

# **Sleep Duration, Quality and Insomnia and the Risk of Falls and Fractures: The Women's Health Initiative**

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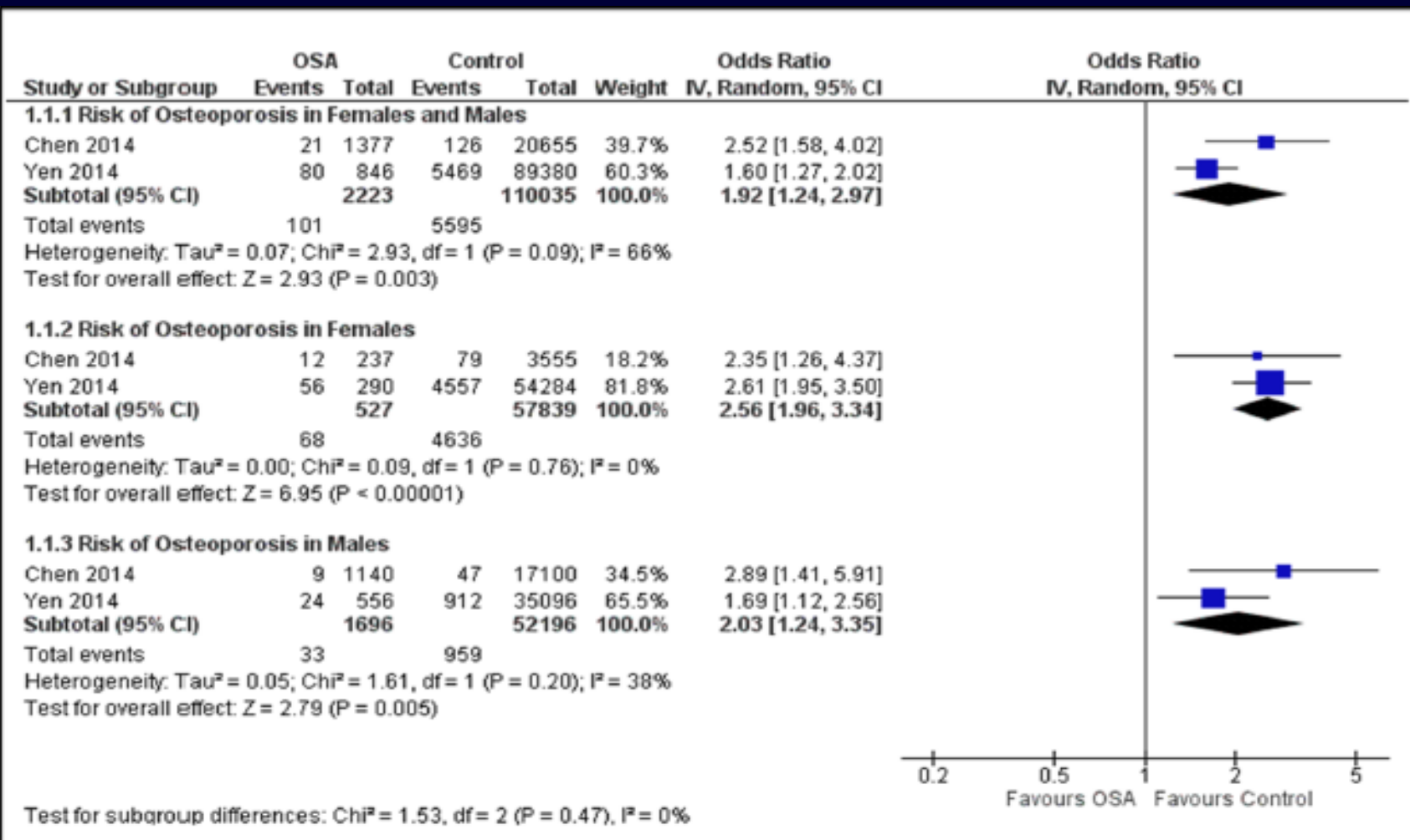
# Background Hypotheses

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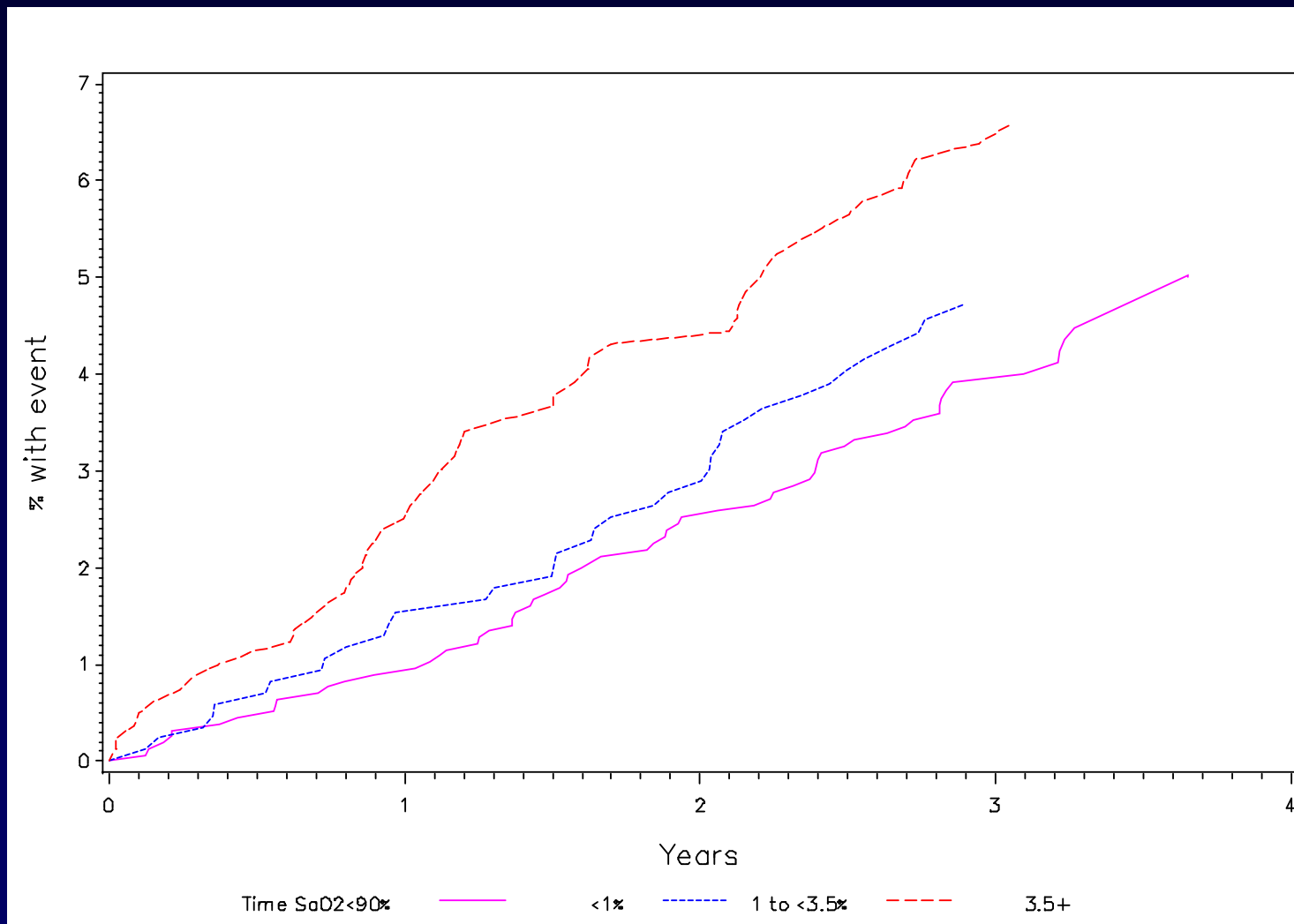
- ❑ Self-reported long sleep and daily napping are associated with a greater risk of falls and fractures.<sup>1</sup>
- ❑ Experimental evidence suggests that hypoxemia promotes osteoblastic differentiation and subsequent transformation to osteocytes.<sup>2</sup>
- ❑ Circadian rhythm genes related to Bone resorption and formation
- ❑ Poor sleep could contribute to the observed higher risk of fractures:
  - ❖ Comorbid conditions (e.g., CVD, COPD)
  - ❖ Poor neuromuscular function.
  - ❖ Shared risk factors (e.g., smoking).
  - ❖ Shared pathways (e.g., inflammation).

<sup>1</sup> Stone KL JAGS 2006; 548:1177. <sup>2</sup> Hirao M JBMR 2007; 25:266.

# Meta-analysis of the Effect of the Sleep Apnea Diagnosis on the Odds Ratio of Osteoporosis



# Cumulative Incidence of Fracture by Nocturnal Hypoxia: MrOS Sleep Study



Adjusted for clinic, age, race, weight

Cauley JA, JAGS. 2014;62(10):1853-9.

# Specific Aims

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- ❑ To test the hypothesis that duration of sleep, sleep quality and insomnia increases the risk of:
  - ❖ Recurrent falls
  - ❖ Fracture
- ❑ To examine if this association is independent of other comorbid conditions and risk factors

# Study Population

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- ❑ OS and CT
- ❑ Follow-up through Extension 2
- ❑ N=157,306
  - ❖ Exclude women with no follow-up or missing sleep data

# Outcomes

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- ❑ Recurrent falls
  - ❑  $\geq 2$  falls over any year of follow-up
  - ❑ Repeated measure
- ❑ Fractures: Form 33
  - ❑ Hip fractures: adjudicated through Extension 1
  - ❑ All other fractures self-report: Agreement=76% but ranged across fractures sites e.g., 52% clinical spine to 85.8%, lower arm or wrist
- ❑ Outcomes
  - ❖ **Total** fractures: any fracture except toes, fingers, sternum and coccyx
  - ❖ **Upper limb** fractures: elbow, hand, lower arm/wrist, upper arm/humerus and shoulder
  - ❖ **Lower limb** fractures: foot, knee/patella, upper leg except hip and lower leg/ankle
  - ❖ **Central body** fractures: Hip, pelvis and spine

# Statistical Analyses

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- ❑ Falls: GEE for repeated logistic regression models (OR; 95% CI)
- ❑ Fractures: Cox Proportional Hazards Models (HR; 95% CI)
- ❑ Covariates: Baseline



# Sleep Assessments

- ❑ Sleep duration (<5, 6, 7, 8, 9, ≥10)
- ❑ Typical night's sleep
  - ❖ Very restless, restless, average, sound or restful, very sound or restful
- ❑ Trouble sleeping; wakeup several times; wakeup earlier than planned, trouble getting back to sleep:
  - ❖ No: not in past 4 weeks
  - ❖ Yes: <1 x/week; 1-2 x/week; 3-4 x/week, >5 x/week

# WHI Insomnia Scale

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- Restlessness
- Difficult falling asleep
- Waking up several times during the night
- Early awakenings
- Inability to fall back a sleep
  - Time frame (past 4 weeks)
  - Yes/No (any vs none)
  - Sum number of symptoms (0-5)
- Insomnia rating score
  - ❖ Summary 0-20 (cutpoint  $\geq 9$ )

# Baseline Characteristics by *Sleep Duration* (N=157,306)

Characteristics	Hours of Sleep					
	<5 (8.3%)	6 (27.5%)	7 (37.5%)	8 (22.3%)	9 (3.9%)	≥ 10 (0.5%)
Age (yrs)	63.2	63.1	63.0	63.5	64.0	63.2
White (%)	66.8	78.5	86.8	88.9	87.4	65.6
Antidepressant (%)	7.0	6.2	6.3	8.1	13.8	21.2
Diabetes (%)	7.4	4.7	3.7	3.7	4.9	7.0
Poor/Fair health (%)	19.8	10.1	6.7	6.8	10.3	25.3

# Sleep Characteristics by Sleep Duration

Characteristics (%)	Hours of Sleep					
	<5 (8.3%)	6 (27.5%)	7 (37.5%)	8 (22.3%)	9 (3.9%)	≥ 10 (0.5%)
Restless/Very restless	54.2	23.5	9.6	6.3	7.1	14.7
Difficulty falling asleep (≥3 week)	36.5	13.3	5.4	4.0	4.9	11.4
Wake-up (≥3 week)	76.0	43.6	34.6	33.7	37.2	45.9
Difficulty getting back to sleep (≥3 week)	47.6	21.2	7.0	5.1	4.9	11.0
Sleep disturbance level (≥11)	59.0	28.8	12.7	7.7	7.2	14.9
Insomnia rating scale (≥9)	69.5	42.3	24.4	16.2	15.3	25.7

# Association of *Sleep Duration* and *Recurrent Falls*

Sleep Duration	Model 1	Model 2
≤5 hrs	1.33 (1.28-1.39)	1.35 (1.29-1.41)
6 hrs	1.13 (1.10-1.16)	1.14 (1.11-1.18)
7 hrs	1.00 (Ref)	1.00 (Ref)
8 hrs	0.95 (0.92-0.98)	0.93 (0.90-0.96)
9 hrs	1.08 (1.02-1.15)	1.01 (0.95-1.07)
≥10 hrs	1.46 (1.27-1.68)	1.29 (1.11-1.48)

*Model 1:* age, weight, height, diabetes (DM), race, region, smoking, health status, current hormone therapy (HT) use, total vitamin D intake, physical activity, alcohol intake, depression, caffeine, HT Trial arm, DM Trial arm. *Model 2:* Model 1 + hypnotics, anti-anxiety meds, antidepressants, analgesic narcotics.

# Association of *Sleep Disturbance Level* and *Recurrent Falls*

Sleep Disturbance	Model 1	Model 2
0-3	1.00 (Ref)	1.00 (Ref)
4-6	1.16 (1.13-1.21)	1.17 (1.13-1.21)
7-10	1.28 (1.24-1.33)	1.27 (1.23-1.32)
≥11	1.43 (1.38-1.48)	1.42 (1.37-1.47)
Insomnia ≥9	1.24 (1.20-1.27)	1.23 (1.20-1.26)

*Model 1:* age, weight, height, diabetes (DM), race, region, smoking, health status, current hormone therapy (HT) use, total vitamin D intake, physical activity, alcohol intake, depression, caffeine, HT Trial arm, DM Trial arm. *Model 2:* Model 1 + hypnotics, anti-anxiety meds, antidepressants, analgesic narcotics.

# Association of Sleep Quality and Recurrent Falls

Sleep Quality	Model 1	Model 2
Very restless	1.31 (1.22-1.41)	1.30 (1.20-1.39)
Restless	1.15 (1.11-1.19)	1.14 (1.10-1.18)
Average	1.00 (Ref)	1.00 (Ref)
Sound or restful	0.95 (0.92-0.98)	0.96 (0.93-0.99)
Very sound or restful	0.90 (0.87-0.94)	0.91 (0.87-0.95)

*Model 1:* age, weight, height, diabetes (DM), race, region, smoking, health status, current hormone therapy (HT) use, total vitamin D intake, physical activity, alcohol intake, depression, caffeine, HT Trial arm, DM Trial arm. *Model 2:* Model 1 + hypnotics, anti-anxiety meds, antidepressants, analgesic narcotics.

# Sleep Duration and Risk of Fracture (Model 2): HR(95% CI)

Sleep Duration	Fractures			
	Total	Upper Limb	Lower Limb	Central
≤5 hrs	1.11 (1.08-1.15)	1.11 (1.05-1.18)	1.14 (1.07-1.21)	1.14 (1.07-1.22)
6 hrs	1.05 (1.02-1.07)	1.05 (1.01-1.09)	1.06 (1.02-1.10)	1.06 (1.01-1.10)
7 hrs	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
8 hrs	0.95 (0.93-0.98)	0.95 (0.91-0.98)	0.96 (0.93-1.00)	0.98 (0.94-1.03)
9 hrs	0.95 (0.91-1.00)	1.00 (0.93- 1.08)	0.96 (0.89-1.04)	0.96 (0.87-1.04)
≥10 hrs	0.98 (0.85-1.13)	0.96 (0.76-1.22)	1.02 (0.82-1.28)	1.12 (0.88-1.43)

**Highlight** =p<0.05. Model 1: age, weight, height, diabetes (DM), race, region, smoking, health status, current hormone therapy (HT) use, total vitamin D and calcium intake, physical activity, previous history of fracture, parental history of fracture, alcohol intake, depression, caffeine, HT Trial arm, DM Trial arm. Model 2: Model 1 + hypnotics, anti-anxiety meds, antidepressants, analgesic narcotics.



# Overall Sleep Quality and Risk of Fracture (Model 2): HR(95% CI)

Sleep Quality	Fractures			
	Total	Upper Limb	Lower Limb	Central
Very Restless	1.01 (0.95-1.08)	0.98 (0.88-1.08)	1.03 (0.93-1.14)	<b>1.14</b> <b>(1.02- 1.20)</b>
Restless	<b>1.05</b> <b>(1.02-1.08)</b>	1.02 (0.97-1.07)	1.08 (1.03-1.13)	1.04 (0.99-1.10)
Average	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Sound/restful	0.98 (0.96-1.00)	<b>0.97</b> <b>(0.93-1.00)</b>	1.00 (0.96-1.04)	0.97 (0.93-1.01)
Very Sound/restful	0.97 (0.94-1.00)	<b>0.95</b> <b>(0.91-1.00)</b>	0.99 (0.94-1.04)	0.94 (0.88-0.99)

**Highlight** =p<0.05. Model 1: age, weight, height, diabetes (DM), race, region, smoking, health status, current hormone therapy (HT) use, total vitamin D and calcium intake, physical activity, previous history of fracture, parental history of fracture, alcohol intake, depression, caffeine, HT Trial arm, DM Trial arm. Model 2: Model 1 + hypnotics, anti-anxiety meds, antidepressants, analgesic narcotics.

# *Sleep Disturbance Level and Risk of Fracture (Model 2): HR(95% CI)*

Sleep Disturbance Level	Fractures			
	Total	Upper Limb	Lower Limb	Central
0-3	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
4-6	<b>1.04</b> <b>(1.01-1.06)</b>	1.02 (0.98-1.07)	1.02 (0.98-1.06)	<b>1.06</b> <b>(1.01-1.11)</b>
7-10	<b>1.04</b> <b>(1.02-1.07)</b>	1.02 (0.99-1.07)	<b>1.04</b> <b>(1.00-1.08)</b>	<b>1.07</b> <b>(1.02-1.13)</b>
≥11	<b>1.09</b> <b>(1.06-1.12)</b>	<b>1.06</b> <b>(1.01-1.11)</b>	<b>1.09</b> <b>(1.04-1.14)</b>	<b>1.14</b> <b>(1.08-1.20)</b>

**Highlight** =p<0.05. Model 1: age, weight, height, diabetes (DM), race, region, smoking, health status, current hormone therapy (HT) use, total vitamin D and calcium intake, physical activity, previous history of fracture, parental history of fracture, alcohol intake, depression, caffeine, HT Trial arm, DM Trial arm. Model 2: Model 1 + hypnotics, anti-anxiety meds, antidepressants, analgesic narcotics.

# Strengths

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- ❑ Well characterized population of older women
- ❑ Multiple fracture outcomes
- ❑ Extended follow-up (11 yrs)
- ❑ Adjustment for important covariates including medications

# Limitations

## ❑ Self-report of sleep

- ❖ Association vary by how sleep is measured
- ❖ U-shape relationship of sleep duration and poor health; Odds ratio

	Hours of sleep				
	<6	>6 - ≤7	>7 - ≤8	>8 - <9	≥9
Self report	4.6	2.2	1.0	1.8	6.9
Actigraphy	2.3	0.9	1.0	0.7	0.8

Lauderdale D. BMJ 2016;70:361

## ❑ Self-reported fractures for non-hip fractures

# Summary

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- ❑ U-shaped relationship of sleep duration with recurrent falls
  - ❖  $\leq 5$  hrs, 6 hrs and  $\geq 10$  hrs
- ❑ Increasing sleep disturbance and insomnia were associated with a 20-40% increased risk of recurrent falls
  - ❖ Adjustment for CNS medications had no effect
- ❑ Poor sleep quality (restlessness) was associated with an increased (30%) risk of recurrent falls while restless sleep was associated with a modest reduction in fall risk
- ❑ Relatively weak relationships of sleep with fractures