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# **Treating Sleep as a Geriatric Syndrome: Nocturia**

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# Support and Disclosures

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- **Consultant: New England Research Institute; Ferring Pharmaceuticals; Georgia Institute of Technology; Vantia Therapeutics; Morehouse School of Medicine; Merck**

# Syndrome vs Disease

(from *Cecil's Medicine*, 24<sup>th</sup> Edition, Philadelphia: Elsevier/Saunders, 2012)

## Syndrome:

“Symptoms and signs...which may be the final pathway of a wide range of pathophysiologic alterations...”

# Definition of Nocturia

- Nocturia defined by International Continence Society (ICS) as:



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the complaint that the individual has to wake at night one or more times to void ...  
each void is preceded and followed by sleep

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# Defining Nocturia: It Gets Complicated

## Nocturia (ICS 2002):

The **complaint** that the individual has to **wake at night one or more times to void**, each void is **preceded and followed by sleep**

## Nocturia (current thinking):

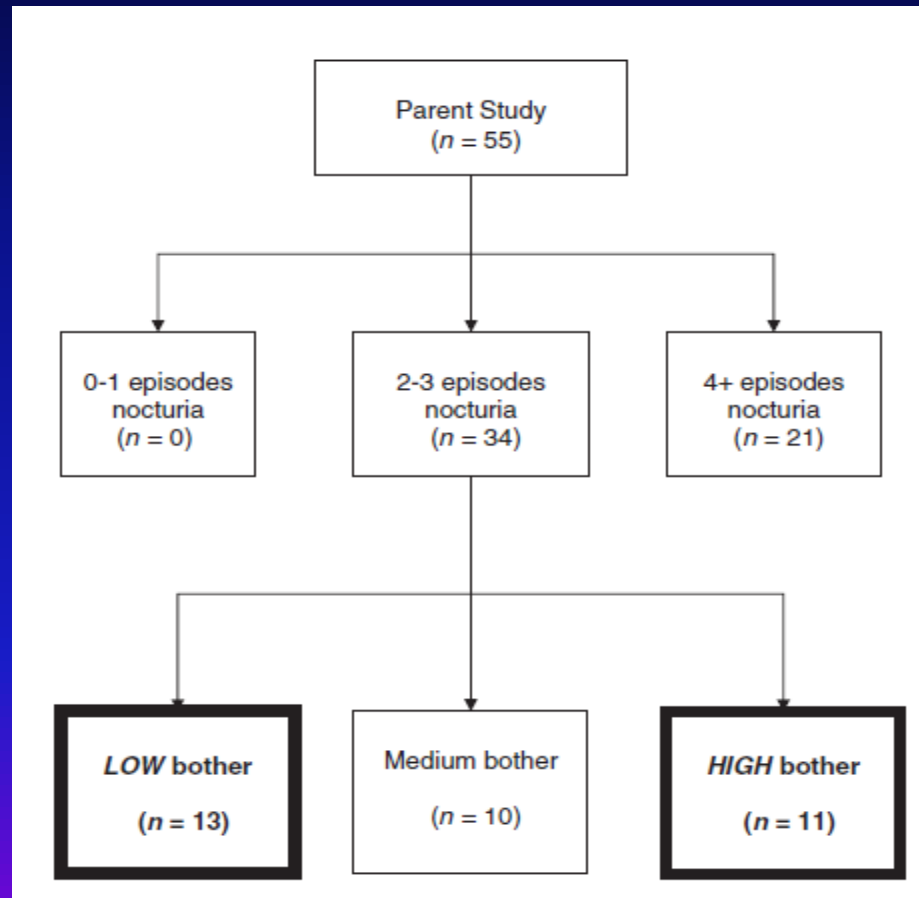
- Need to intervene? “Bother” vs sleep disruption
- How many voids (>1, > 2, > 3, etc)?
- Pathophysiology of sleep disruption (sleep apnea)?
- Reason for awakening (chicken vs egg)?
- Shiftwork (“nocturia” as a misnomer)

**Should Bother Dictate  
Treatment?**

# Nocturia ≠ Bother

## Selected AUA-7 items in relation to sleep diaries

(Vaughan et al, Int J Clin Prac 2012; 66: 369-73)



# Nocturia Frequency Does Not Always Equate With Bother to Patients

- Patients with nocturia who report high levels of bother are significantly more likely to have difficulty initiating sleep, difficulty returning to sleep, and greater morning fatigue

Sleep Characteristic	High Bother <sup>a</sup>	Low Bother <sup>a</sup>	P
Sleep duration, min	n = 8 380.0 ± 90.1	n = 12 425.0 ± 80.7	0.3
Time to initiate sleep, min	n = 11 47.7 ± 34.4	n = 13 23.5 ± 13.6	0.05
Time to return to sleep, min	n = 10 28.9 ± 16.1	n = 12 15.4 ± 9.6	0.03
Morning fatigue <sup>b</sup>	n = 11 3.3 ± 0.7	n = 13 2.5 ± 1.0	0.04

<sup>a</sup>Mean ± standard deviation.

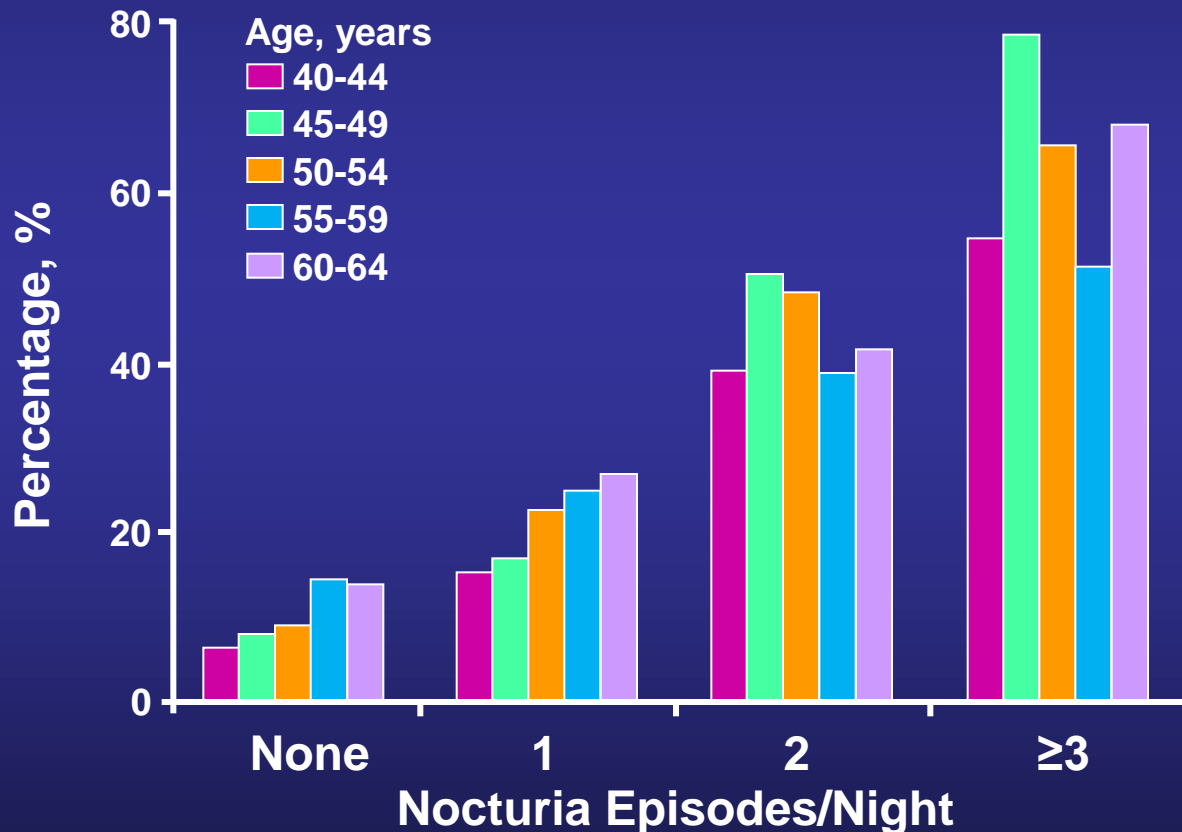
<sup>b</sup>Subjective morning fatigue and sleep ratings: higher scores = worse fatigue or sleep characteristics; scores range from 1 to 7.

Vaughan CP et al. *Int J Clin Pract.* 2012;66(4):369-373.



# Nocturia Is a Widely Reported Cause of Poor Sleep

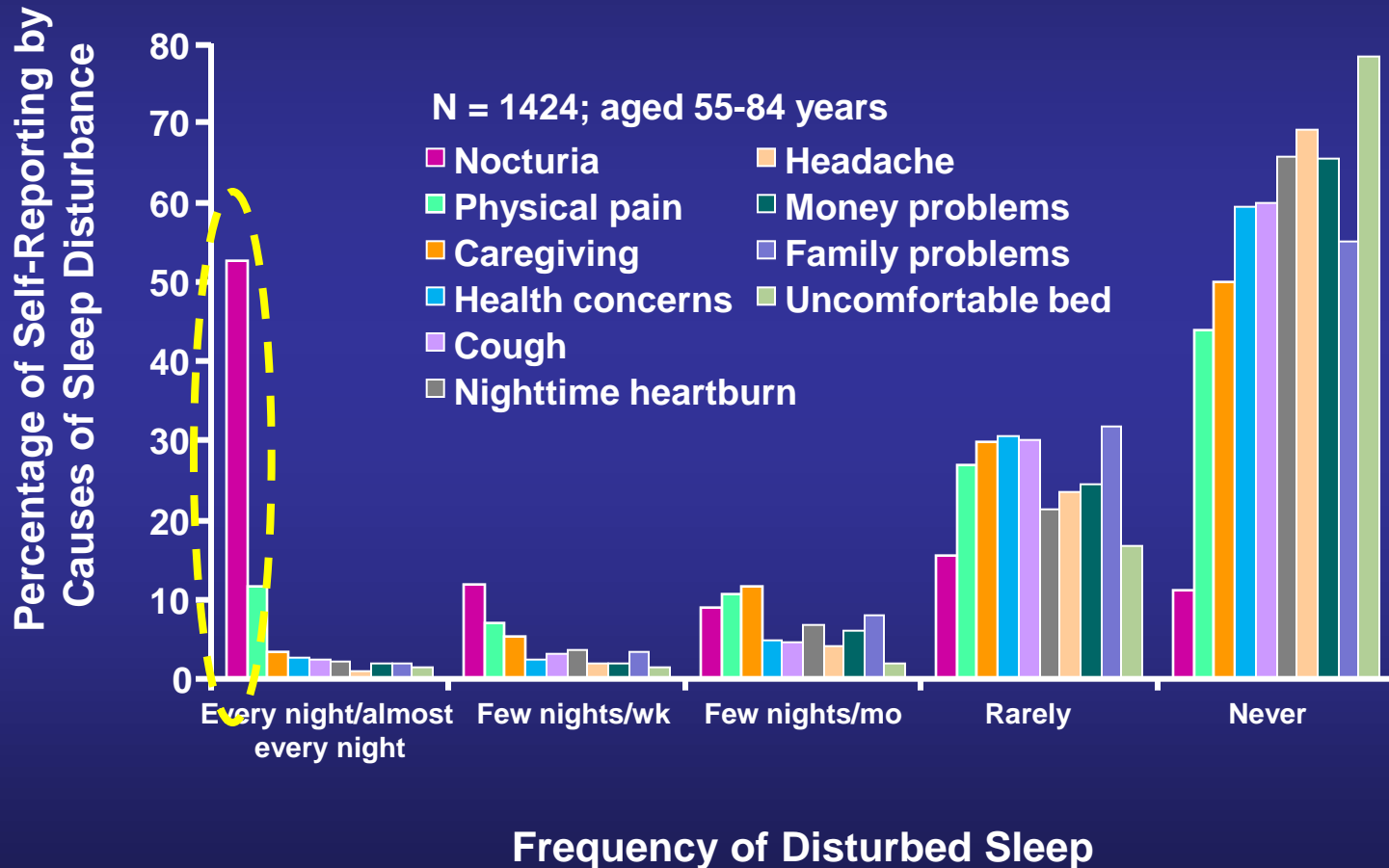
Prevalence of poor sleep in 3669 Swedish women aged 40 to 64 years according to nocturia severity



From: Asplund & Aberg, Maturitas 1996:24,73-81

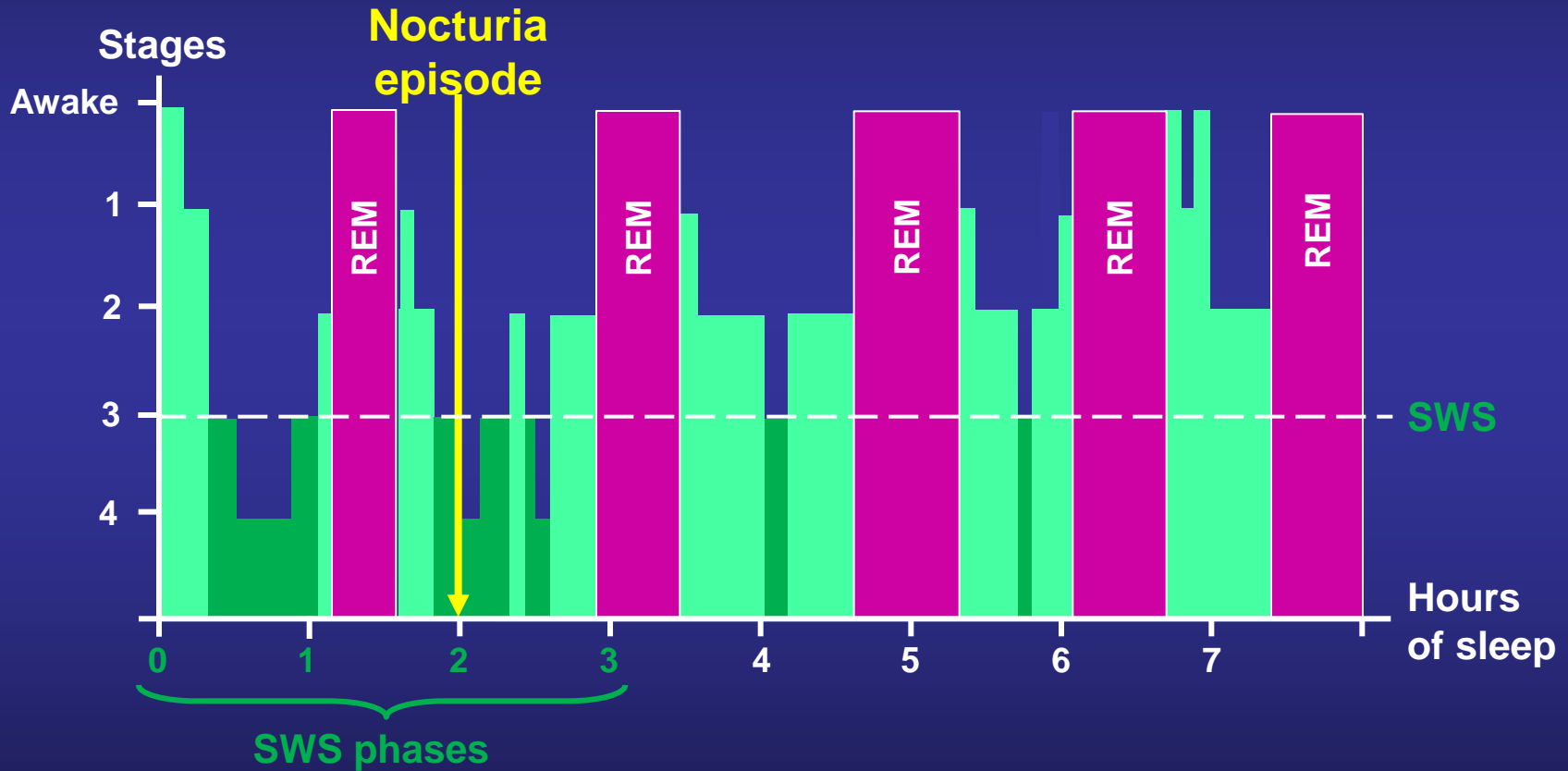
# Nocturia Is the Leading Cause of Sleep Disturbance in Older Adults

How often do the following disturb your sleep?



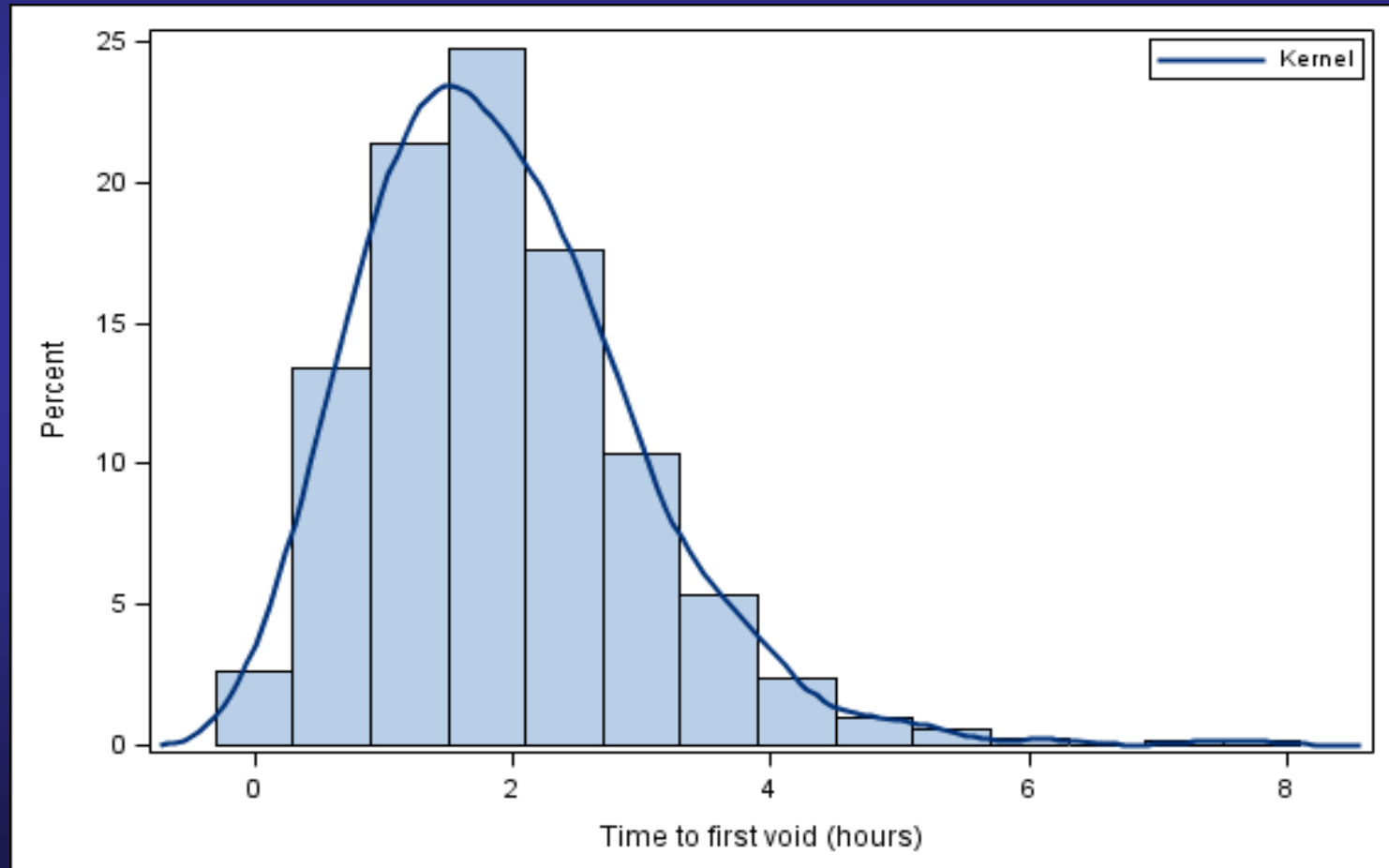
# SWS May Be Interrupted by Nocturia

The first nocturia episode occurs within 2 to 3 hours on average



# Frequency Distribution of Time to First Void (also called First Uninterrupted Sleep Period, FUSP) in Untreated Nocturia

(Bliwise et al, *J Clin Sleep Med* 2015; 11: 53-5)

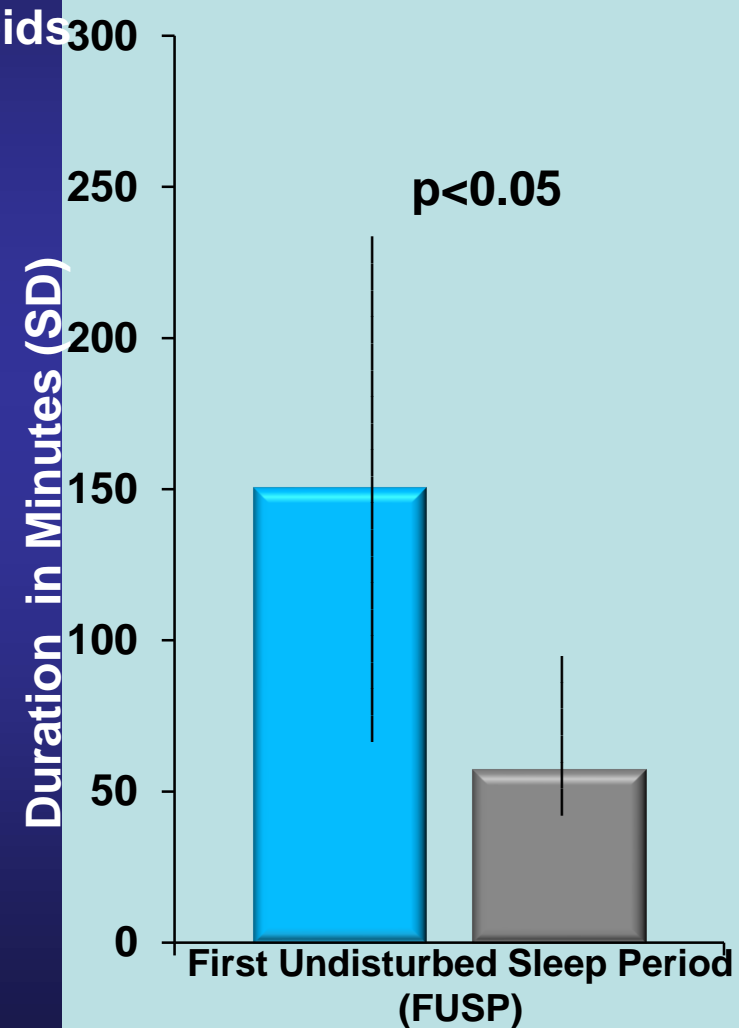
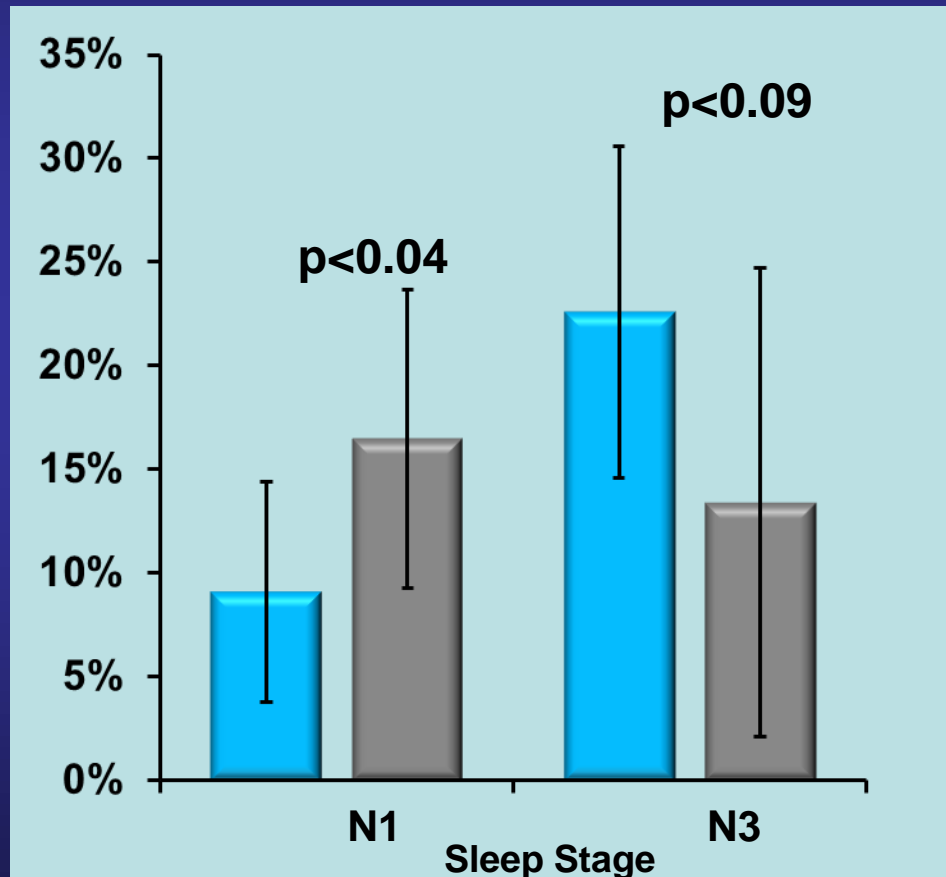


# Polysomnographic Comparison of Nocturia Patients with 1-2 Voids vs 3-4 Voids on Lab Night: All Patients with AHI < 5.0

(Bliwise, Dijk, Juul. *NeuroUrol Urodyn* 2015; 34: 392)

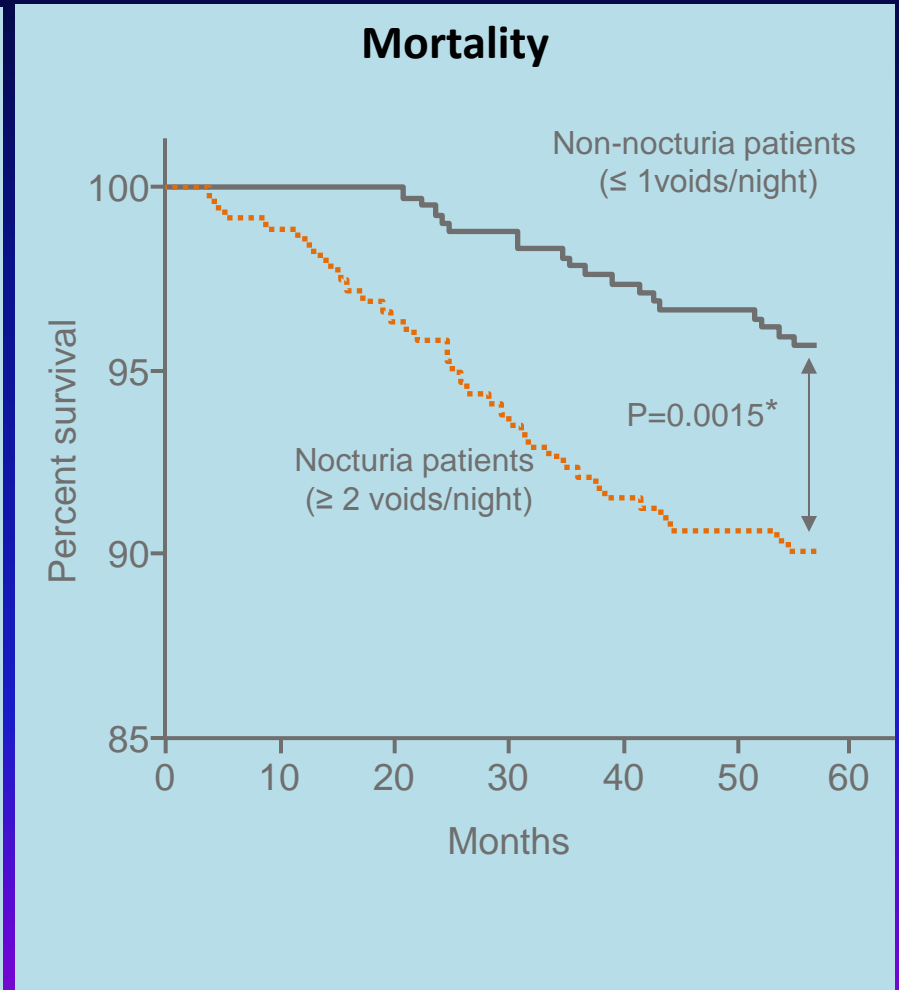
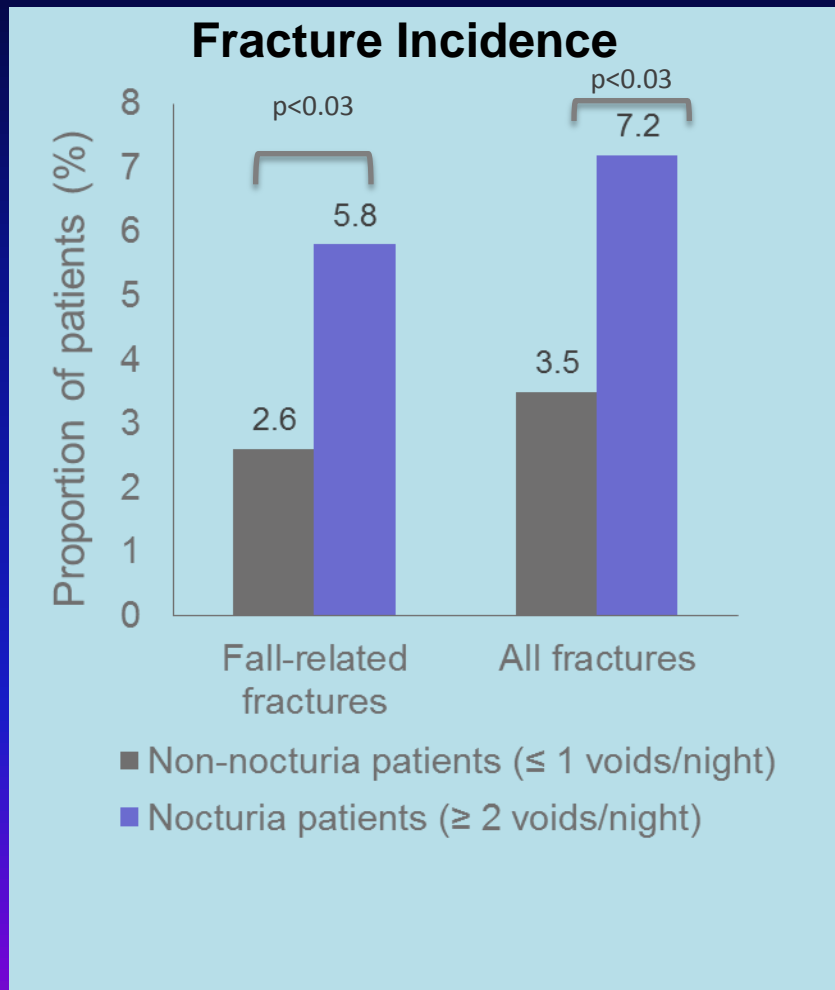
■ 1-2 voids ■ 3-4 voids

Sleep Stage % (SD) (whole night)



# Outcomes of Nocturia

# Nocturia Predicts Fall-related Fractures and Mortality in the Elderly



Kaplan-Meier estimates show significantly lower mortality in patients without nocturia than patients with nocturia (log rank test  $p=0.0015$ ); CI, confidence interval (Nakagawa H et al. *J Urol* 2010;184:1413–1418)

# Nocturia and/or Urge Incontinence Increase Risk for Falls

## Nocturia

- Stewart et al, JAGS 1992; 40: 1217-20
- Asplund et al, Arch Gerontol Geriatr 1996; 43: 319-26
- Jensen et al J Scand J Public Health 2002; 30: 54-61

## Urge Incontinence

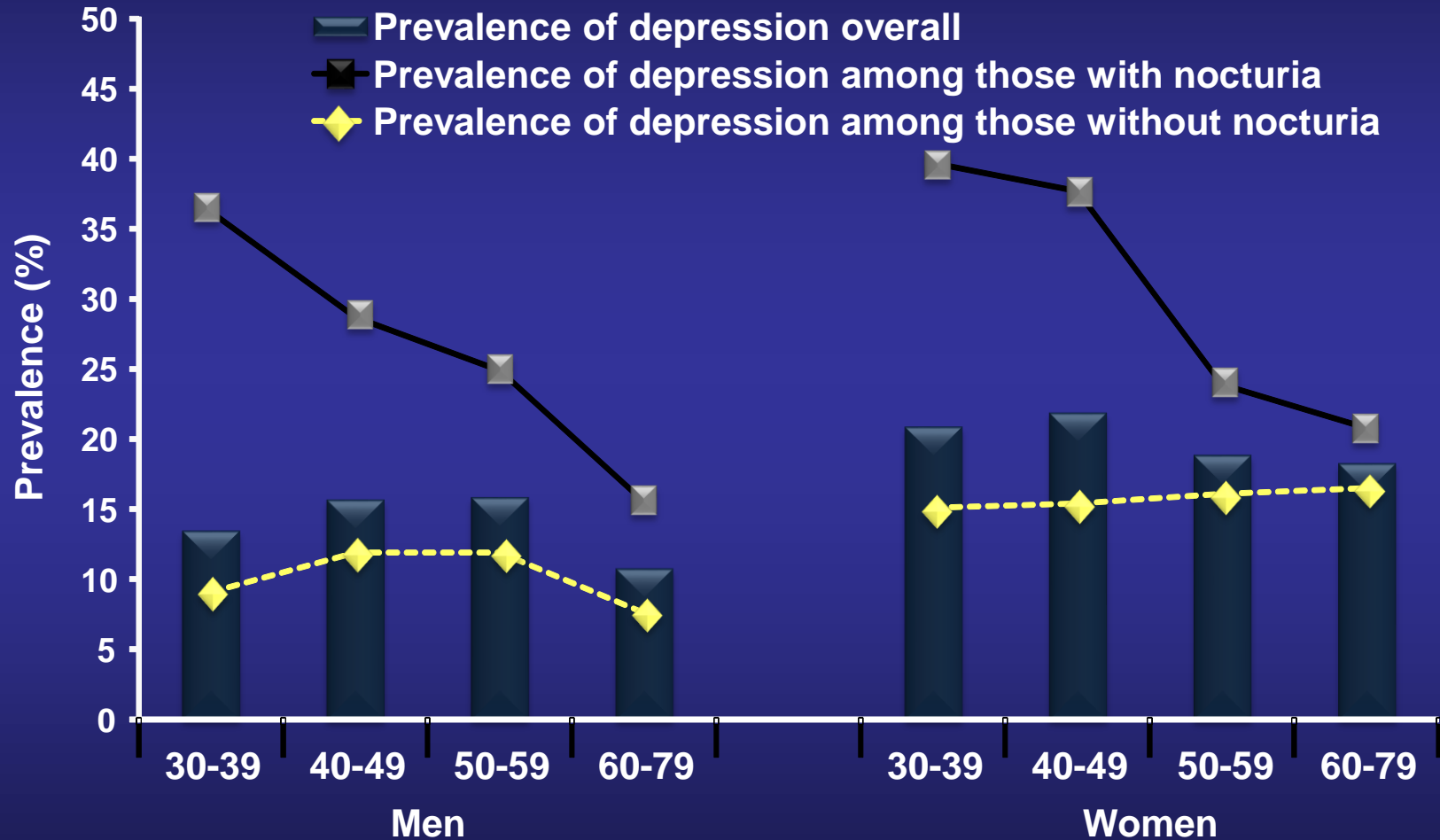
- Kutner et al, JAGS 1994; 42: 757-62
- Brown et al, JAGS 2000; 48: 721-5
- Wagner et al, Am J Manag Care 2002; 8: S598-607



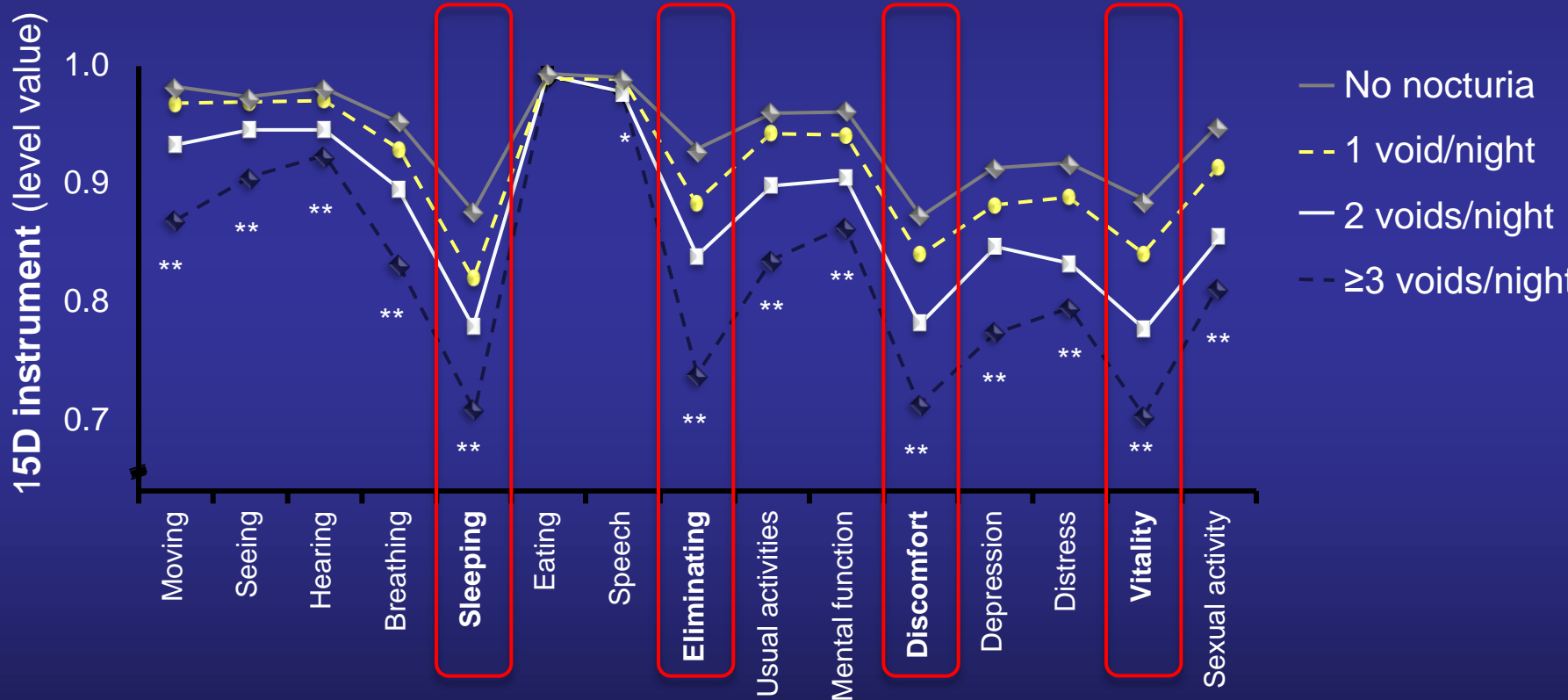
# Poor Sleep Quality or Short Sleep Duration Associated with Falls Independently of Sedative/Hypnotics

- Brassington et al, JAGS 2000; 48: 1234-40
- Avidan et al, JAGS 2005; 53: 955-62
- Stone et al, Arch Inter Med 2008; 168: 1768-75
- Latimer Hill et al, J Gerontol A: Biol. Med Sci 2007; 62: 62-6
- Mesas et al, J Sleep Res 2011; 20: 21-7.

# Nocturia and Increased Risk for Depression: BACH Survey Results



# Nocturia Associated with Significantly Lower Scores on 14/15 Dimensions of HRQoL



n=1,888 Finnish women (similar results in males)

\* $P < 0.05$ ; \*\* $P < 0.001$  (test for trend)

Tikkinen KA et al. *Eur Urol.* 2010;57:488–496.

# Nocturia and Sleep Disordered Breathing in a Community-Dwelling Elderly Population

## RDI Level

	0-9 ( <u>n=26</u> )	10-24 ( <u>n=21</u> )	25+ ( <u>n=11</u> )	<u>p</u>
Age	76.9 (6.0)	79.7 (6.9)	76.5 (7.2)	.26
BMI	24.5 (3.8)	23.4 (3.0)	28.0 (5.7)	.01
Mean Arterial Pressure	99.9 (11.5)	91.9 (11.3)	105.2 (14.7)	.015
# NOC Voids (3-day voiding diary)	1.7 (1.1)	1.6 (0.9)	2.6 (1.4)	.028

Note: Subjects with CHF, uncontrolled diabetes and men with post-void residual volumes > 100 cc excluded; loop diuretics excluded.

From: Endeshaw et al, JAGS 2004; 52: 957-60

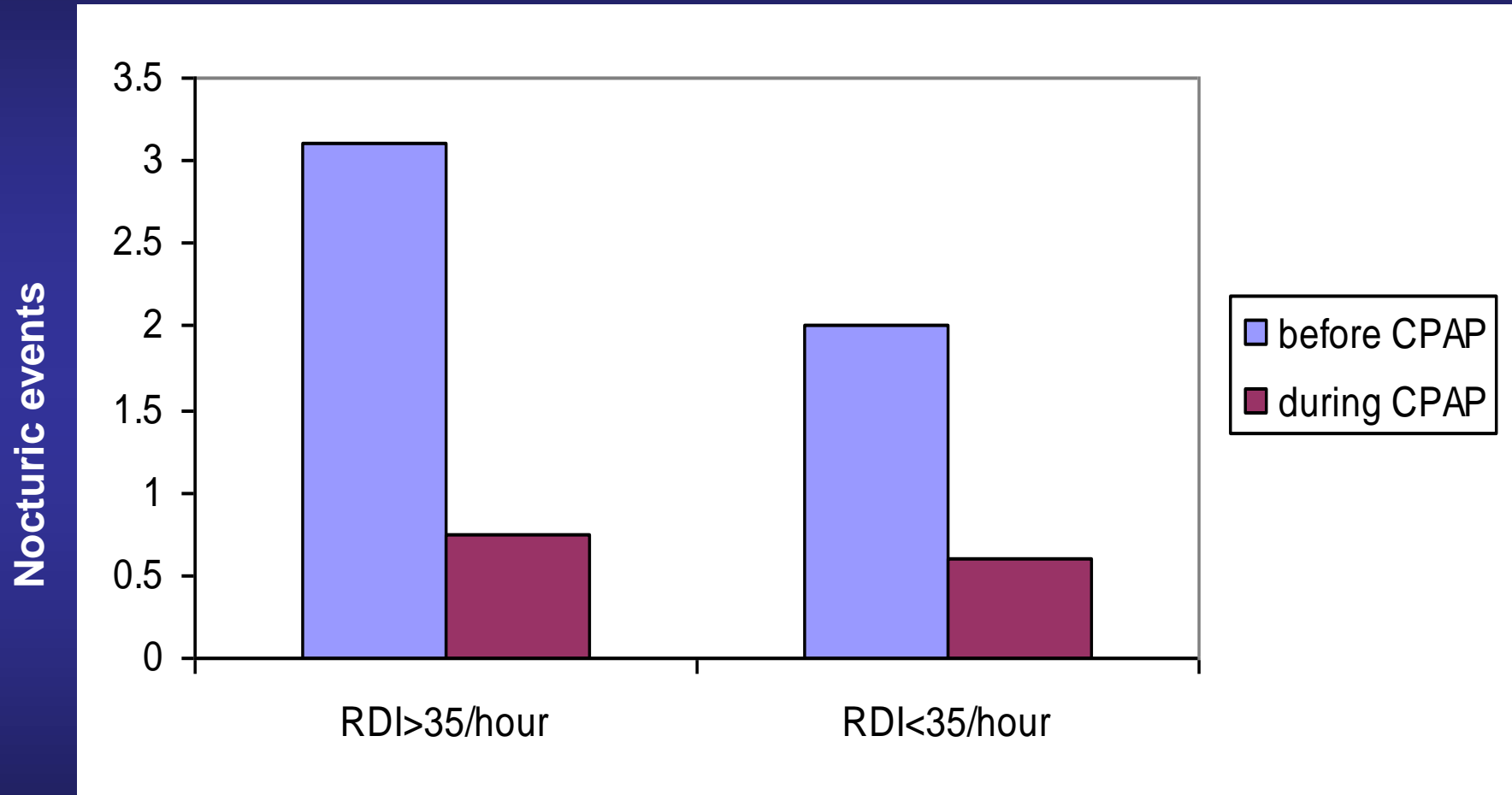
# Polysomnographic (PSG) Measures and Nocturia\*

## Sleep Heart Health Study (n = 6342)

\*NOTES: Nocturia defined as at least 1 awakening to use the bathroom  $\geq 5$  nts/month;  
 Values represent median (IQR) or %'s  
 (Parthasarathy et al PLoS One 2012: 7:e30969)

PSG Measure	Nocturia	No Nocturia	Comparison (p)
Sleep Duration	365 (317, 404)	367 (322, 408)	.06
Sleep Efficiency	82.8 (75.4, 88.0)	85.1 (77.4, 90.1)	< .0001
WASO	55.5 (34.0, 87.0)	43.5 (26.5, 76.5)	< .0001
N1%	4.6 (2.8, 7.2)	4.5 (2.8, 7.1)	.32
N2%	57.5 (49.3, 65.4)	57.2 (49.3, 64.9)	.30
N3%	16.7 (8.2, 25.7)	17.0 (8.2, 24.6)	.36
REM%	19.8 (15.4, 23.7)	20.5 (16.5, 24.3)	< .0001
AHI > 15 (%)	23.2	17.4	< .0001

# Nocturia Episodes Reduced by CPAP

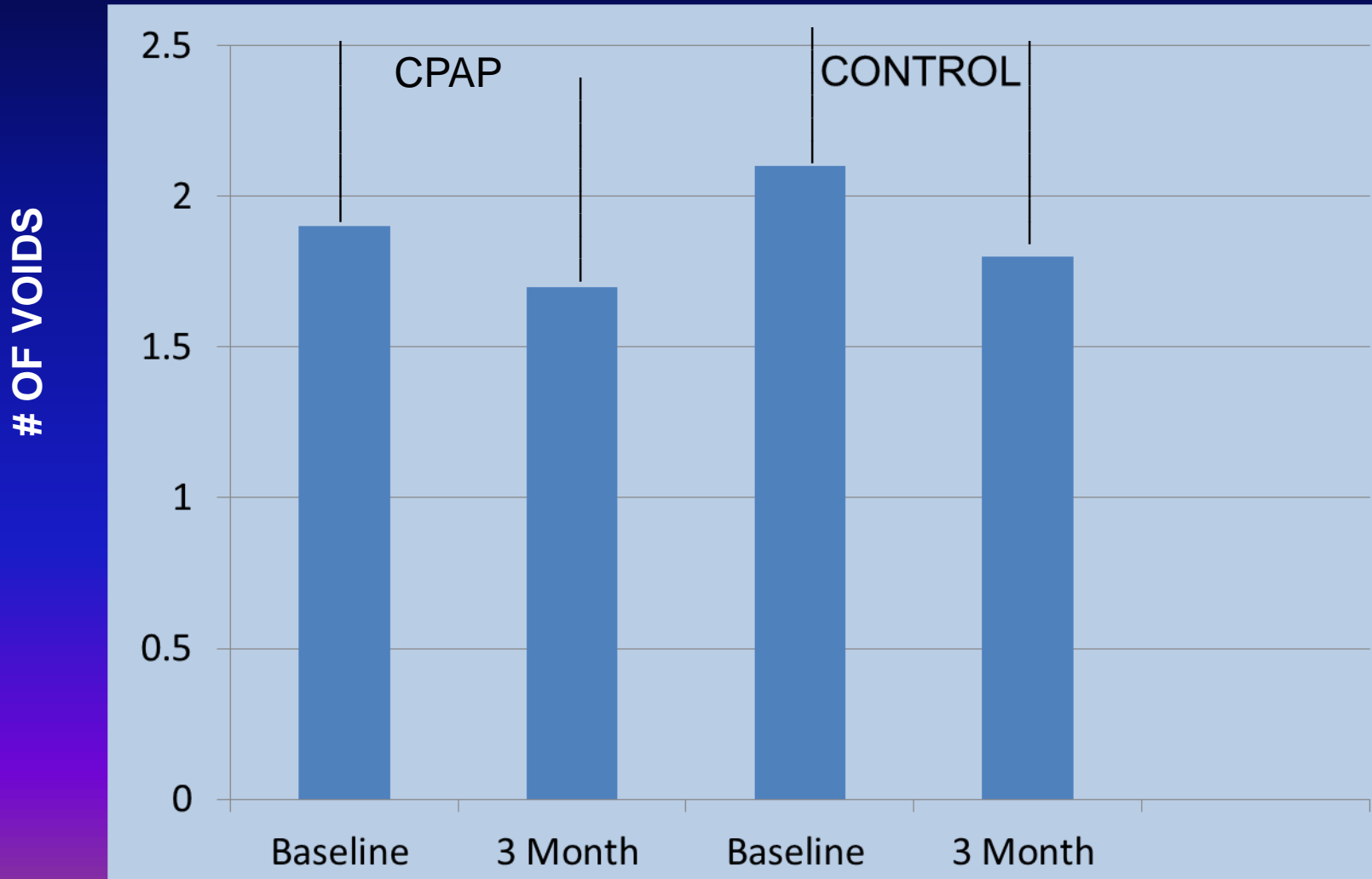


From: Margel et al, Urology 2006; 67:974-7.

# No Effect of CPAP on Nocturia

## The PREDICT Trial

(McMillan et al, *Lancet Respir Med* 2014; 2: 804-12)



# Chicken and Egg

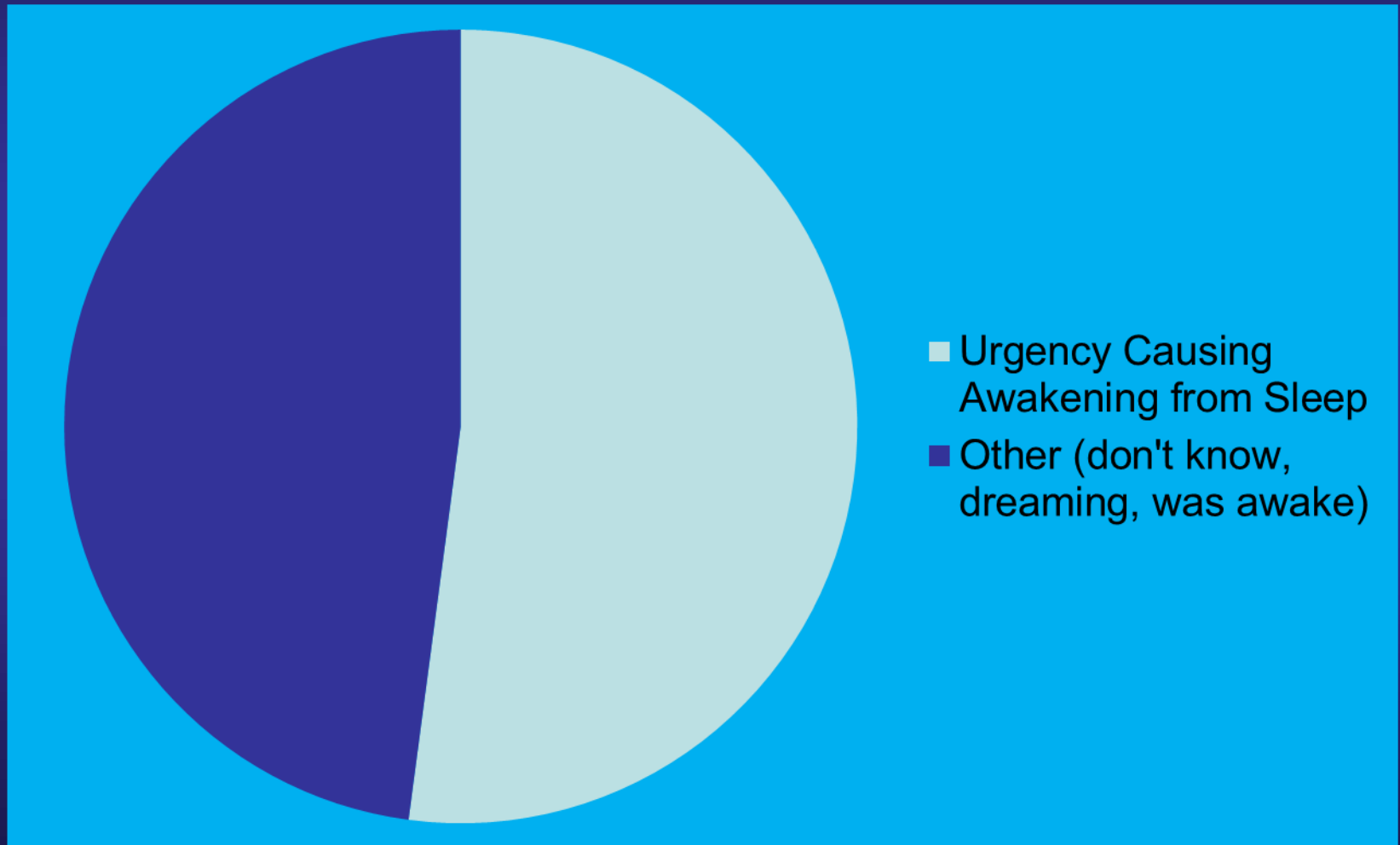
- Do patients awaken because of the need to void? *OR...*
- Do patients awaken from other causes and then appreciate bladder sensations that prompt the bathroom trip?



# Nocturia in the Sleep Lab

*Only half of 121 awakenings to void attributed to urinary urgency*

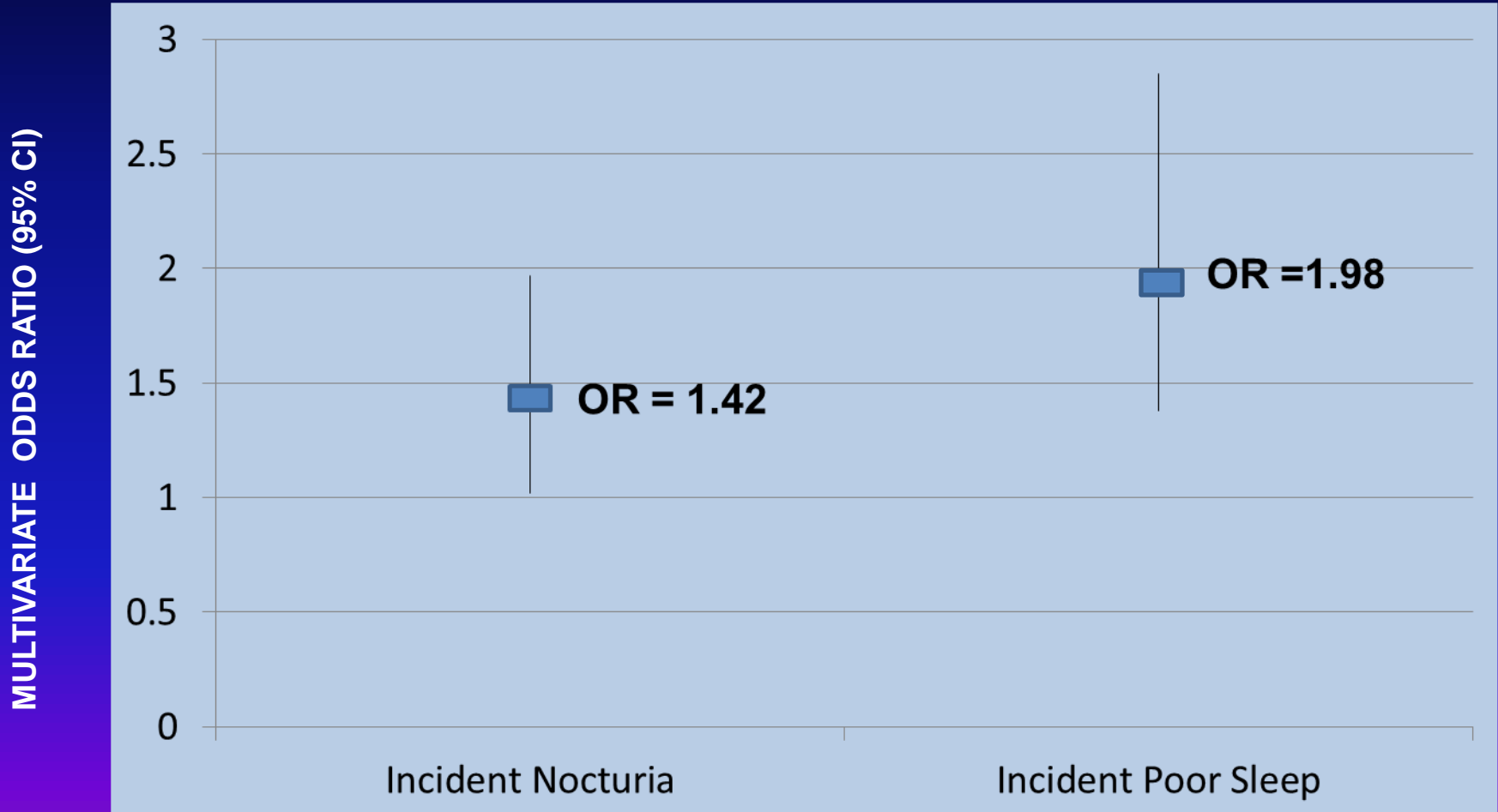
(Pressman et al, *Arch Int Med* 1996; 156: 545-60)



# Bidirectionality in a Longitudinal Study of Nocturia and Poor Sleep

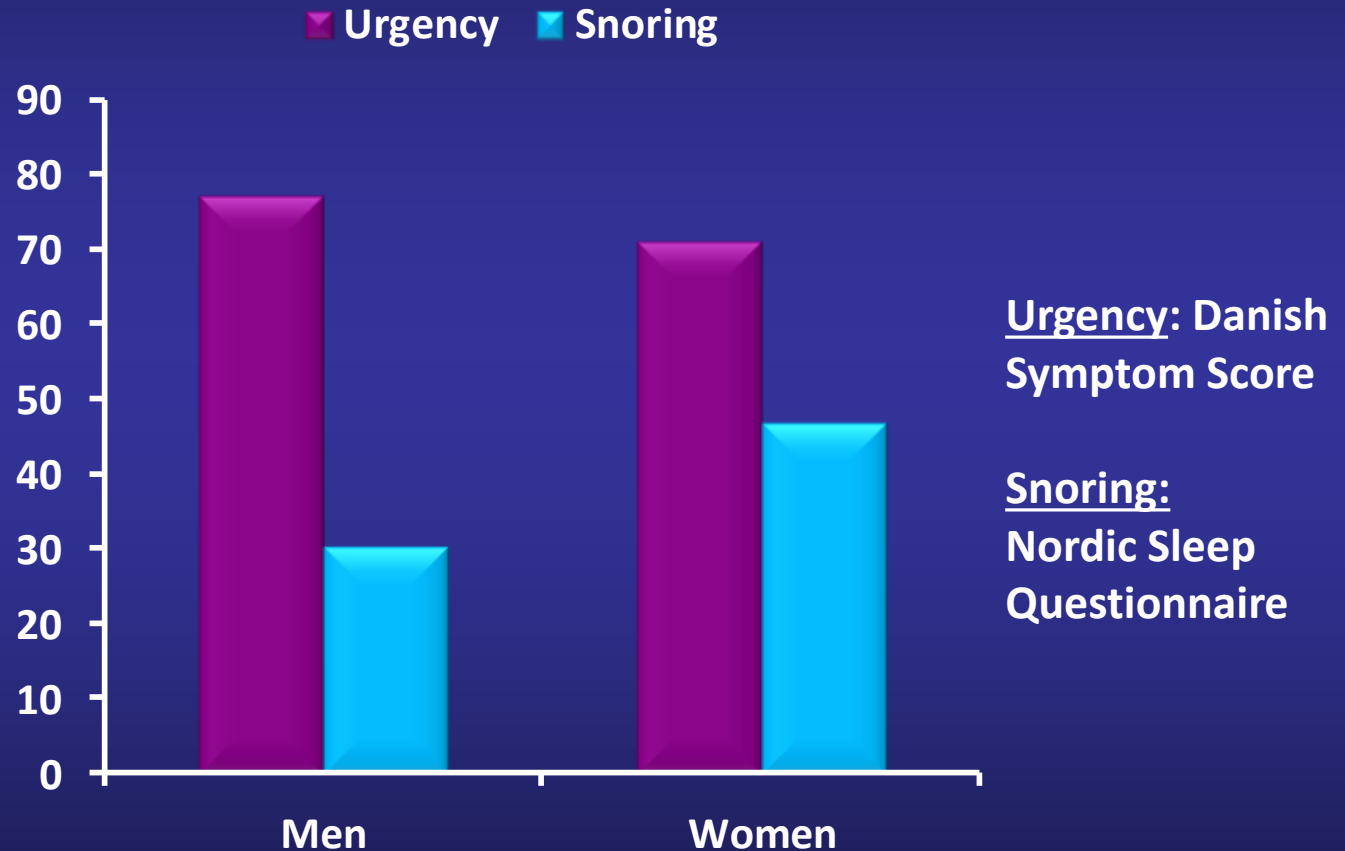
*5-year follow up of the BACH Cohort*

(Araujo et al, *J Urol* 2014; 191: 100-6)

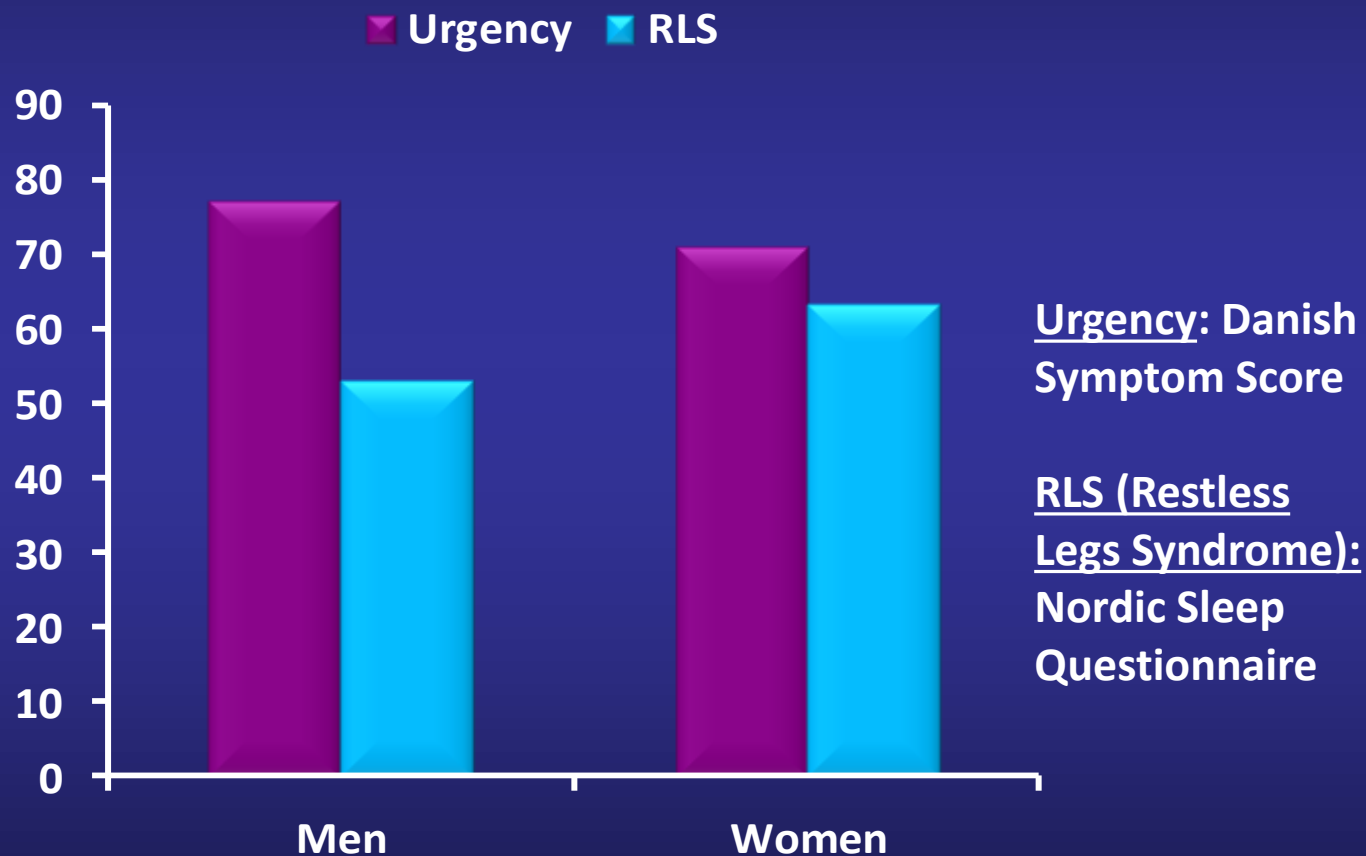


Controlling for baseline sleep (or nocturia) and controlling for age, sex, race, SES, diabetes, heart disease, alcohol, physical Activity, smoking, anti-depressants, sedative/hypnotics, stimulants

# Attributable Fraction (%) of Nocturia Cases Eliminated If Exposure was Eliminated (Finland Study): Snoring Awakening Because of Urge vs. Voiding When Awake



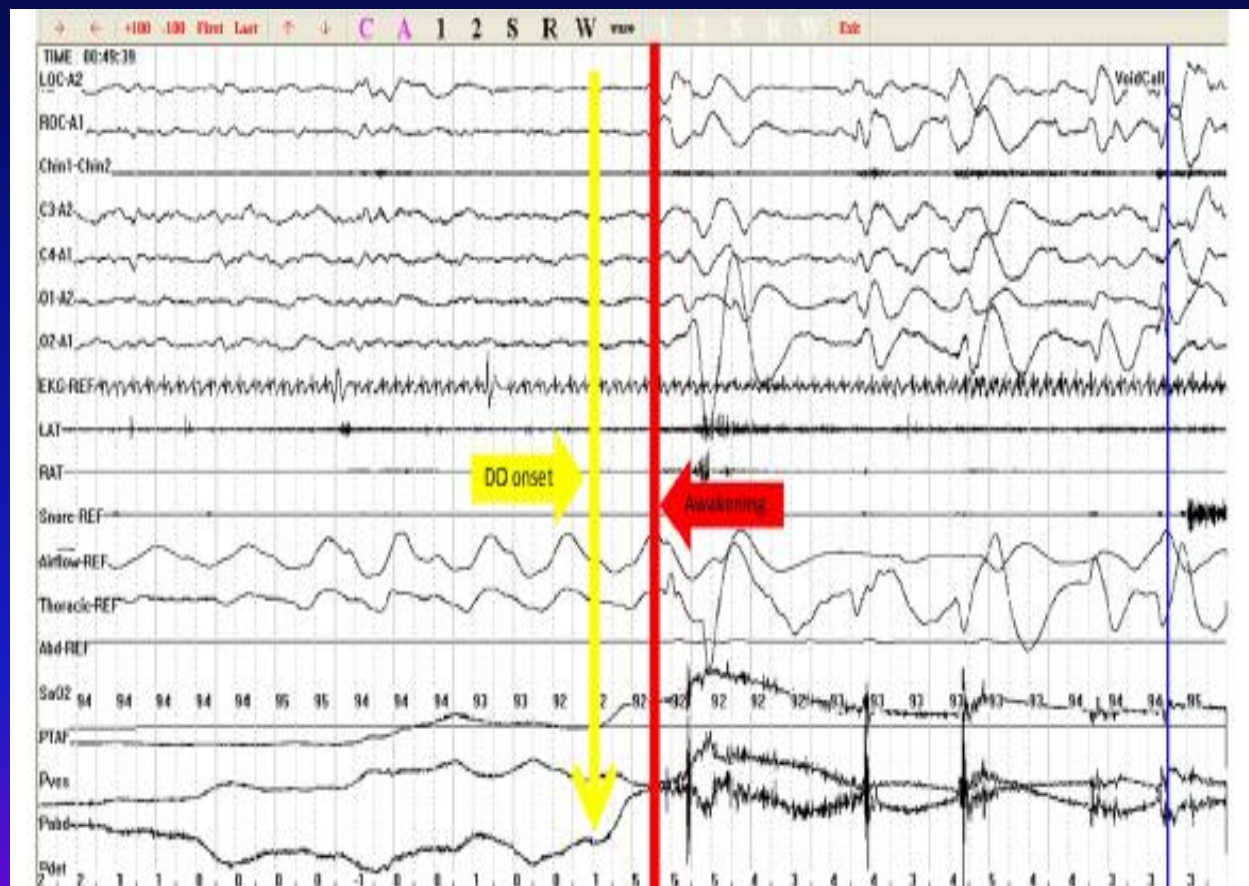
# Attributable Fraction (%) of Nocturia Cases Eliminated If Exposure was Eliminated (Finland Study): Restless Legs Awakening Because of Urge vs. Voiding When Awake



# Detrusor Overactivity (DO) during Sleep in Patients with Overactive Bladder (OAB)

7 of 9 OAB pts also had nocturnal polyuria; control groups show neither DO nor NP

DO defined as pressure of  $\geq 2$  cm H<sub>2</sub>O for  $\geq 1$  sec



Pves: bladder pressure  
Pabd: abdominal pressure  
Pdet: detrusor pressure  
(Pves – Pabd)

(Krystal et al, *J Urol* 2010; 184: 623-8)

# Sleep Apnea and Incontinence in the Nursing Home

*Wetness Episodes Can Begin During Apneic Events*



(Bliwise, Adelman & Ouslander, Sleep 2004;27:153-157)

# TREATMENTS

# TURP has Limited Effect on Nocturia

- 118/138 (85.5%) BPO patients had nocturia before TURP
- After treatment, 91 of these (77.1%) still reported nocturia
- Improvement in nocturia score (1.0) significantly inferior to improvements for all other IPSS symptoms

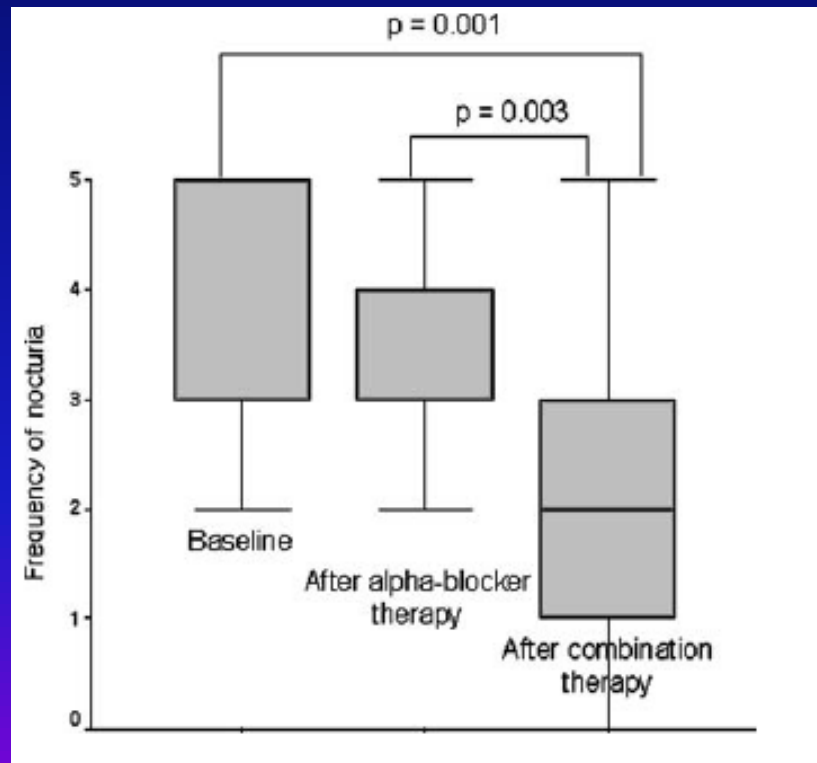
	Patients scoring $\geq 2$ score before TURP	Patients scoring $\geq 2$ score after TURP	Rate of response (%)
Emptying	102	27	54.3
Voiding frequency	116	63	38.4
Intermittency	101	33	49.3
Urgency	103	70	37.0
Weak stream	122	35	63.0
Hesitancy	84	18	47.8
Nocturia	118	91	19.6

**TURP not the answer – are other mechanisms involved?**



# GABAergic Medication May Enhance Efficacy of Nocturia Rx

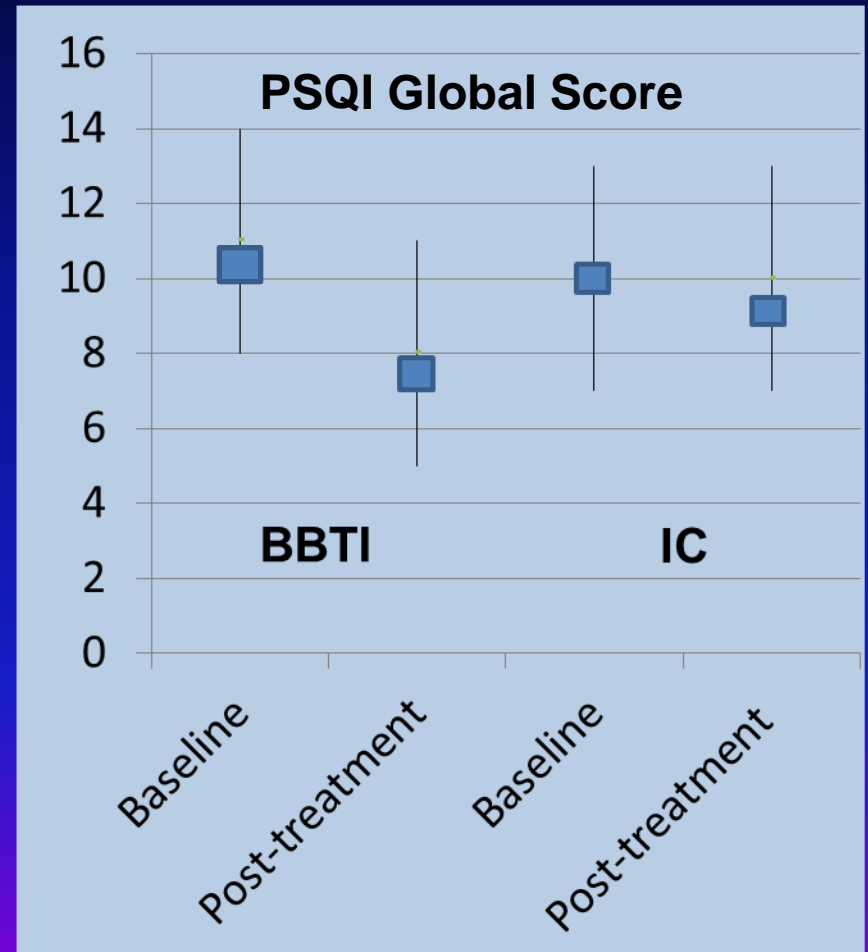
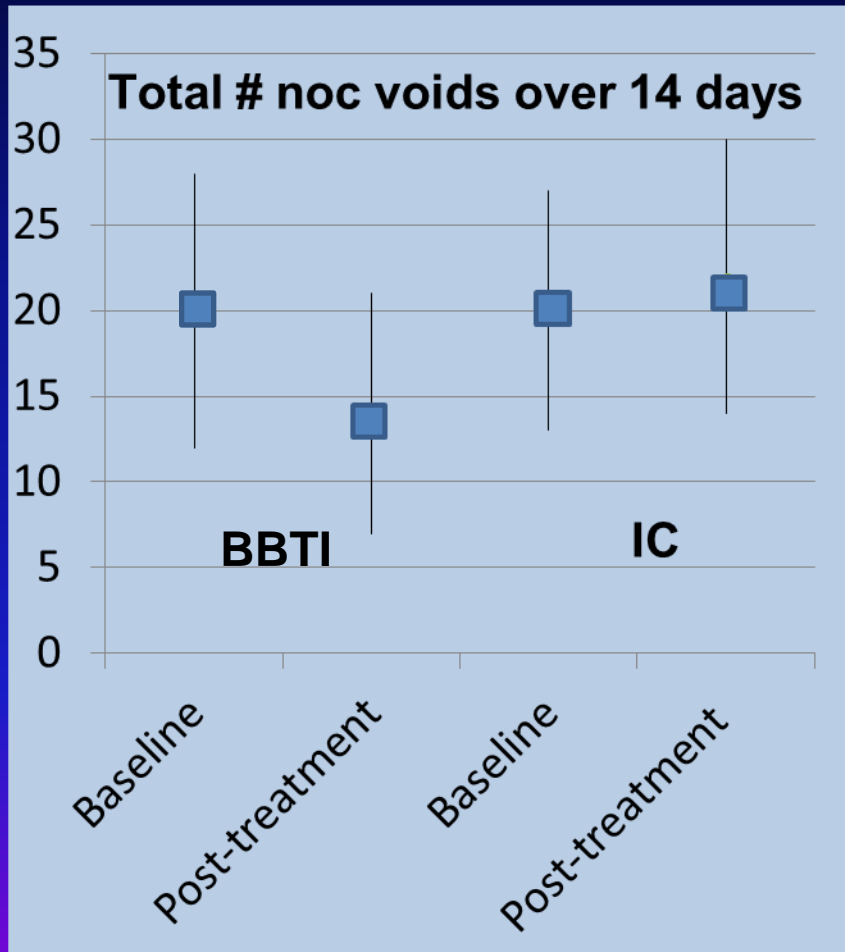
Additive Effects of Zolpidem +  $\alpha$  Blocker



# Can Treating Insomnia Behaviorally Benefit Nocturia in the Elderly?

*Brief Behavioral Treatment for Insomnia (BBTI) vs Information Control (IC)*

(Tyagi et al, *J Am Geriatr Soc* 2014; 62: 54-60)



# Solifenacin-related Improvements in Sleep Quality: Assessment with Wrist Actigraphy

*Open label, single-group design of a muscarinic antagonist*

(Takao et al, *Urology* 2011; 78: 648-652)

	BASELINE	8 WEEKS	P
SLEEP LATENCY (mins)	13.8 (13.9)	13.1 (10.8)	.683
TOTAL SLEEP TIME (mins)	352.2 (46.4)	368.8 (44.4)	.030
SLEEP EFFICIENCY (%)	73.0 (7.2)	75.7 (6.2)	.007
WAKE AFTER SLEEP ONSET (mins)	98.0 (40.0)	89.6 (35.5)	.096
NUMBER OF AWAKENINGS	30.8 (7.7)	29.6 (7.7)	.272

# Excessive Nocturnal Urine Production is a Major Contributing Factor to the Etiology of Nocturia

Jeffrey P. Weiss,<sup>\*,†</sup> Philip E. V. van Kerrebroeck,<sup>‡</sup> Bjarke M. Klein<sup>§</sup>  
and Jens Peter Nørgaard<sup>§</sup>

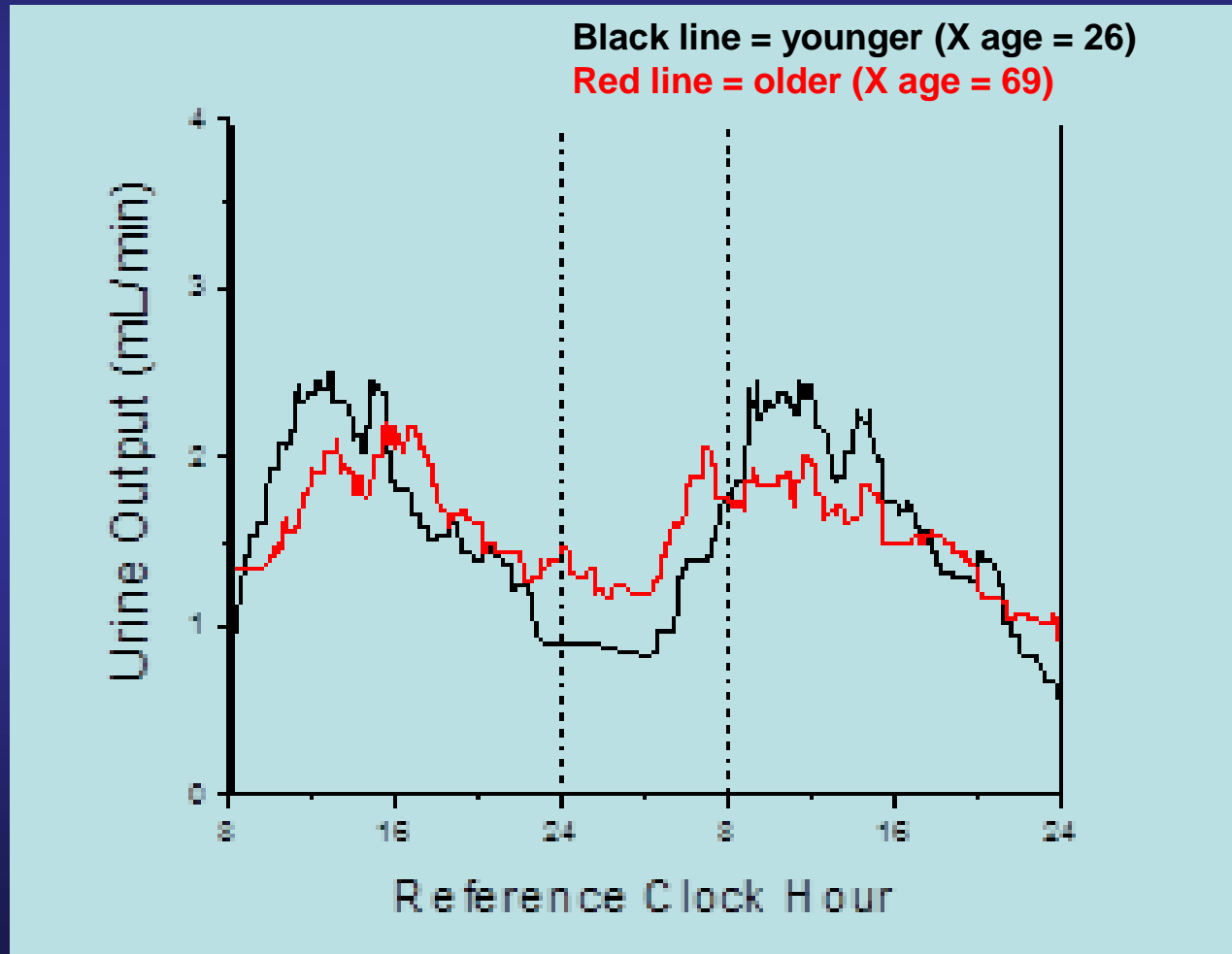
*From the Department of Urology, State University of New York Downstate Medical School (JPW), Brooklyn, New York, Department of Urology, Maastricht University Medical Center (PEVvK), Maastricht, The Netherlands, and Clinical Research and Development, Global Biometrics (BMK) and Medical Science Urology (JPN), Ferring International Pharmascience Center, Copenhagen, Denmark*

**“...this study and others show that **NP** (nightly urine overproduction) **is present in most patients with nocturia**, including those with persistent nocturia despite BPH and OAB therapy. This finding is consistent regardless of gender, age and ethnicity.”**

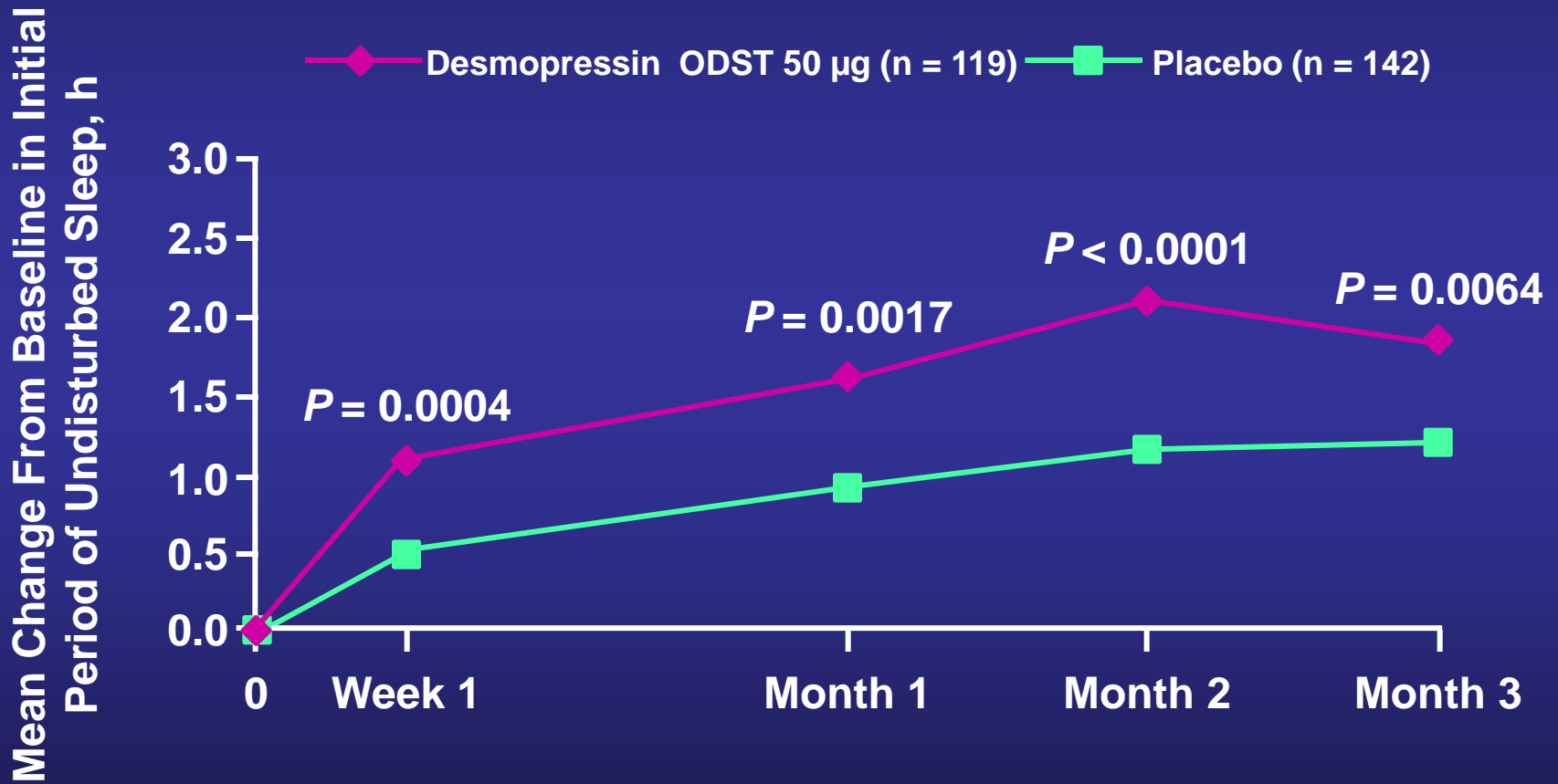
# Age Differences in Urine Production during the Constant Routine

*Controlling for fluid and food intake, posture, sleep and lighting*

(from Hares et al, J Sleep Res 2006; 15(Suppl 1): 182-3)



# Increase in FUSP With Desmopressin Melt (50 µg) in Men Over 3 Months' Nightly Administration



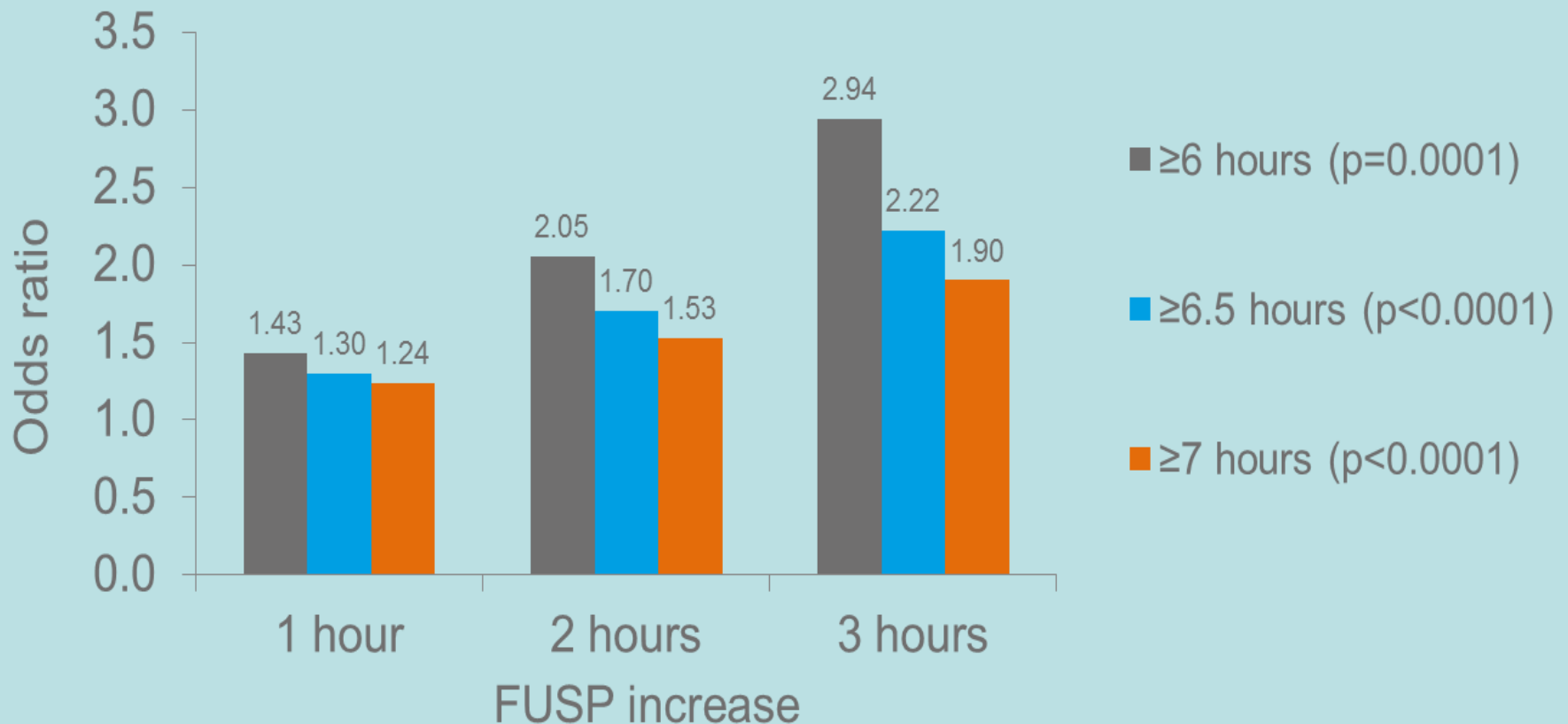
# Improvement in Nocturia is Associated with Improvements in Sleep Quality

*One hour increase in FUSP was associated with a significant improvement in 7 out of 8 components of the PSQI*

PSQI Scale Component	n	Parameter estimate	SE	p-value
Global	607	-0.488	0.054	<0.0001
Sleep Quality	633	-0.106	0.012	<0.0001
Sleep Latency	609	-0.079	0.015	<0.0001
Sleep Duration	632	-0.068	0.013	<0.0001
Sleep Efficiency	632	-0.102	0.018	<0.0001
Sleep Disturbances	634	-0.044	0.012	=0.0002
Sleep Medication	634	-0.016	0.016	=0.30
Daytime Dysfunction	634	-0.075	0.014	<0.0001

# Lengthening of FUSP in Nocturia Increases the Odds of a Longer Total Sleep Duration

(Bliwise et al, *Sleep Health* 2015; 1: 211-3)





# Conclusions

- **Nocturia most assuredly meets criteria for a syndrome, particularly important for geriatrics**
- **It is associated with many morbidities (symptoms and signs), none the least of which is poor sleep itself**
- **Knowledge of successful treatments lags behind and is an important area for future research**

**Thank you for your attention**  
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