacemakers.

^dOsteoporosis medications: fluorides, calcitonin, bisphosphonates, raloxifene, or teriparatide.

^eSleep medications: non-benzodiazepines, non-barbiturate sedatives, hypnotics.

^fCorticosteroids: oral, nasal or inhaled.

^gBenzodiazepine medication: estazolam, alprazolam, temazepam, lorazepam, triazolam, oxazepam, midazolam, chlordiazepoxide, clonazepam, flurazepam, and clonazepam.

^hAntipsychotic medication: hydroxyzine, resperidone, quetiapine, olanzapine, aripiprazole, clozapine, perphenazine.

ⁱOpioid medication: opioid analgesics, codeine, dihydrocodeine, hydrocodone.

Table 2

The association between sleep time with SaO₂<90% and falls: Relative Risk and 95% confidence intervals.

Models	0 – <1%	Oxygen saturation levels			P trend
		1 to <3.5%	3.5 to <10%	10 – 97%	
>= 1 Fall, n (%)	359 (25.7)	210 (27.4)	116 (31.4)	135 (38.0)	---
>= 2 Falls, n (%)	166 (11.9)	101 (13.3)	58 (15.8)	71 (20.1)	---
Base Model ^a					
>= 1 Fall	1.0	1.05 (0.91, 1.21)	1.19 (0.99, 1.42)	1.42 (1.21, 1.67)	<0.0001
>= 2 Falls	1.0	1.09 (0.87, 1.37)	1.28 (0.97, 1.69)	1.62 (1.25, 2.1)	0.0003
Full MV Model ^b					
>= 1 Fall	1.0	1.00 (0.86, 1.16)	1.09 (0.90, 1.31)	1.25 (1.04, 1.51)	0.03
>= 2 Falls	1.0	1.04 (0.82, 1.33)	1.16 (0.86, 1.57)	1.43 (1.06, 1.92)	0.02
Full MV Model ^b + AHI					
>= 1 Fall	1.0	0.99 (0.85, 1.16)	1.08 (0.88, 1.32)	1.24 (1.01, 1.52)	0.06
>= 2 Falls	1.0	1.02 (0.79, 1.32)	1.12 (0.81, 1.55)	1.36 (0.97, 1.91)	0.10
Full MV Model ^b excluding men w/resting SaO ₂ 92%					
>= 1 Fall	1.0	0.98 (0.84, 1.15)	1.10 (0.91, 1.34)	1.25 (1.02, 1.53)	0.04
>= 2 Falls	1.0	1.04 (0.81, 1.34)	1.21 (0.89, 1.65)	1.39 (1.00, 1.93)	0.04
Full MV Model ^b dropping CPAP/oxygen therapy users in 1st yr of use					
>= 1 Fall	1.0	1.00 (0.85, 1.16)	1.05 (0.86, 1.28)	1.24 (1.02, 1.51)	0.06
>= 2 Falls	1.0	1.01 (0.79, 1.30)	1.13 (0.82, 1.55)	1.29 (0.94, 1.77)	0.12

^aBase model: age, race, clinic.

^bMV=Multivariate model: Base + weight, health status, history of COPD, CHF, and diabetes, # IADL impairments, uses arms to stand, unable to complete narrow walk, smoking, alcohol consumption, physical activity, benzodiazepine use, total sleep time and sleep fragmentation.

Reference = for >=1 fall, those who did not fall within the 1 year of follow-up; for >=2 falls, those who had none or 1 fall.

Table 3

The association between sleep time with $\text{SaO}_2 < 90\%$ and risk of non-spine fracture: Relative hazards and 95% confidence intervals.

Models	Oxygen saturation levels				P trend
	0 - <1%	1 to <3.5%	3.5 to <10%	10 - 97%	
Non-spine fractures, n (%)	167 (11.8)	97 (12.7)	49 (13.1)	49 (13.6)	---
Base Model ^a	1.00	1.1 (0.86, 1.42)	1.19 (0.86, 1.64)	1.26 (0.91, 1.75)	0.12
Full MV Model ^b	1.00	1.26 (0.97, 1.65)	1.29 (0.92, 1.82)	1.29 (0.89, 1.85)	0.08
Full MV Model ^b + AHI	1.00	1.31 (0.99, 1.72)	1.38 (0.96, 2.00)	1.42 (0.94, 2.15)	0.047
Full MV Model ^b excluding men w/baseline $\text{SaO}_2 < 92\%$	1.00	1.25 (0.95, 1.64)	1.29 (0.91, 1.84)	1.36 (0.92, 2.02)	0.056
Full MV Model ^b truncated follow-up to start of CPAP/oxygen therapy use	1.00	1.24 (0.94, 1.64)	1.41 (1.00, 2.00)	1.31 (0.88, 1.95)	0.049

^aBase model: age, race, clinic.

^bMV = Multivariate model: Base + weight, health status, history of COPD, CHF, diabetes and falls, # IADL impairments, uses arms to stand, unable to complete narrow walk, smoking, alcohol consumption, physical activity, total sleep time, sleep fragmentation and total hip BMD.