Characteristics of self-reported sleep and the risk of falls and fractures: The Women's Health Initiative (WHI)

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Sleep disturbances are common and may influence falls and fracture directly by influencing bone turnover and muscle strength or indirectly through high comorbidity or poor physical function. To investigate the association between self-reported sleep and falls and fractures, we prospectively studied 157,306 women in the WHI using information on sleep quality, sleep duration, and insomnia from questionnaires. Annual self-report of falling ≥2 times (i.e., "recurrent falling") during each year of follow-up was modeled with repeated measures logistic regression models fit by generalized estimating equations. Cox proportional hazards models were used to investigate sleep disturbance and time to first fracture. We examined the risks of recurrent falls and fracture by sleep duration with 7 hours as referent. We examined the risks across categories of sleep disturbance, insomnia status, and sleep quality. The average follow-up time was 7.6 years for falls and 12.0 years for fractures. In multivariable adjusted models, including adjustment for comorbidity, medications and physical function, women who were short (≤5 hours) and long (≥10 hours) sleepers had increased odds of recurrent falls (odds ratio (OR) = 1.28, 95% confidence interval (CI) 1.23-1.34 and OR=1.25, 95% CI 1.09-1.43, respectively). Poor sleep quality, insomnia and more sleep disturbances were also associated with an increased odds of recurrent falls. Short sleep was associated with an increased risk of all fractures, and upper limb, lower limb and central body fractures but not hip fractures, with hazard ratios ranging from 1.10-1.13, $p<0.05$. There was little association between other sleep characteristics and fracture. In conclusion, short and long sleep duration and poor sleep quality were independently associated with increased odds of recurrent falls. Short sleep was associated with modest increase in fractures. Future long-term trials of sleep interventions should include falls and fractures as endpoints.

Words = 290 (allowed, 300 words)

Introduction

Sleep disturbances are common in older adults, with up to 36-69% of older adults reporting sleep disturbances [1]. Sleep disturbances not only reduce quality of life but have been linked to physical functional impairment [2], depression [3], and an increased risk of mortality [4], type 2 diabetes [5], cardiovascular disease [6], cancer [7] and cognitive decline [8]. In contrast, much less is known about the relationship of sleep disturbances with the risk of falls and fractures.

Previous studies have reported associations between napping [9,10]; short sleep duration [9,11], long sleep duration [11] and excessive daytime sleepiness with an increased risk of falls [12]. However, in general these prospective studies limited follow-up for falls to a single year. A cross-sectional study showed a higher risk of osteoporosis defined by T-scores or self-reported osteoporosis among those reporting <6 hours sleep duration [13]. A retrospective case-control study also reported an association between sleep disturbance and hip fracture in men but the authors only adjusted for age and body mass index [14]. To our knowledge, there are 3 prospective studies of sleep and fractures. In older women, self-reported napping and long sleep duration were associated with an increased risk of fracture [10]. In the Osteoporotic Fracture in Men Study (MrOS), greater nocturnal hypoxemia was association with an increased risk of falls and fractures [15]. In the Malmo Preventive Study of middle aged men and women, self-reported premature awakening was associated with a higher risk of fractures in both men and women [16] but these associations were attenuated in the multivariate (MV) models. Another study from Malmo reported a significant 50% increased risk of hip fracture in men (but not women) with premature awakening compared to men without premature awakening [17]

An association between sleep and fracture is, indeed, biologically plausible [18]. As reviewed in Swanson et al; the diurnal rhythm of bone turnover is likely important for bone remodeling.

Poor sleep may disrupt this rhythm and/or affect bone metabolism through other mechanisms and predispose individuals to fracture. Sleep disturbances may affect bone resorption directly via hypoxemia, inflammation, increased sympathetic tone, alterations in melatonin and/or other hormonal factors [18]. Sleep disturbances may also increase the risk of falls and fractures by increasing inflammation, a risk factor for fractures [19] but may also lead to decreases in muscle strength and physical function which have been linked with falls and fractures [20,21]. In the Osteoporotic Fractures in Men (MrOS) Sleep Study, prolonged wakefulness after sleep onset (>90 mins), poor sleep efficiency and hypoxemia were each associated with slower walking speed [12]. Sleep disturbances may indirectly influence falls and fractures through several additional mechanisms including vitamin D deficiency, hypogonadism, obesity, insulin resistance, cognitive impairments, depression and medication use [18]. Poor self-reported sleep may also be a marker of chronic disease and polypharmacy which are both strong risk factors for falls and fractures [22].

In the current analysis, we prospectively test the hypothesis that women with self-reported sleep issues specifically short or long sleep duration, poor sleep quality, greater sleep disturbances and insomnia will have an increased risk of recurrent falls and fractures, independent of established risk factors.

Material and Methods

Study population

The study population includes all women enrolled in the Women's Health Initiative (WHI). The WHI, carried out at 40 U.S. clinical centers, is a study of postmenopausal women aged 50–79 years and free of serious medical conditions at baseline (1993-1998) [23-26]. The current analysis

used data from participants in the WHI Observational Study (WHI-OS) and WHI Clinical Trials (WHI-CT). The WHI-OS was designed to examine important causes of morbidity and mortality in postmenopausal women [24]. The WHI-CTs examined the effects of menopausal hormone therapy (WHI Hormone Therapy Trials), calcium and vitamin D supplementation (WHI CaD Trial), and a low-fat eating pattern (WHI Dietary Modification Trial) [23]. The WHI-OS and WHI-CT main studies were conducted between 1993 and 2005. Of 150,076 participants who were in active follow-up at the end of the main studies, 76.9% consented to participate in an extension study conducted between 2005 and 2010 and 86.9% of those eligible in Extension Study 2, 2010-2020.

Of the 93,676 WHI-OS participants and 68,132 WHI-CT participants enrolled, we excluded data from 878 participants who provided no follow-up information, 948 with no fall data and 605 participants who provided no information on sleep, resulting in an analytic sample of 157,306 participants.

Assessment of self-reported sleep characteristics

All self-reported sleep characteristics including information on sleep duration, sleep quality, sleep disturbance level and insomnia were collected on baseline questionnaires. Participants were asked: "About how many hours of sleep did you get on a typical night during the last 4 weeks?" Item response choices were 5 or less hours, 6 hours, 7 hours, 8 hours, 9 hours, or 10 or more hours.

A sleep disturbance construct was developed using the WHI Insomnia Rating Scale (WHIIRS) [27,28]. The five-item sleep disturbance scale included questions on whether participants over the past 4 weeks had trouble falling asleep, woke up several times at night, woke up earlier than

planned and had trouble getting back to sleep after awakening early. Response categories were as follows: (0) no, not in the past 4 weeks; (1) yes, less than once per week; (2), yes, 1-2 times per week; (3) yes, 3 or 4 times per week and (4) yes, 5 or more times per week. The sleep disturbance construct also included overall sleep quality: (0), very sound or restful; (1), sound or restful; (2), average quality; (3), restless or (4), very restless. Possible scores on the WHIIRS ranged from 0 to 20, with scores >9 indicating high risk for insomnia [27]. This sleep disturbance scale was also categorized in quartiles as 0-3, 4-6, 7-10 and ≥11. THE WHIIRS consisting of the questions on sleep disturbances and overall sleep quality has been validated [27,28]. Reliability of the WHIIRS was estimated using a re-sampling approach; the mean alpha coefficient was 0.78. Test reliability coefficients were 0.96 for same day administration. A between group difference of approximately 0.5 for a standard deviation on the WHIIRS may be clinically meaningful [27].

Falls

Women were asked on annual self-reported health updates, "How many times did you fall and land on the floor or ground (do not include falls due to sports activities such as snow or water skiing or horseback riding)". The falls outcome was defined as annually repeated assessment of self-report of falling ≥2 times in the past year (recurrent falls), similar to a previous WHI report [29]. Self-reporting of 2 or more falls in a given year was considered an event. Self-report of falls was discontinued during the extension phase, limiting the average follow-up for falls to 7.6 years.

Outcomes: Fracture

Information regarding incident fractures was obtained semi-annually for the WHI-CT and annually for the WHI-OS. At each assessment, questionnaires asked whether participants had

experienced a first fracture event since the previous visit: "Has a doctor told you for the first time that you have a new broken, fractured, or crushed bone? Which bone(s) did you break, fracture, or crush?" Response choices included: hip, upper leg (not hip), pelvis, knee (patella), lower leg or ankle, foot (not toe), tailbone (coccyx), spine or back (vertebra), upper arm or shoulder, elbow, lower arm or wrist, hand (not finger), jaw, nose, face, and/or skull, ribs and/or chest or breast bone, and "other".

All hip fractures were adjudicated by trained staff using medical record review for both WHI-OS and WHI-CTs during the main study and Extension 1. Adjudication of non-hip fractures was limited to a subset of participants during the main WHI study [30], including 1) fractures among participants of the WHI Clinical Trials and 2) fractures among participants in the WHI Bone Mineral Density (BMD) Cohort. Any fractures that occurred during the WHI Extension 2 phase in the WHI-OS and WHI-CTs were self-reported.

All fractures reported up to 9/30/2015 were included in these analyses for an average follow-up of 12.0 years. We studied all fractures (any fractures except those of the fingers, toes, ribs, coccyx, face, skull and sternum), hip fractures, upper limb fractures (elbow, hand except fingers, lower arm/wrist, upper arm/ humerus or shoulder), lower limb fracture (foot except toes, knee/patella, upper leg except hip, lower leg/ankle), and central body fractures (hip, pelvis, spine).

Other measurements

Demographic characteristics, medical history, lifestyle factors (alcohol, smoking), and health status were collected using standardized questionnaires at the baseline examination. Weight was measured on a balanced beam scale while wearing indoor clothing. Height was measured with a

fixed stadiometer. Weight and height were used to calculate the body mass index (BMI): weight in kilograms divided by height in meters squared. Calcium intake was defined as the dietary calcium intake assessed by food-frequency questionnaires developed and validated by the Fred Hutchinson Cancer Research Center (Seattle, WA, USA) [31]. Information was also obtained about intake of calcium from supplements in the previous 2 weeks. Total vitamin D intake was similarly determined. Caffeine intake was also assessed by the food frequency questionnaire. Physical activity was assessed by a detailed questionnaire on the frequency and duration of walking and mild, moderate, and strenuous activities in the prior week. Walking was assessed by a series of questions about the frequency of walks outside the home for more than 10 minutes without stopping, the average duration of each walk, and the usual walking pace. Vigorous exercise was defined as that in which "you work up a sweat and your heart beats fast," and examples included aerobics, aerobic dancing, jogging, tennis, and swimming laps. Moderate exercise was defined as that which was "not exhausting," and examples included biking outdoors, using an exercise machine (such as a stationary bicycle or a treadmill), calisthenics, easy swimming, and popular or folk dancing. Examples of mild exercise were slow dancing, bowling and golf. Total weekly kilocalories of energy expended were calculated (metabolic equivalent [MET]) [32]. Assessment of depression was done with baseline questions drawn from the Center for Epidemiologic Studies–Depression Scale (CES-D) [33].

Information regarding current use of menopausal hormone therapy, daily oral corticosteroid use, baseline use of drugs for osteoporosis (bisphosphonates, selective estrogen receptor modulators [SERMs], calcitonin, parathyroid hormone), use of oral or injectable drugs for the treatment of diabetes (e.g., thiazolidinediones, dipeptidyl peptidase-4 inhibitors, meglitinides, glucagon-like peptide-1 agonists, insulin injection, amylin analog, sulfonylureas, biguanides, and alpha-

glucosidase inhibitors), sleep medications (over the counter sleep aids e.g., Tylenol PM; Ambien, Temazepam), analgesic narcotics (narcotic agonists, narcotic antagonists, codeine combinations, dihydrocodeine combinations, fentanyl combinations, hydrocodone combinations, hydromorphone combinations, propoxyphene combinations, meperidine combinations, pentazocine combinations, tramadol combinations), antidepressants (Alpha-2 receptor antagonists (Tetracyclics)), Mao inhibitors, modified cyclics, selective serotonin reuptake inhibitors (SSRIS), tricyclic agents) and hypnotics (barbiturates; benzodiazepines, selective alpha-2 adrenorecptor agonist sedative, antihistamine hypnotics) was obtained. Participants were asked to bring medications they were regularly taking to the clinic visit, medication name, strength and duration of use was recorded. Physical function was measured by the 10-item Rand-36 physical function score [34].

Statistical analyses

We used chi-square tests and ANOVA to compare characteristics of women by self-reported duration of sleep. For the analysis of recurrent falls (falling ≥2 year), we used the generalized estimating equation (GEE) approach for repeated measures logistic regression models with independence working covariance mixture. We used Cox proportional hazard regression to estimate the association between self-reported sleep and time to first fracture, using separate regression models for total fractures and for each anatomical fracture location: hip, lower limb, upper limb and central. Among women who experienced a fracture, duration of follow- up was defined as time to first fracture. Among women who did not experience a fracture during follow-up, duration of follow-up was defined as time until last follow-up visit or death, whichever came first. The proportional hazard assumption of the main exposure variables all (sleep) variables were tested by adding sleep x log (time) interaction variables and plots of Schoenfeld residuals

were evaluated. No gross violations were observed. We tested for a quadratic or linear trend, as appropriate. We examined the risk of fracture over the full follow-up and truncating follow-up to 5 years after baseline.

We examined the recurrent risk of falls and fractures across self-reported sleep duration with 7 hours per night as the referent group since the highest percentage of women reported 7 hours of sleep per day. Other self-reported sleep characteristics examined were sleep quality (average quality as referent), sleep disturbance level (0-3 as referent) and insomnia symptoms (<9 as referent). All covariates were measured at baseline. We adjusted models for risk factors for falls and fractures including age, region, ethnicity/race, weight, height, treated diabetes, smoking status, general health status, hormone therapy, total calcium and vitamin D intake, physical activity, alcohol intake, depressive symptoms score, caffeine intake, hormone therapy trial arm and Diet Modification trial arm, medications (hypnotics, antianxiety, antidepressants and analgesic narcotics), physical functioning and number of comorbidities (stroke, myocardial infarction (MI), congestive heart failure (CHF), Parkinson's disease, chronic obstructive pulmonary disease (COPD, asthma and any prevalent cancer). Fracture models were additionally adjusted for parental history of hip fracture, oral glucocorticoid use, and previous fracture. Missing data on categorical covariates were recoded as unknown and included in our modeling. All analyses were completed in SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

Baseline characteristics of women by self-reported duration of sleep are shown in Table 1. The majority of women reported sleeping on average 7 hours per night (37%); 8.3%, slept ≤5 hours and 4.4% reporting ≥9 hours per night. Women who reported sleeping 8-9 hours per night tended to be slightly older than short sleepers (≤5 hours). Asian and African American women and

women with a high school degree or less tended to be short sleepers. Many of the characteristics of women across self-reported sleep duration were statistically significant but absolute differences were small. However, large differences were observed for depressive symptoms, use of antidepressants and self-reported health status. Both short (≤5 hours) and long sleepers (≥10 hours) were more likely to report a higher number of depressive symptoms with approximately 21% of women who reported ≥10 hours of sleep reporting use of an antidepressant compared with 6% of those reporting sleeping 7 hours per night. Use of hypnotics, antianxiety, and analgesic narcotic medications was low with slightly greater prevalence among the very short and very long sleepers. Twenty percent of short sleepers and 25% of long sleepers reported fair/poor health status compared to 7% of the referent group. Use of diabetes medication was also highest among short and long sleepers. Long sleepers weighed on average 2 kg more than short sleepers. A history of falling in the past 12 months was almost double among both short and long sleepers compared to those sleeping 7 hours per night.

Self-reported sleep characteristics by hours of sleep duration are shown in Supplemental Table 1. Women who reported sleeping ≤5 hours per night were more likely to report restless sleep, trouble falling asleep, waking up during the night, waking up earlier than planned and having trouble falling back to sleep. Among short sleepers (≤5 hours per night), almost 60% had the highest sleep disturbance level and 70% had insomnia.

Falls

The annualized rate of recurrent fall events was 10.6% among women reporting ≤5 hours of sleep per night, lowest (about 7.0%) among women sleeping 7-8 hours per night and highest among women sleeping ≥10 hours per night (11.8%), Table 2. Women who reported ≤5 hours of

sleep were 27% more likely to experience recurrent falls, multivariable (MV) Model, odds ratio (OR)=1.27, 95% confidence interval (CI); 1.22-1.33) compared to women reporting 7 hours per night. Women reporting ≥10 hours of sleep per night were 24% more likely to experience recurrent falls in the MV adjusted model, (OR=1.24, 95% CI; 1.08-1.42). The model fit a significant quadratic pattern.

The annualized rate of recurrent falls was greatest among women who self-reported very restless sleep. Women with very restless sleep and restless sleep were 21% and 11%, respectively more likely to experience recurrent falls compared to women who self-reported average sleep quality in MV models. In contrast, women who reported sound or very sound or restful sleep had the lowest annualized rate of recurrent falls and were about 4-8% less likely to experience recurrent falls, an association that remained after MV adjustment. The risk of recurrent falls increased with increasing sleep disturbance levels in MV models, p linear trend, $p<0.0001$. Women with the greatest sleep disturbance were 34% more likely to experience recurrent falls compared to women with the lowest sleep disturbance levels in MV models. Women with insomnia had an annualized rate of recurrent falls of 10% and were 18% (OR=1.18, 95% CI; 1.15-1.21) more likely to experience recurrent falls.

Fractures

Generally, the annualized (%) incidence of fracture was greatest among self-reported short and long sleepers, those with very restless sleep, the highest sleep disturbance level and insomnia, Table 3. There was a modest association between short sleep duration (≤5 hours) and an increased risk of any fracture, upper limb fracture, lower limb fracture and central fracture but no association with hip fractures alone. The hazard ratios (HR) showed a significant 10-13%

increased risk of fracture among self-reported short sleepers compared to women who slept 7 hours per night, an association that was independent of established risk factors for fracture. There was no association between long duration of sleep and fracture at any site.

In unadjusted models, women who self-reported the greatest sleep disturbance had a 22-36% increased risk of any fracture, upper and lower limb fracture and central body fracture compared to women with the lowest sleep disturbance. Adjustment for established risk factors for fracture attenuated the magnitude of the association to about a 5-11% increased risk of total, upper body, lower limb and central fractures among women with the greatest sleep disturbance level but the HR remained statistically significant. There was little association between overall sleep quality and fracture at any site in the MV models. Women with insomnia had a modest elevated risk of all fractures except hip in the MV adjusted model (3-5%).

Discussion

Women who reported short (≤5 hours) and long (≥10 hours) sleep had about a 27% and 24%, respectively, increased odds of recurrent falls (≥2 falls/year) during any year of follow-up in MV models. This U-shaped relationship between self-reported sleep duration and recurrent falls was independent of established risk factors for falls including use of CNS active medications, physical function and comorbidity. In addition, women reporting restless and very restless sleep had a 11-21% increased odds of recurrent falls while women reporting sound, restful, very sound or very restful sleep had lower odds of falls in comparison to women reporting average quality sleep. Increasing self-reported sleep disturbances were associated with an increasing risk of recurrent falls. Women whose insomnia rating scale indicated the presence of insomnia had about a 19% increased odds of recurrent falls. The magnitude of the associations between sleep

and falls may be clinically significant. The majority of falls are not the result of a single cause. We adjusted for many of these additional risk factors for falls but associations with sleep remained. This suggest that sleep disturbances should be considered when evaluating patients at high risk of falls.

Our results of the association of self-reported sleep characteristics and falls are generally consistent with previous prospective studies. Among Australian assisted living care residents followed for one year duration, those who napped >30 minutes during the day or reported <6 hours of sleep were 3 times more likely to suffer multiple falls [9]. The higher risk in the latter study may have reflected high falling rates in institutions. In the Osteoporotic Fractures in Men Sleep study, (MrOS Sleep Study), participants with excessive daytime sleepiness had greater odds of falling in the subsequent year but there was no association between duration of sleep and falls [12]. In MrOS, greater nocturnal hypoxemia was also independently related to an increased risk of falls over one year of follow-up [15]. In the Study of Osteoporotic Fractures (SOF), napping daily and long duration of sleep by self-report was associated with a 1.3-fold higher risk of ≥2 falls over one year of follow-up [10]. Using objective measures of sleep duration (actigraphy), women enrolled in SOF who slept ≤5 hours per night had a 50% increased risk of ≥2 falls but there was no association with long duration of sleep [11]. These discrepant results in SOF regarding short vs long sleep and risk of falls may reflect the poor correlation between self-reported nighttime sleep duration and objectively assessed total sleep time based on actigraphy (r=0.26) [11]. However, our results extend these previous studies by examining the risk of repeated recurrent falls over almost 8 years. In addition, we were able to examine overall sleep quality and used a validated scale of sleep disturbance [27,28].

The association between self-reported sleep characteristics and fractures was more modest showing a 10-13% increased risk of all fractures, upper limb, lower limb and central fractures among short sleepers but no association with long sleep. It is unclear why long sleep was associated with an increased risk of recurrent falls but had no effect on fractures because most fractures occur due to a fall. This may have reflected the fact that we adjusted for baseline history of falls in our fracture models. In addition, the incidence of fracture is substantially lower than the incidence of falls (e.g., about 10% of falls results in a fracture). Therefore, the ability for detecting a statistically significant association with falls exceeds that for fractures. Poor sleep quality, increasing sleep disturbance and the presence of insomnia were weakly associated with an increased risk of fracture at most fracture sites but these associations were largely attenuated in the MV models. The weaker associations with hip fracture may have reflected reduced power since associations were maintained using central body fracture as the outcome which includes hip fracture.

To our knowledge, there have been three prospective studies of sleep and clinical outcomes of fractures. In the MrOS Sleep Study, longer periods of nocturnal arterial oxygen saturation <90% were associated with a 40% increased risk of fractures [35]. In SOF, self-reported napping and long sleep duration (but not short sleep duration) were each associated with an increased risk of fracture [10]. In the Malmo study, premature awakening was associated with hip fractures but in men only [17]. Thus, there are several suggestive findings of an association between sleep characteristics and fractures that are consistent with our modest associations. Given the widespread prevalence of sleep disorders in the population, more information is needed on whether sleep influences the risk of fracture. These studies should be carried out with objective assessments of sleep duration and quality.

There are a number of strengths to our study. We prospectively evaluated associations with recurrent falls and a number of fracture outcomes in a large cohort of women over an average follow-up of 12 years. We also adjusted for important risk factors for falls and fractures. We used validated measures of sleep disturbances and insomnia but we were limited to self-reported sleep characteristics. Associations between sleep duration and poor health outcomes have been shown to vary by how sleep was measured [36]. For example, long sleep (>9 hours) was associated with poor health status only if self-report was used. In our study, adjusting the association between long sleep and recurrent was attenuated to a greater degree after MV adjustment than associations between short sleep and recurrent falls. Self-reported total sleep time associations with poor health may be due principally to confounding or reverse causality whereby sicker people spend more time in bed or need more sleep precisely because they are sick. Long sleep could reflect the presence of other sleep disorders e.g., sleep disordered breathing. Future studies should rely on objective measures of sleep using actigraphy and polysomnography since certain sleep characteristics, such as, sleep duration may not be accurately reported, especially in older adults.

Despite the strengths to our study, there are several limitations. In addition to reliance on self-report of sleep characteristics, we relied on self-report of non-hip fractures in women enrolled in WHI-OS and during Extension 2, but we previously showed that 76% of all self-reported fractures were confirmed by radiographic report [30]. While monthly fall calendars are the gold standard, the annual self-report assessment of falls used in our study was standardized, allowing the study of an association with sleep patterns. Given our sample size, we could detect small effects and it is uncertain whether these effects are clinically significant. Bone mineral density was measured at only 3 WHI clinics and thus, we could not adjust for BMD. We had no

information on bone turnover makers. We assessed sleep only once at baseline. We adjusted for many covariates in our models but relied only on baseline measures. Our study was observational and residual confounding by unmeasured factors is an inherent limitation.

In conclusion, both self-reported short sleep (≤5 hours) and long (≥10 hours) sleep, poor sleep quality, greater sleep disturbances and insomnia were each associated with recurrent falls, independent of traditional risk factors. Modest but statistically significant associations were observed for short sleep and an increased risk of total, upper body, lower body and central fractures but not hip fractures. Associations of other sleep characteristics and fractures were largely explained by other risk factors supporting conceptual models of how sleep may prospectively influence biological outcomes. Future prospective studies of objective measures of sleep are needed and long-term trials of sleep interventions should include falls and fractures as endpoints.

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References

1. Foley D, Ancoli-Israel S, Britz P, Walsh J. Sleep disturbances and chronic disease in older adults: results of the 2003 National Sleep Foundation Sleep in America Survey. J Psychosom Res. 2004;56(5):497-502.
2. Luyster FS, Strollo PJ, Jr., Zee PC, Walsh JK, Boards of Directors of the American Academy of Sleep M, the Sleep Research S. Sleep: a health imperative. Sleep. 2012;35(6):727-34.
3. Jaussent I, Bouyer J, Ancelin ML, et al. Insomnia and daytime sleepiness are risk factors for depressive symptoms in the elderly. Sleep. 2011;34(8):1103-10.
4. Hall MH, Smagula SF, Boudreau RM, et al. Association between sleep duration and mortality is mediated by markers of inflammation and health in older adults: the Health, Aging and Body Composition Study. Sleep. 2015;38(2):189-95.
5. Gottlieb DJ, Punjabi NM, Newman AB, et al. Association of sleep time with diabetes mellitus and impaired glucose tolerance. Arch Intern Med. 2005;165(8):863-7.
6. Shahar E, Whitney CW, Redline S, et al. Sleep-disordered breathing and cardiovascular disease: cross-sectional results of the Sleep Heart Health Study. Am J Respir Crit Care Med. 2001;163(1):19-25.
7. Christensen AS, Clark A, Salo P, et al. Symptoms of sleep disordered breathing and risk of cancer: a prospective cohort study. Sleep. 2013;36(10):1429-35.
8. Blackwell T, Yaffe K, Laffan A, et al. Associations between sleep-disordered breathing, nocturnal hypoxemia, and subsequent cognitive decline in older community-dwelling men: the Osteoporotic Fractures in Men Sleep Study. J Am Geriatr Soc. 2015;63(3):453-61.

9. St George RJ, Delbaere K, Williams P, Lord SR. Sleep quality and falls in older people living in self- and assisted-care villages. Gerontology. 2009;55(2):162-8.

10. 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):1177-83.

11. Stone KL, Ancoli-Israel S, Blackwell T, et al. Actigraphy-measured sleep characteristics and risk of falls in older women. Arch Intern Med. 2008;168(16):1768-75.

12. Stone KL, Blackwell TL, Ancoli-Israel S, et al. Sleep disturbances and risk of falls in older community-dwelling men: the outcomes of Sleep Disorders in Older Men (MrOS Sleep) Study. J Am Geriatr Soc. 2014;62(2):299-305.

13. 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):1401-6.

14. Kanis J, Johnell O, Gullberg B, et al. Risk factors for hip fracture in men from southern Europe: the MEDOS study. Mediterranean Osteoporosis Study. Osteoporos Int. 1999;9(1):45-54.

15. 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):1853-9.

16. 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):2185-94.

17. 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):1065-77.

18. Swanson CM, Shea SA, Stone KL, et al. Obstructive sleep apnea and metabolic bone disease: insights into the relationship between bone and sleep. J Bone Miner Res. 2015;30(2):199-211.

19. Tchalla AE, Wellenius GA, Travison TG, et al. Circulating vascular cell adhesion molecule-1 is associated with cerebral blood flow dysregulation, mobility impairment, and falls in older adults. Hypertension. 2015;66(2):340-6.

20. Barbour KE, Lui LY, McCulloch CE, et al. Trajectories of Lower Extremity Physical Performance: Effects on Fractures and Mortality in Older Women. J Gerontol A Biol Sci Med Sci. 2016;71(12):1609-15.

21. Harvey NC, Oden A, Orwoll E, et al. Falls Predict Fractures Independently of FRAX Probability: A Meta-Analysis of the Osteoporotic Fractures in Men (MrOS) Study. J Bone Miner Res. 2018;33(3):510-6.

22. Sibley KM, Voth J, Munce SE, Straus SE, Jaglal SB. Chronic disease and falls in community-dwelling Canadians over 65 years old: a population-based study exploring associations with number and pattern of chronic conditions. BMC Geriatr. 2014;14:22.

23. Design of the Women's Health Initiative clinical trial and observational study. The Women's Health Initiative Study Group. Control Clin Trials. 1998;19(1):61-109.

24. Langer RD, White E, Lewis CE, Kotchen JM, Hendrix SL, Trevisan M. The Women's Health Initiative Observational Study: baseline characteristics of participants and reliability of baseline measures. Ann Epidemiol. 2003;13(9 Suppl):S107-21.

25. Cauley JA, Wampler NS, Barnhart JM, et al. Incidence of fractures compared to cardiovascular disease and breast cancer: the Women's Health Initiative Observational Study. Osteoporos Int. 2008;19(12):1717-23.

26. Anderson GL, Manson J, Wallace R, et al. Implementation of the Women's Health Initiative study design. Ann Epidemiol. 2003;13(9 Suppl):S5-17.

27. Levine DW, Kripke DF, Kaplan RM, et al. Reliability and validity of the Women's Health Initiative Insomnia Rating Scale. Psychol Assess. 2003;15(2):137-48.

28. Levine DW, Kaplan RM, Kripke DF, Bowen DJ, Naughton MJ, Shumaker SA. Factor structure and measurement invariance of the Women's Health Initiative Insomnia Rating Scale. Psychol Assess. 2003;15(2):123-36.

29. Cauley JA, Smagula SF, Hovey KM, et al. Optimism, Cynical Hostility, Falls, and Fractures: The Women's Health Initiative Observational Study (WHI-OS). J Bone Miner Res. 2016.

30. 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):264-74.

31. Patterson RE, Kristal AR, Tinker LF, Carter RA, Bolton MP, Agurs-Collins T. Measurement characteristics of the Women's Health Initiative food frequency questionnaire. Ann Epidemiol. 1999;9(3):178-87.

32. Manson JE, Greenland P, LaCroix AZ, et al. Walking compared with vigorous exercise for the prevention of cardiovascular events in women. N Engl J Med. 2002;347(10):716-25.

33. Tuunainen A, Langer RD, Klauber MR, Kripke DF. Short version of the CES-D (Burnam screen) for depression in reference to the structured psychiatric interview. Psychiatry Res. 2001;103(2-3):261-70.

34. Hays RD, Sherbourne CD, Mazel RM. The RAND 36-Item Health Survey 1.0. Health Econ. 1993;2(3):217-27.

35. Eriksen EF, Lyles KW, Colon-Emeric CS, et al. Antifracture efficacy and reduction of mortality in relation to timing of the first dose of zoledronic acid after hip fracture. J Bone Miner Res. 2009;24(7):1308-13.

36. Lauderdale DS, Chen JH, Kurina LM, Waite LJ, Thisted RA. Sleep duration and health among older adults: associations vary by how sleep is measured. J Epidemiol Community Health. 2016;70(4):361-6.

Table 1. Baseline Characteristics by hours of sleep excluding those with no following or missing exposure or falls data

	Hours of sleep						
	5 or less	6	7	8	9	10 or more	P -value
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	Test of
N	13,119 (8.3%)	43,306 (27.5%)	58,962 (37.4%)	35,029 (22.2%)	6,080 (3.9%)	810 (0.5%)	trend
Age (Mean (SD))	63.2 (7.6)	63.1 (7.4)	63.0 (7.2)	63.5 (7.0)	64.0 (7.1)	63.2 (7.4)	<0.001
Race/Ethnicity							<0.001
American Indian or Alaskan Native	107 (0.8)	190 (0.4)	209 (0.4)	140 (0.4)	26 (0.4)	4 (0.5)	
Asian or Pacific Islander	628 (4.8)	1,614 (3.7)	1,305 (2.2)	464 (1.3)	69 (1.1)	10 (1.2)	
Black or African-American	2,580 (19.7)	5,086 (11.8)	3,754 (6.4)	1,849 (5.3)	410 (6.8)	152 (18.8)	
Hispanic/Latino	794 (6.1)	1,806 (4.2)	1,944 (3.3)	1,105 (3.2)	206 (3.4)	107 (13.2)	
White (not of Hispanic origin)	8,735 (66.8)	33,925 (78.5)	51,042 (86.8)	31,047 (88.9)	5,303 (87.4)	531 (65.6)	
Other	239 (1.8)	573 (1.3)	573 (1.0)	331 (0.9)	53 (0.9)	5 (0.6)	
Education							<0.001
High school or less	3,847 (29.6)	10,038 (23.4)	11,986 (20.5)	7,383 (21.2)	1,381 (22.9)	262 (32.7)	
Some college or vocational training	5,426 (41.7)	16,792 (39.1)	21,655 (37.0)	12,882 (37.0)	2,289 (37.9)	292 (36.4)	
College grad or more	3,725 (28.7)	16,129 (37.5)	24,927 (42.6)	14,525 (41.8)	2,372 (39.3)	248 (30.9)	
Control	2,314 (17.6)	7,991 (18.5)	10,842 (18.4)	6,268 (17.9)	1,047 (17.2)	133 (16.4)	
Physical activity (MET hrs/wk)							<0.001
≤ 2.5	4,034 (32.0)	11,201 (27.0)	13,240 (23.6)	7,861 (23.5)	1,577 (27.2)	263 (34.1)	
2.5 - < 5	1,594 (12.7)	4,836 (11.7)	6,104 (10.9)	3,748 (11.2)	666 (11.5)	100 (13.0)	
5 - < 12	2,865 (22.8)	9,778 (23.6)	13,734 (24.4)	7,949 (23.8)	1,355 (23.4)	171 (22.2)	
≥12	4,095 (32.5)	15,676 (37.8)	23,128 (41.1)	13,847 (41.5)	2,190 (37.8)	238 (30.8)	
Alcohol intake							<0.001
≤ 2 Drinks/day	12,746 (97.4)	41,829 (96.8)	56,586 (96.3)	33,203 (95.1)	5,641 (93.2)	756 (93.8)	
> 2 Drinks/day	338 (2.6)	1,365 (3.2)	2,191 (3.7)	1,725 (4.9)	414 (6.8)	50 (6.2)	
Smoking status							<0.001
Never Smoked	6,758 (52.1)	21,768 (50.9)	29,890 (51.3)	17,533 (50.6)	2,896 (48.2)	367 (45.9)	
Past Smoker	5,063 (39.1)	17,788 (41.6)	24,604 (42.2)	14,969 (43.2)	2,702 (45.0)	351 (43.9)	
Current Smoker	1,138 (8.8)	3,245 (7.6)	3,802 (6.5)	2,122 (6.1)	409 (6.8)	81 (10.1)	
Hormone Therapy							<0.001
Never used	6,415 (49.0)	19,399 (44.8)	24,907 (42.3)	14,775 (42.2)	2,632 (43.3)	404 (49.9)	
Past user	2,362 (18.0)	7,072 (16.3)	9,099 (15.4)	5,527 (15.8)	1,002 (16.5)	123 (15.2)	
Current user	4,326 (33.0)	16,795 (38.8)	24,907 (42.3)	14,706 (42.0)	2,439 (40.2)	282 (34.9)	
Depressive symptoms (CESD > 0.06)							<0.001
No	9,514 (75.0)	36,628 (86.6)	53,040 (91.8)	31,901 (92.8)	5,298 (89.4)	597 (76.1)	
Yes	3,173 (25.0)	5,644 (13.4)	4,768 (8.2)	2,461 (7.2)	625 (10.6)	188 (23.9)	
Dietary Caffeine (mg)	150.6 (140.8)	164.7 (137.3)	169.7 (133.4)	168.6 (131.2)	166.9 (137.1)	146.6 (142.3)	<0.001
Total Calcium (mg/d) (Mean, SD)	1059 (705)	1137 (710)	1200 (708)	1201 (705)	1195 (725)	1108 (752)	<0.001
Anti-Depressants (Yes)	922 (7.0)	2,675 (6.2)	3,710 (6.3)	2,820 (8.1)	836 (13.8)	172 (21.2)	<0.001
Anti-Anxiety (Yes)	607 (4.6)	1,481 (3.4)	1,645 (2.8)	1,003 (2.9)	237 (3.9)	34 (4.2)	<0.001
Hypnotics (Yes)	576 (4.4)	1,449 (3.3)	1,435 (2.4)	757 (2.2)	146 (2.4)	22 (2.7)	<0.001
Analgesic narcotics (Yes)	517 (3.9)	878 (2.0)	957 (1.6)	582 (1.7)	150 (2.5)	33 (4.1)	<0.001

Oral glucocorticosteroid (Yes)	140 (1.1)	326 (0.8)	332 (0.6)	225 (0.6)	45 (0.7)	8 (1.0)	<0.001
Fracture (age ≥55)	1,705 (17.4)	5,488 (16.7)	7,140 (15.9)	4,415 (16.2)	843 (17.7)	96 (15.9)	<0.001
Parental history of broken bone (age > 40) (Yes)	4,397 (37.7)	15,630 (39.4)	22,280 (40.6)	13,028 (39.8)	2,225 (39.5)	242 (33.4)	<0.001
Parental history of broken hip (Yes)	1,488 (12.7)	5,429 (13.7)	7,726 (14.1)	4,715 (14.4)	805 (14.3)	85 (11.7)	<0.001
Weight, kg (Mean, SD)	75.8 (18.6)	73.9 (17.2)	72.7 (16.4)	73.3 (16.4)	74.6 (17.2)	77.8 (19.3)	<0.001
Height, cm (Mean, SD)	160.7 (6.8)	161.4 (6.7)	162.0 (6.6)	162.2 (6.6)	162.4 (6.4)	161.2 (7.1)	<0.001
Diabetes treated (pills or shots) (Yes)	976 (7.4)	2,039 (4.7)	2,174 (3.7)	1,290 (3.7)	299 (4.9)	57 (7.0)	<0.001
In general, health is (Fair/Poor)	2586 (19.8)	4305 (9.9)	3950 (6.7)	3798 (6.8)	633 (10.3)	203 (25.3)	<0.001
Times fell down last 12 months							<0.001
None	8,124 (64.3)	27,647 (66.3)	38,506 (68.1)	23,247 (69.2)	3,931 (67.5)	511 (66.0)	
1	2,413 (19.1)	8,462 (20.3)	11,519 (20.4)	6,661 (19.8)	1,130 (19.4)	124 (16.0)	
2	1,258 (10.0)	3,778 (9.1)	4,427 (7.8)	2,462 (7.3)	503 (8.6)	80 (10.3)	
≥3	843 (6.7)	1,812 (4.3)	2,052 (3.6)	1,240 (3.7)	261 (4.5)	59 (7.6)	
Physical Function Construct (Mean, SD)	73.9 (24.1)	80.4 (20.3)	83.1 (18.4)	82.3 (19.1)	78.4 (21.7)	69.5 (25.8)	<0.001

Table 2: Association of hours of sleep, sleep quality and sleep disturbance with risk of ≥2falls in past year.

	Events N (%)	Crude	Multivariable Model
	96,981 (7.9)	OR (95%CI)	OR (95%CI)
How many hours of sleep			
≤5 hours	10,548 (10.6)	1.54 (1.48-1.60)	1.27 (1.22-1.33)
6 hours	28,350 (8.4)	1.17 (1.14-1.21)	1.13 (1.10-1.16)
7 hours	33,877 (7.3)	1 (ref)	1 (ref)
8 hours	19,446 (7.1)	0.97 (0.94-1.00)	0.92 (0.90-0.95)
9 hours	4,041 (8.6)	1.19 (1.13-1.26)	0.99 (0.94-1.05)
≥10 hours	719 (11.8)	1.80 (1.57-2.05)	1.24 (1.08-1.42)
Quadratic p-value		<0.001	<0.001
Overall Sleep Quality			
Very restless	3,524 (13.0)	1.75 (1.64-1.87)	1.21 (1.13-1.30)
Restless	17,641 (10.3)	1.32 (1.28-1.36)	1.11 (1.07-1.14)
Average quality	41,475 (8.1)	1 (ref)	1 (ref)
Sound or restful	24,501 (6.9)	0.84 (0.82-0.87)	0.96 (0.94-0.99)
Very sound or restful	9,840 (6.2)	0.75 (0.73-0.78)	0.92 (0.88-0.96)
p-value		<0.001	<0.001
Sleep Disturbance Level			
0 - 3	19,902 (5.9)	1 (ref)	1 (ref)
4 - 6	24,820 (7.4)	1.27 (1.23-1.31)	1.15 (1.11-1.19)
7 - 10	27,175 (8.6)	1.51 (1.46-1.56)	1.24 (1.20-1.28)
≥ 11	25,084 (10.5)	1.88 (1.83-1.95)	1.34 (1.30-1.39)
Linear p-value		<0.001	<0.001
Insomnia Scale			
No	59,364 (7.0)	1 (ref)	1 (ref)
Yes (sleep disturbance ≥ 9)	37,617 (10.0)	1.49 (1.45-1.52)	1.18 (1.15-1.21)
p-value		<0.001	<0.001

% is annualized percent
P-value represents chi-square Wald statistic
Event is defined as 2 or more falls in the past year
OR are estimated from repeated logistic models.
Multivariable model: age, weight, height, treated diabetes, ethnicity/race, region, smoking status, general health status, current HT use, total vitamin D intake, physical activity, alcohol intake, depressive symptom score, caffeine intake, HT trial arm, DM trial arm, hypnotics medication use, anti-anxiety medication use, antidepressant medication use, analgesic narcotic medication use, physical functioning construct and # chronic conditions (stroke, MI, CHF, diabetes, Parkinson's disease, COPD, asthma, any cancer).

Table 3: Association of hours or sleep, sleep quality and sleep disturbance with risk of fracture

	Events	Crude	Multivariable model	Multivariable model* 5 years Follow-up
		157,306	141,079	141,079
	N (%)	HR (95%CI)	HR (95%CI)	HR (95%CI)
Total Fracture	50,601 (2.7)			
How many hours of sleep				
5 or less hours	4,052 (2.8)	1.11 (1.07-1.15)	1.10 (1.06-1.14)	1.12 (1.05-1.20)
6 hours	13,904 (2.7)	1.04 (1.02-1.07)	1.05 (1.02-1.07)	1.07 (1.03-1.12)
7 hours	19,306 (2.6)	1 (Ref)	1 (Ref)	1 (Ref)
8 hours	11,149 (2.6)	0.98 (0.96-1.00)	0.95 (0.93-0.97)	0.96 (0.91-1.00)
9 hours	1,975 (2.8)	1.06 (1.01-1.11)	0.95 (0.90-0.99)	0.94 (0.86-1.03)
10 or more hours	215 (2.5)	1.01 (0.88-1.16)	0.96 (0.83-1.11)	0.99 (0.77-1.26)
Overall Sleep Quality				
Very restless	1,145 (2.9)	1.09 (1.03-1.16)	0.99 (0.93-1.06)	1.04 (0.93-1.17)
Restless	7,593 (2.9)	1.10 (1.07-1.13)	1.04 (1.01-1.07)	1.09 (1.04-1.15)
Average quality	21,362 (2.7)	1 (Ref)	1 (Ref)	1 (Ref)
Sound or restful	14,338 (2.6)	0.94 (0.92-0.96)	0.98 (0.96-1.01)	1.03 (0.99-1.08)
Very sound or restful	6,163 (2.5)	0.89 (0.87-0.92)	0.97 (0.94-1.00)	1.02 (0.96-1.08)
Sleep Disturbance Level				
0 - 3	12,922 (2.4)	1 (Ref)	1 (Ref)	1 (Ref)
4 - 6	13,768 (2.6)	1.10 (1.07-1.13)	1.03 (1.01-1.06)	1.02 (0.97-1.07)
7 - 10	13,386 (2.8)	1.16 (1.14-1.19)	1.03 (1.01-1.06)	0.98 (0.93-1.03)
≥ 11	10,525 (3.0)	1.26 (1.23-1.29)	1.08 (1.05-1.11)	1.03 (0.97-1.08)
Insomnia Scale				
No	34,156 (2.6)	1 (Ref)	1 (Ref)	1 (Ref)
Yes (sleep disturbance ≥ 9)	16,445 (2.9)	1.15 (1.13-1.17)	1.03 (1.01-1.06)	1.00 (0.96-1.04)
Hip Fracture	5,670 (0.26)			
How many hours of sleep				
5 or less hours	439 (0.26)	1.08 (0.97-1.19)	1.01 (0.91-1.14)	0.82 (0.61-1.09)
6 hours	1,506 (0.25)	1.00 (0.94-1.07)	1.00 (0.93-1.07)	0.94 (0.79-1.13)
7 hours	2,177 (0.26)	1 (Ref)	1 (Ref)	1 (Ref)
8 hours	1,287 (0.26)	1.01 (0.94-1.08)	0.93 (0.87-1.00)	0.88 (0.72-1.06)
9 hours	234 (0.28)	1.12 (0.98-1.28)	0.93 (0.81-1.07)	1.07 (0.77-1.50)
10 or more hours	27 (0.28)	1.19 (0.81-1.74)	1.06 (0.71-1.59)	1.46 (0.69-3.11)
Overall Sleep Quality				
Very restless	109 (0.23)	0.90 (0.74-1.08)	0.96 (0.78-1.18)	0.90 (0.52-1.55)
Restless	794 (0.26)	0.97 (0.90-1.05)	0.98 (0.90-1.06)	1.01 (0.81-1.27)
Average quality	2,478 (0.27)	1 (Ref)	1 (Ref)	1 (Ref)
Sound or restful	1,652 (0.25)	0.93 (0.88-0.99)	1.01 (0.94-1.08)	1.29 (1.08-1.53)
Very sound or restful	637 (0.22)	0.80 (0.73-0.87)	0.96 (0.87-1.05)	1.41 (1.12-1.77)
Sleep Disturbance Level				
0 - 3	1,396 (0.23)	1 (Ref)	1 (Ref)	1 (Ref)

4 - 6	1,502 (0.25)	1.10 (1.02-1.18)	0.97 (0.89-1.04)	0.90 (0.74-1.10)
7 - 10	1,574 (0.28)	1.25 (1.16-1.34)	1.00 (0.92-1.08)	0.88 (0.72-1.07)
≥ 11	1,198 (0.28)	1.30 (1.20-1.41)	0.98 (0.90-1.07)	0.79 (0.63-0.98)
Insomnia Scale				
No	3,777 (0.24)	1 (Ref)	1 (Ref)	1 (Ref)
Yes (sleep disturbance ≥ 9)	1,893 (0.28)	1.19 (1.12-1.25)	1.00 (0.94-1.06)	0.87 (0.74-1.02)
Upper limb Fracture	19,486 (0.92)			
How many hours of sleep				
5 or less hours	1,580 (0.98)	1.10 (1.04-1.16)	1.10 (1.04-1.17)	1.11 (1.00-1.23)
6 hours	5,383 (0.94)	1.04 (1.01-1.08)	1.05 (1.01-1.09)	1.06 (0.99-1.14)
7 hours	7,428 (0.92)	1 (Ref)	1 (Ref)	1 (Ref)
8 hours	4,235 (0.89)	0.97 (0.93-1.01)	0.94 (0.91-0.98)	0.95 (0.88-1.03)
9 hours	780 (0.98)	1.09 (1.01-1.17)	1.00 (0.93-1.08)	0.99 (0.85-1.15)
10 or more hours	80 (0.86)	0.98 (0.79-1.22)	0.97 (0.76-1.22)	0.93 (0.61-1.41)
Overall Sleep Quality				
Very restless	434 (0.98)	1.05 (0.96-1.16)	0.97 (0.87-1.08)	1.00 (0.83-1.22)
Restless	2,912 (1.0)	1.07 (1.02-1.11)	1.02 (0.97-1.06)	1.10 (1.01-1.19)
Average quality	8,294 (0.94)	1 (Ref)	1 (Ref)	1 (Ref)
Sound or restful	5,469 (0.88)	0.93 (0.90-0.96)	0.97 (0.94-1.01)	1.04 (0.97-1.11)
Very sound or restful	2,377 (0.86)	0.90 (0.86-0.94)	0.96 (0.91-1.01)	0.96 (0.88-1.06)
Sleep Disturbance Level				
0 - 3	4,984 (0.84)	1 (Ref)	1 (Ref)	1 (Ref)
4 - 6	5,280 (0.91)	1.08 (1.04-1.12)	1.02 (0.98-1.07)	1.06 (0.99-1.15)
7 - 10	5,157 (0.95)	1.14 (1.10-1.18)	1.03 (0.98-1.07)	1.00 (0.92-1.08)
≥ 11	4,065 (1.0)	1.22 (1.17-1.28)	1.05 (1.01-1.11)	1.01 (0.93-1.11)
Insomnia Scale				
No	13,096 (0.89)	1 (Ref)	1 (Ref)	1 (Ref)
Yes (sleep disturbance ≥ 9)	6,390 (1.0)	1.15 (1.11-1.18)	1.03 (1.00-1.07)	0.97 (0.91-1.03)
Lower limb Fracture	19,433 (0.92)			
How many hours of sleep				
5 or less hours	1,632 (1.0)	1.16 (1.10-1.22)	1.13 (1.07-1.20)	1.16 (1.05-1.29)
6 hours	5,421 (0.95)	1.06 (1.03-1.10)	1.06 (1.02-1.10)	1.10 (1.02-1.17)
7 hours	7,332 (0.90)	1 (Ref)	1 (Ref)	1 (Ref)
8 hours	4,223 (0.89)	0.98 (0.94-1.02)	0.96 (0.93-1.00)	1.00 (0.93-1.07)
9 hours	737 (0.93)	1.03 (0.96-1.12)	0.96 (0.88-1.04)	0.93 (0.80-1.08)
10 or more hours	88 (0.95)	1.09 (0.88-1.35)	1.01 (0.80-1.26)	0.88 (0.58-1.33)
Overall Sleep Quality				
Very restless	465 (1.1)	1.16 (1.06-1.28)	1.01 (0.91-1.12)	1.04 (0.87-1.25)
Restless	3,032 (1.1)	1.14 (1.10-1.19)	1.07 (1.02-1.12)	1.06 (0.98-1.15)
Average quality	8,086 (0.92)	1 (Ref)	1 (Ref)	1 (Ref)
Sound or restful	5,474 (0.88)	0.95 (0.92-0.99)	1.00 (0.96-1.04)	1.01 (0.95-1.08)
Very sound or restful	2,376 (0.86)	0.92 (0.88-0.97)	0.99 (0.94-1.04)	1.05 (0.96-1.15)

Sleep Disturbance Level				
0 - 3	5,004 (0.85)	1 (Ref)	1 (Ref)	1 (Ref)
4 - 6	5,202 (0.90)	1.06 (1.02-1.10)	1.01 (0.97-1.06)	1.00 (0.93-1.08)
7 - 10	5,143 (0.96)	1.13 (1.09-1.18)	1.03 (0.99-1.08)	0.99 (0.92-1.07)
≥ 11	4,084 (1.0)	1.22 (1.18-1.28)	1.07 (1.02-1.12)	1.03 (0.94-1.12)
Insomnia Scale				
No	13,105 (0.89)	1 (Ref)	1 (Ref)	1 (Ref)
Yes (sleep disturbance ≥ 9)	6,328 (1.00)	1.13 (1.10-1.17)	1.04 (1.00-1.07)	0.99 (0.93-1.05)
Central Fracture	15,111 (0.70)			
How many hours of sleep				
5 or less hours	1,234 (0.75)	1.16 (1.09-1.24)	1.13 (1.05-1.20)	0.94 (0.80-1.10)
6 hours	4,100 (0.70)	1.05 (1.01-1.09)	1.05 (1.01-1.10)	1.02 (0.92-1.13)
7 hours	5,683 (0.68)	1 (Ref)	1 (Ref)	1 (Ref)
8 hours	3,424 (0.70)	1.03 (0.99-1.08)	0.97 (0.93-1.02)	0.92 (0.83-1.03)
9 hours	601 (0.73)	1.10 (1.01-1.20)	0.94 (0.86-1.03)	0.95 (0.77-1.17)
10 or more hours	69 (0.72)	1.15 (0.91-1.46)	1.08 (0.84-1.38)	1.04 (0.61-1.77)
Overall Sleep Quality				
Very restless	352 (0.78)	1.11 (0.99-1.23)	1.10 (0.98-1.24)	0.94 (0.70-1.25)
Restless	2,289 (0.77)	1.07 (1.02-1.12)	1.03 (0.98-1.08)	1.11 (0.98-1.25)
Average quality	6,510 (0.72)	1 (Ref)	1 (Ref)	1 (Ref)
Sound or restful	4,246 (0.67)	0.91 (0.87-0.94)	0.97 (0.93-1.01)	1.11 (1.01-1.23)
Very sound or restful	1,714 (0.60)	0.81 (0.77-0.86)	0.94 (0.89-1.00)	1.08 (0.94-1.25)
Sleep Disturbance Level				
0 - 3	3,565 (0.59)	1 (Ref)	1 (Ref)	1 (Ref)
4 - 6	4,070 (0.68)	1.17 (1.12-1.23)	1.05 (1.00-1.10)	0.99 (0.88-1.11)
7 - 10	4,141 (0.75)	1.29 (1.24-1.35)	1.05 (1.00-1.11)	0.95 (0.84-1.07)
≥ 11	3,335 (0.81)	1.44 (1.37-1.51)	1.11 (1.05-1.17)	0.99 (0.88-1.13)
Insomnia Scale				
No	9,944 (0.65)	1 (Ref)	1 (Ref)	1 (Ref)
Yes (sleep disturbance ≥ 9)	5,167 (0.79)	1.24 (1.20-1.28)	1.05 (1.01-1.09)	1.00 (0.91-1.09)

Fractures are through end of extension 2 (9/30/2015)
Fracture sites are defined as:
Total fracture: any fracture except toes, fingers, coccyx, and sternum
Hip fracture
Upper limb fractures: elbow, hand except fingers, lower arm/wrist, upper arm/humerus or shoulder
Lower limb fractures: foot except toes, knee/patella, upper leg except hip, lower leg/ankle
Central body fractures: hip, pelvis and spine
% is annualized percent
Multivariable model: age, weight, height, treated diabetes, ethnicity/race, region, smoking status, times fell down last 12 months, general health status, current HT use, oral corticosteroid use, total calcium intake, total vitamin D intake, physical activity, history of fracture after age 55, parental history of broken hip, alcohol intake, depressive symptom score, caffeine intake, HT trial arm and DM trial arm, hypnotics medication use, anti-anxiety medication use, antidepressant medication use, and analgesic narcotic medication use, physical functioning construct and

number of chronic conditions (stroke, MI, CHF, diabetes, Parkinson's disease, COPD, asthma, any cancer)
NOTE: missing data for history of fracture after age 55 and parental history of broken hip has been recoded as "unknown" and included in the analysis to preserve sample size