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Center for Sleep and Circadian Neurobiology
Penn Behavioral Sleep Medicine Program Philadelphia, PA

A Personal Retrospective: Past Work on Sleep & Aging and the Possibilities for the Future

alt title: Poor Sleep in the Elderly:
A Role for Nocturia?

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Support and Disclosures

- My prior work has been supported by AG-020269; AG-10643; AG-06066; AG-025688; AT-00611; NS-050595; and a grant from the Alzheimer's Association
- Consultant: Ferring Pharmaceuticals; Merck; Respicardia

A photograph of the Wesley Woods Geriatric Hospital entrance. In the foreground, a low white concrete wall features the hospital's name in dark, raised letters. Behind the wall, a paved road leads to a building with a prominent white portico supported by several columns. A dark sedan is parked on the left side of the road, and a white van is partially visible behind it. The building has light-colored siding and a gabled roof. The scene is set outdoors with trees and shrubs in the background.

WESLEY WOODS GERIATRIC HOSPITAL

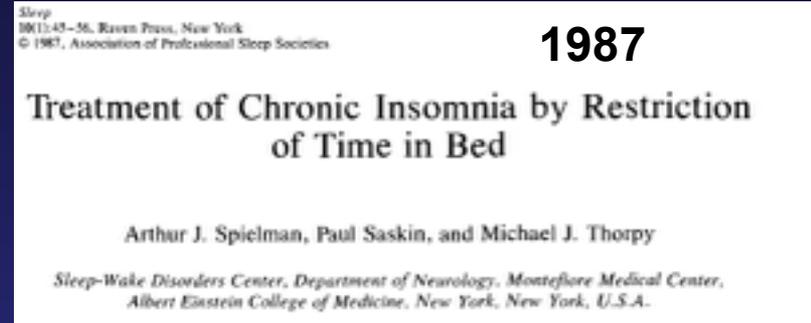
The Personal Retrospective Thing

Allan Rechtschaffen
1974-1982



William Dement
1982-1992

Art Spielman



Jerry Yesavage



Leah Friedman

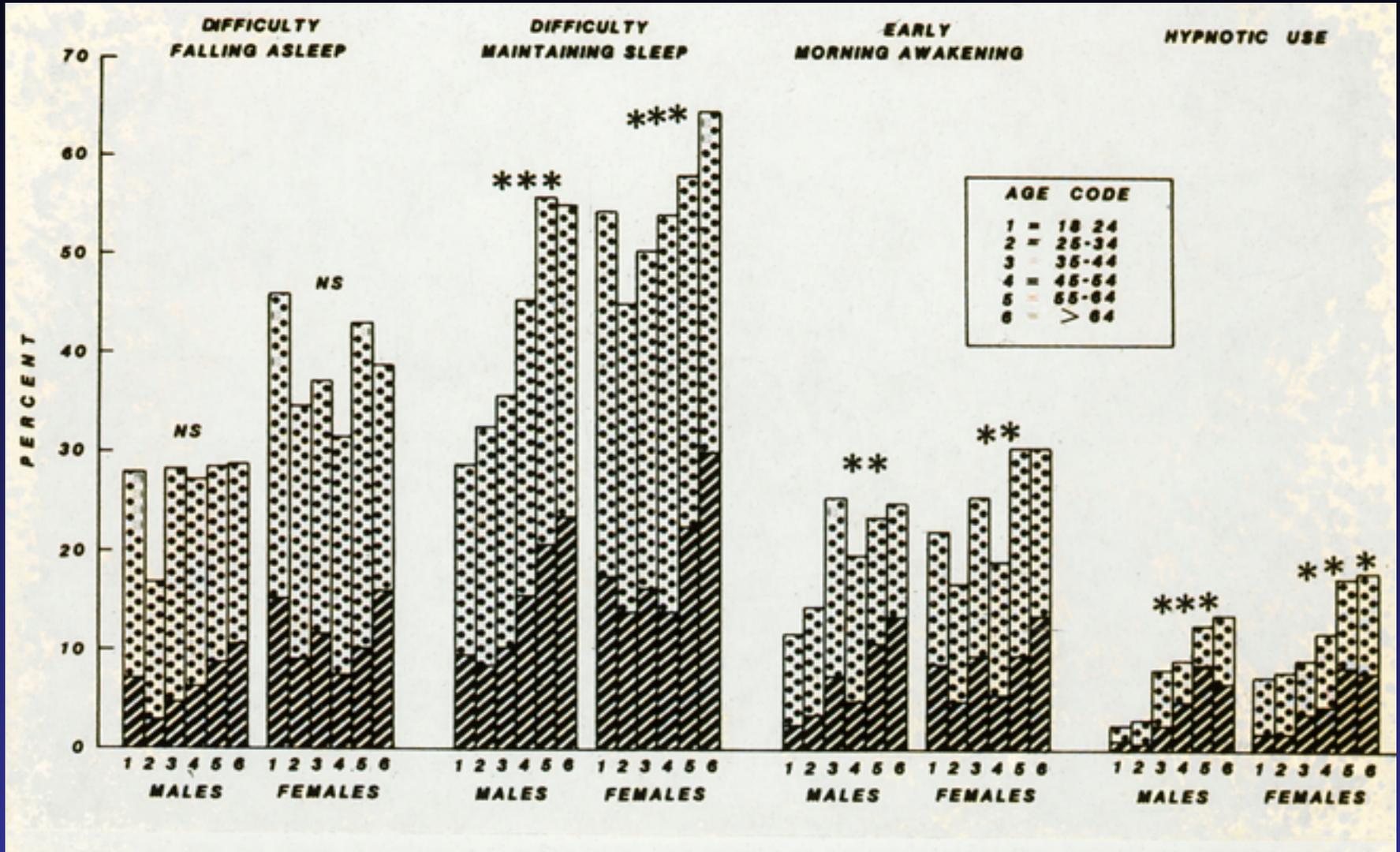


OUTLINE

- **Epidemiology (Prevalence, Outcomes)**
- **Mechanistic Issues**
- **Chicken and Egg Problem**
- **Treatments**

Prevalence of Chronic Insomnia Increases with Age

(Karacan et al. In: Guilleminault C, Lugaresi E (eds.) *Sleep/Wake Disorders: Natural History, Epidemiology and Long-Term Evolution*. New York: Raven, 1983, pp 37-60)



Epidemiology of Insomnia: Population-based Cross-Sectional Odds Ratios (95% CI) for Co-morbidities (the usual suspects)

(Katz & McHorney, *Arch Intern Med* 1998; 158: 1099-1107)

Risk Factor	Mild Insomnia	Sev Insomnia
Depression	2.6 (1.9-3.5)	8.2 (5.7-12.0)
Dysthymia	2.2 (1.7-2.7)	3.4 (2.6-4.6)
MI	1.9 (1.2-2.9)	0.9 (0.4-1.9)
CHF	1.6 (1.1-2.2)	2.5 (1.5-3.9)
Angina	1.3 (1.0-1.7)	1.3 (1.0-1.8)
COPD	1.6 (1.1-2.2)	1.5 (1.0-2.3)
Back Pain	1.4 (1.1-1.7)	1.5 (1.2-2.0)
Hip Pain	2.2 (1.3-3.8)	2.7 (1.4-5.1)
Osteoarthritis	1.4 (1.0-2.0)	1.6 (1.0-2.5)

Proportion of Elderly Men and Women who State “I Sleep Well at Night” in Relation to Number of Nocturnal Voids¹

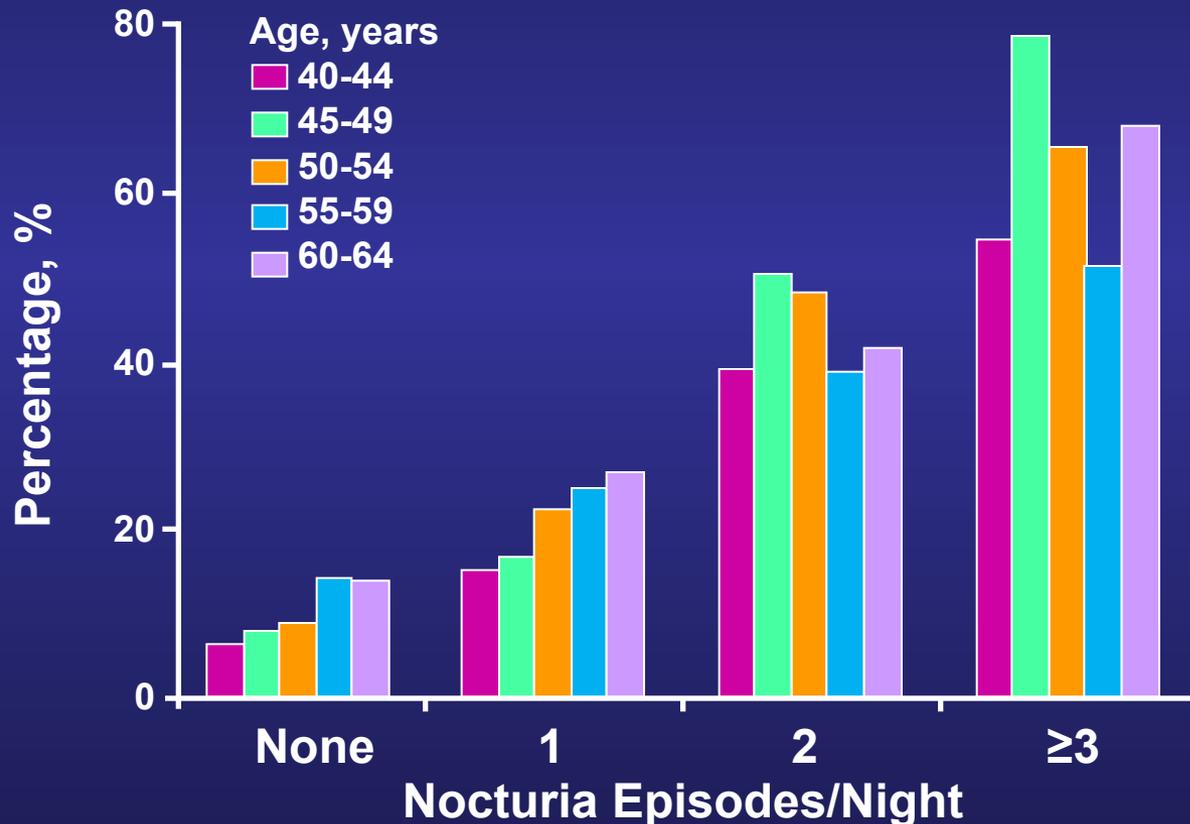
	Number of Voids			
	0	1	2	3+
Men ²	89.9	91.3	78.3	75.5
Women ³	79.9	75.4	56.8	43.6

¹Asplund and Åberg. Scan J Prim Health Care 1992;10:98-104

^{2, 3}p <.0001

Nocturia Is a Widely Reported Cause of Poor Sleep

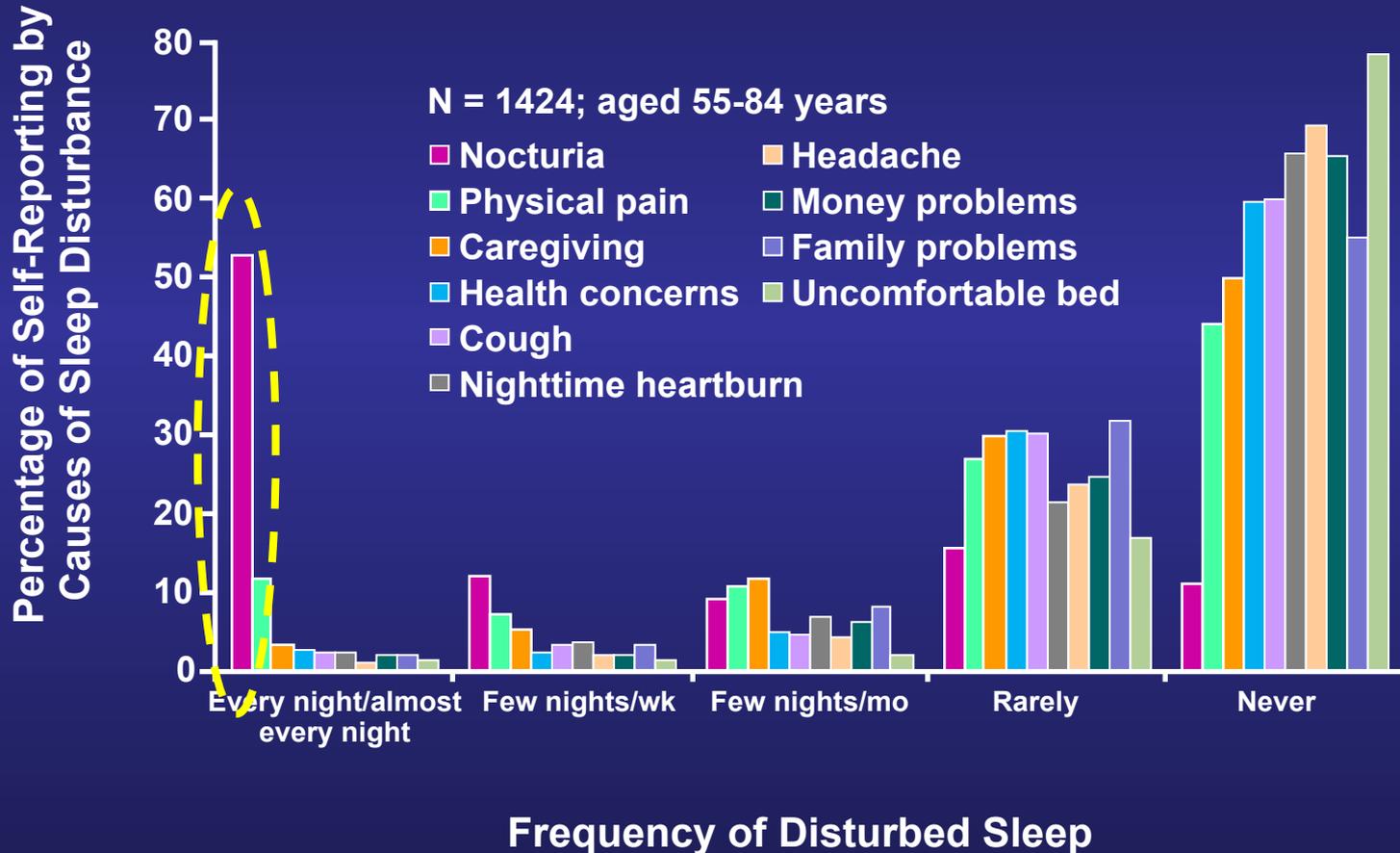
Prevalence of poor sleep in 3669 Swedish women aged 40 to 64 years according to nocturia severity



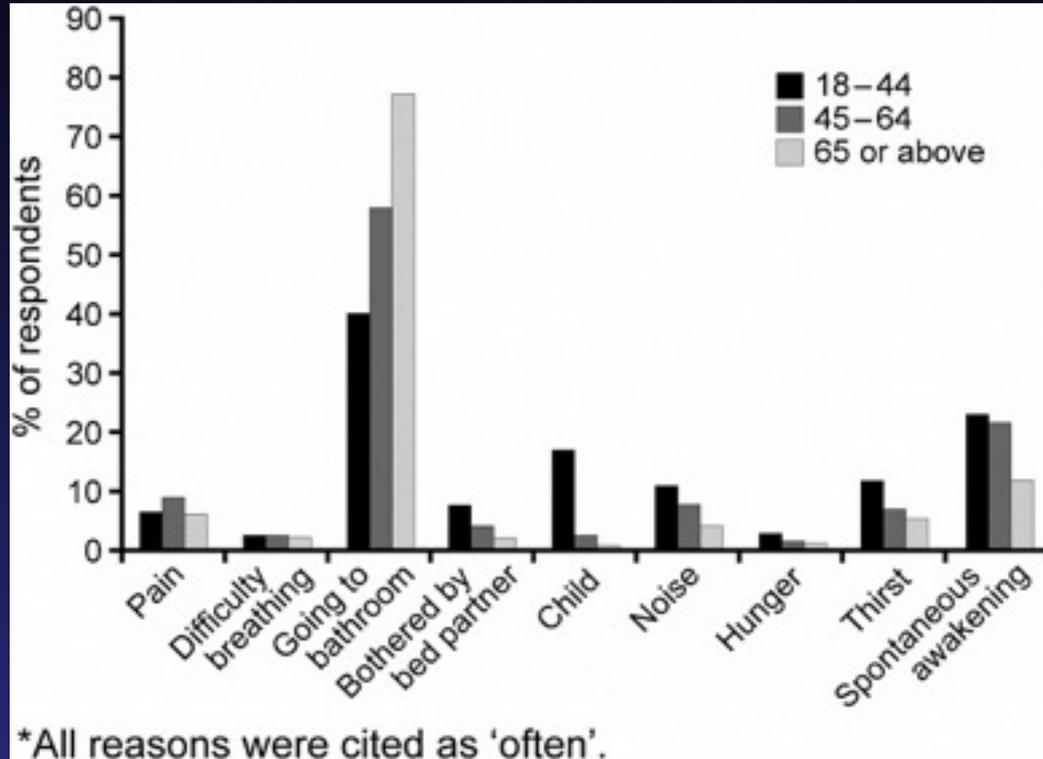
From: Asplund & Aberg, *Maturitas* 1996:24,73-81

Nocturia Is the Leading Cause of Sleep Disturbance in Older Adults (US data)

How often do the following disturb your sleep?



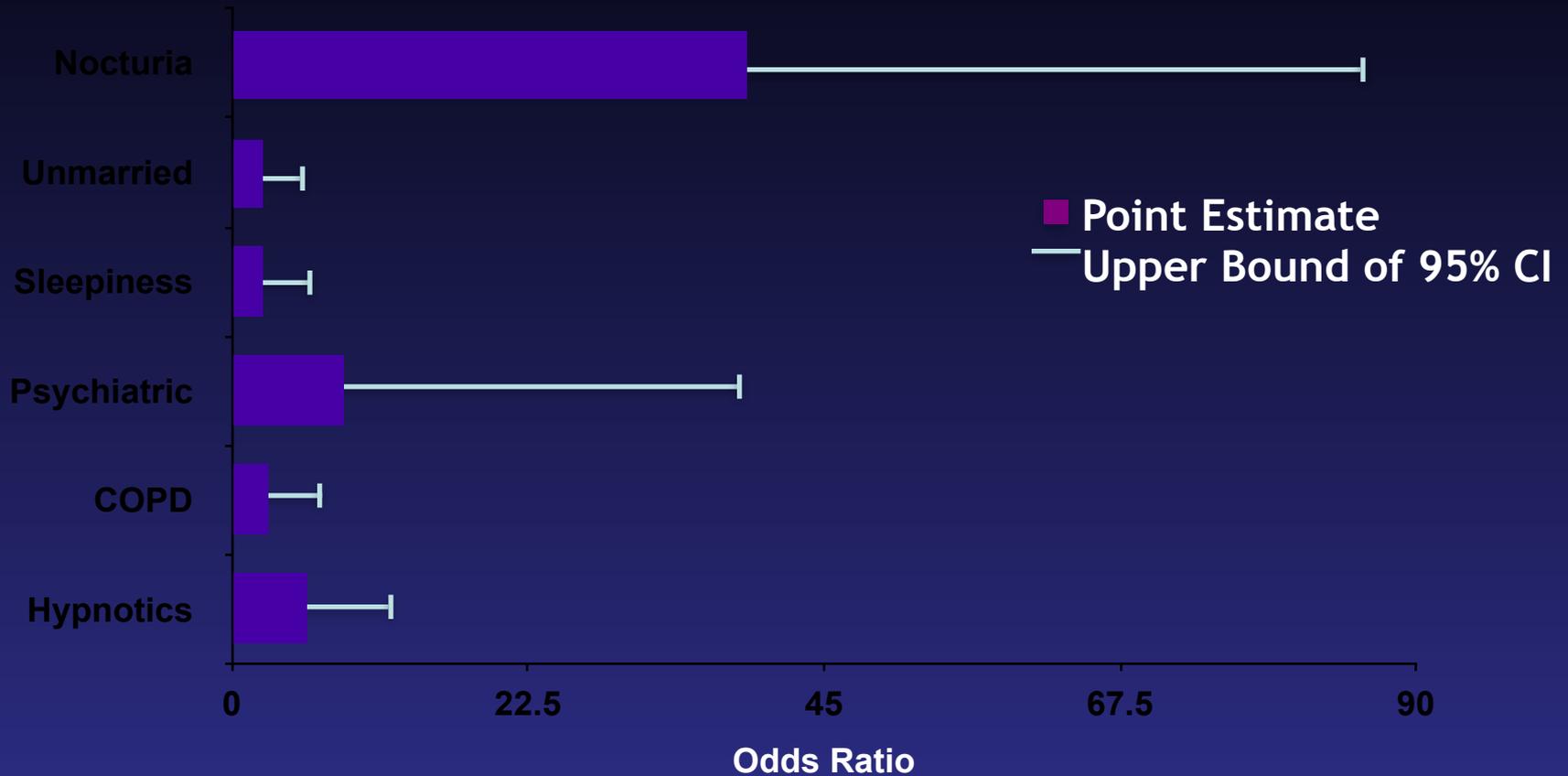
Nocturia as the Leading Cause of Disturbed Sleep across All Adult Age Groups(US population)



Ohayon. *J Psychiatr Res* 2008;43:48-54

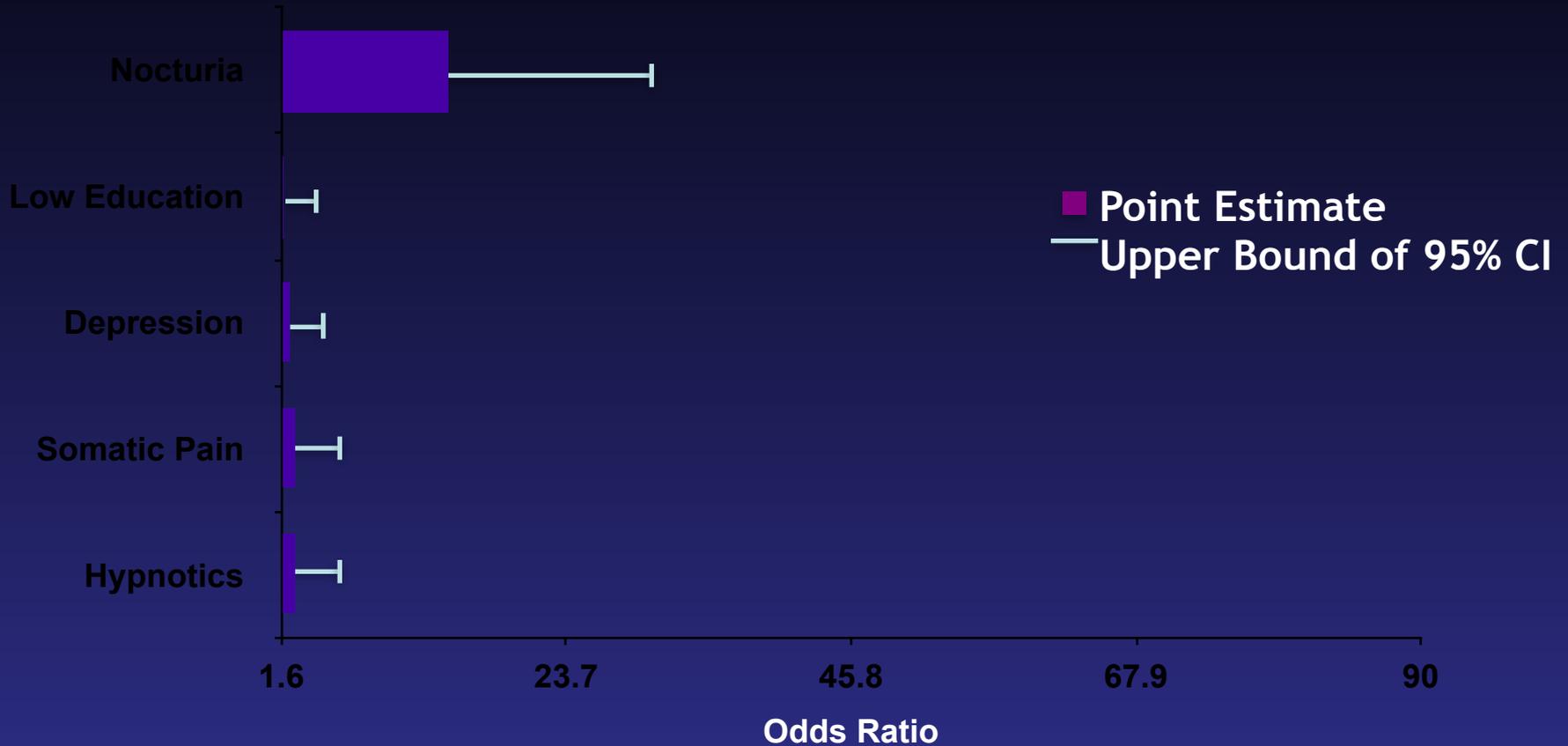
Multivariate Risk Factors for Insomnia in Elderly Taiwanese Men

Su et al, *Aust NZ J Psychiat* 2004; 38:706-13



Multivariate Risk Factors for Insomnia in Elderly Taiwanese Women

Su et al, *Aust NZ J Psychiat* 2004; 38:706-13.



Proportion of Nightly Awakenings Associated with Nocturnal Voiding Among 119 Elderly Volunteers with Self-reported Insomnia (unselected for nocturia)

(from Bliwise, Friedman et al, *Health Psychol* 2014: 33: 1362-5)

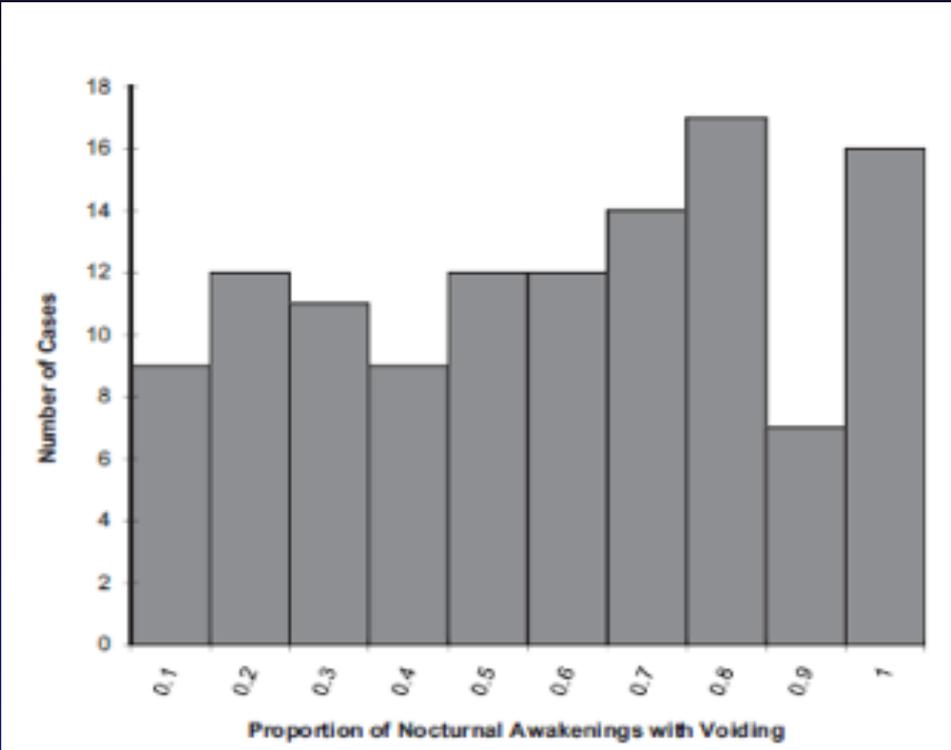


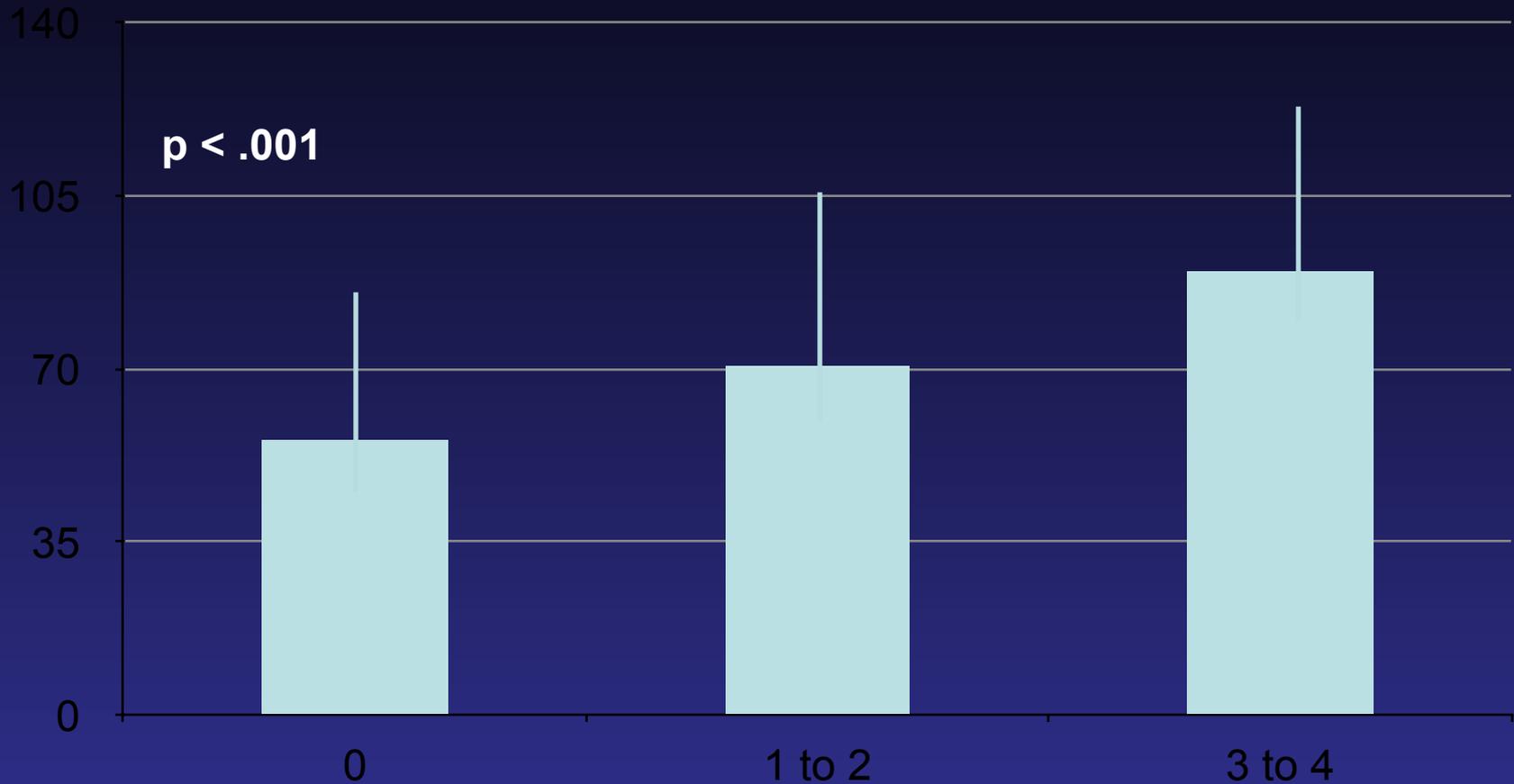
Figure 1. Frequency distribution for proportion of nocturnal awakenings accompanied by voids as reported in daily sleep diaries across 119 study participants. Nocturia was defined when at least two-thirds of the awakenings were associated with nocturnal voids for any given case. Proportions represent the mean of all nights for each study participant.

Median Split at 50%:
No diff: RDI, prostate Hx (men)
Sig Diff: arthritis Hx, urgency

Nocturia Associated with Higher Actigraphically Measured WASO in the Study of Osteoporotic Fractures (SOF) (n = 826)

(Fung et al, *JAGS* 2017; in press)

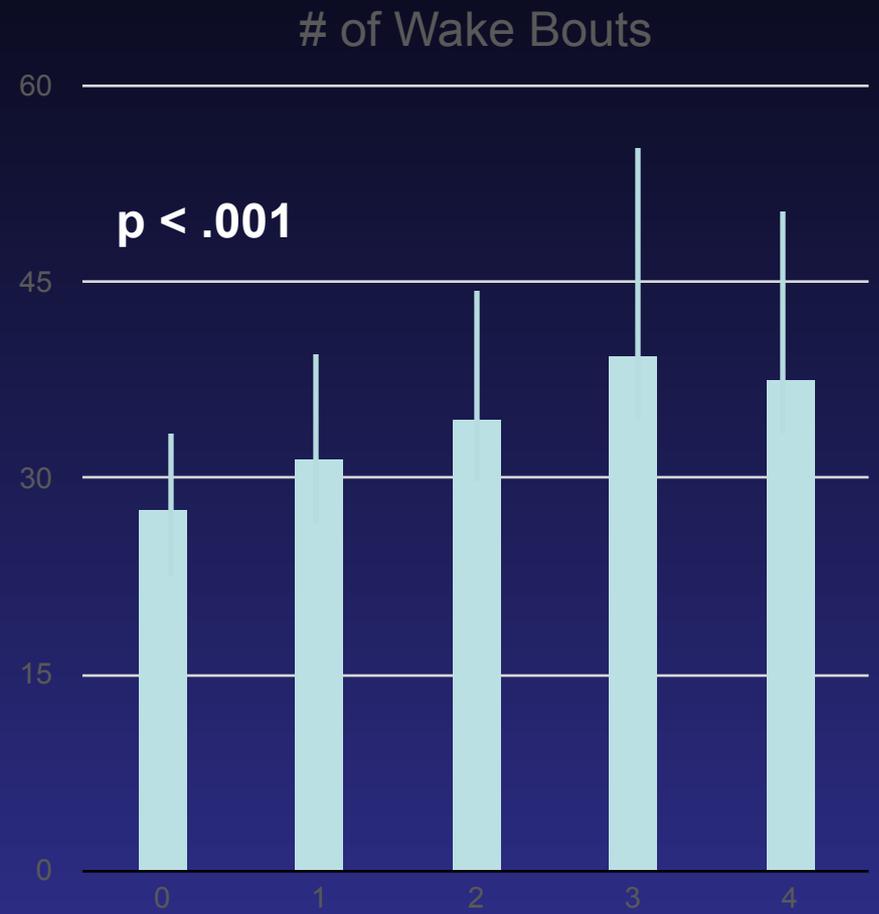
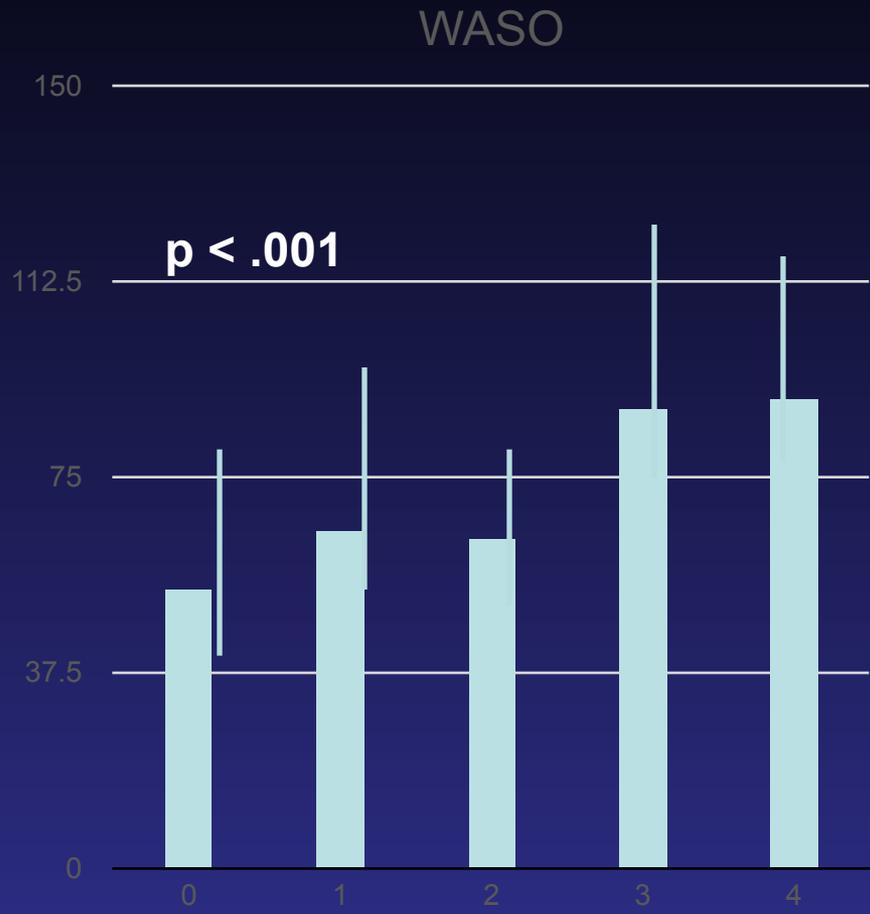
WASO



Typical Number of Nocturnal Voids

Actigraphic Measurements Confirm Higher WASO and Higher Number of Wake Bouts with Greater # of Voids

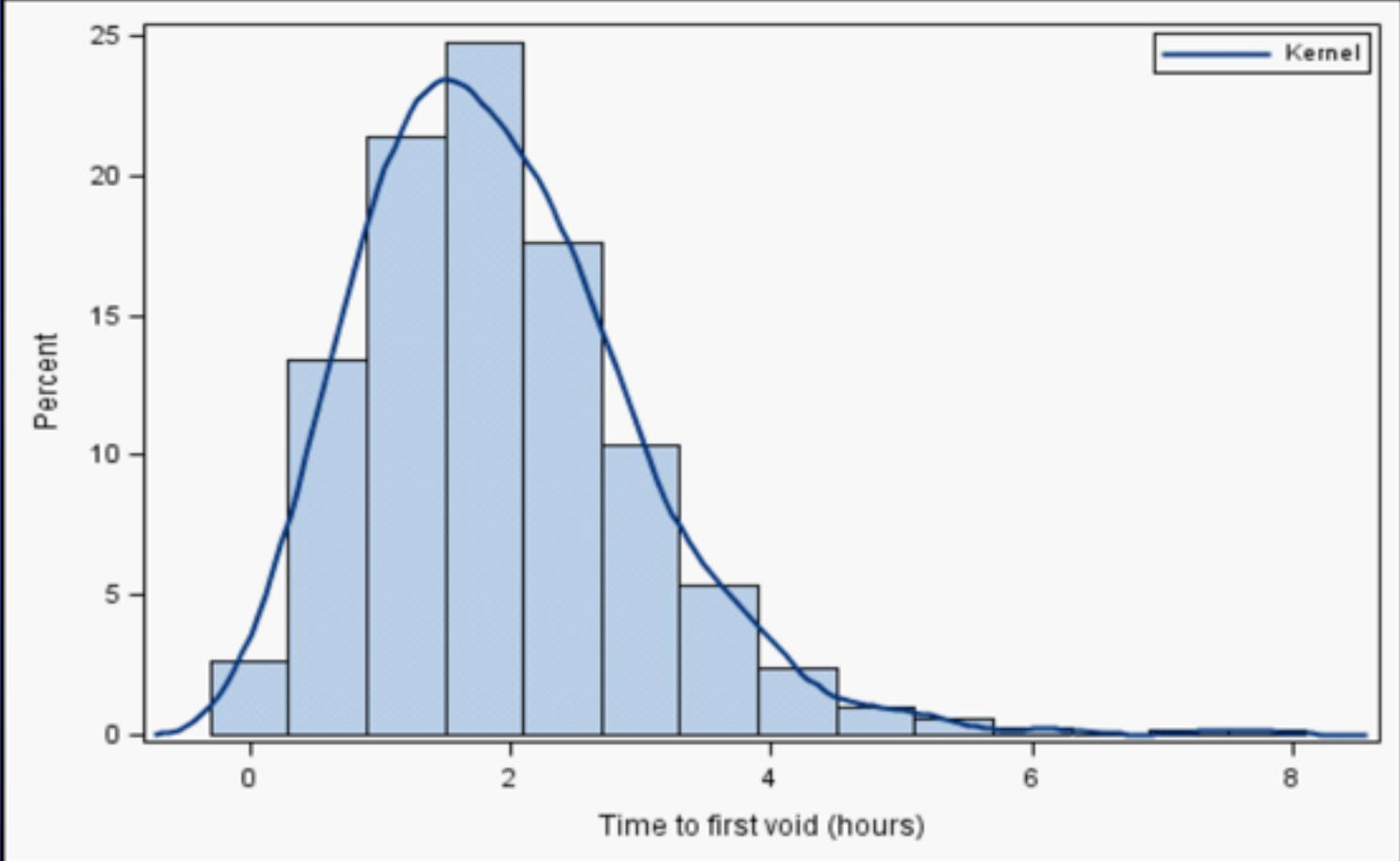
(n = 147; 1,774 individual nts)
(from Zeitzer et al, *JCSM* 2013; 9: 259-62)



Number of Nocturnal Voids on Actigraphy Night

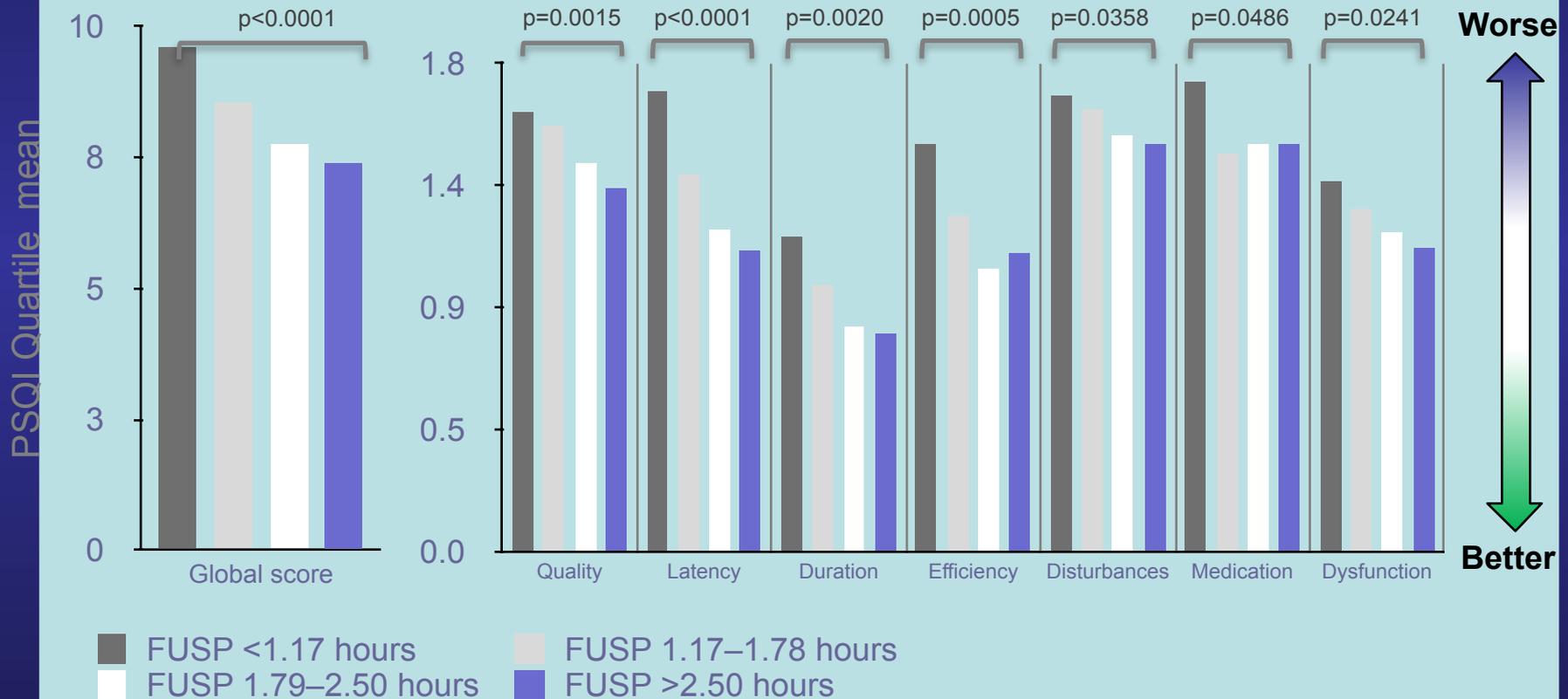
Frequency Distribution of Time to First Void (also called First Uninterrupted Sleep Period, FUSP) in Untreated Nocturia

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



Short FUSP Associated with Worse Whole-night Sleep in Nocturia Patients

PSQI scores indicate that the shorter the FUSP, the worse the patient's rating of depth, length, and quality of their sleep for the entire night



NOTE: p values indicate differences in the Pittsburgh Sleep Quality Index (PSQI) scores between patients with shortest and longest first uninterrupted sleep period (FUSP) (from Bliwise DL et al. *J Clin Sleep Med* 2015;11:53–55)

**Other Adverse Outcomes Associated with Nocturia
(in addition to poor sleep)**

Nocturia and/or Urge Incontinence Increase Risk for Falls

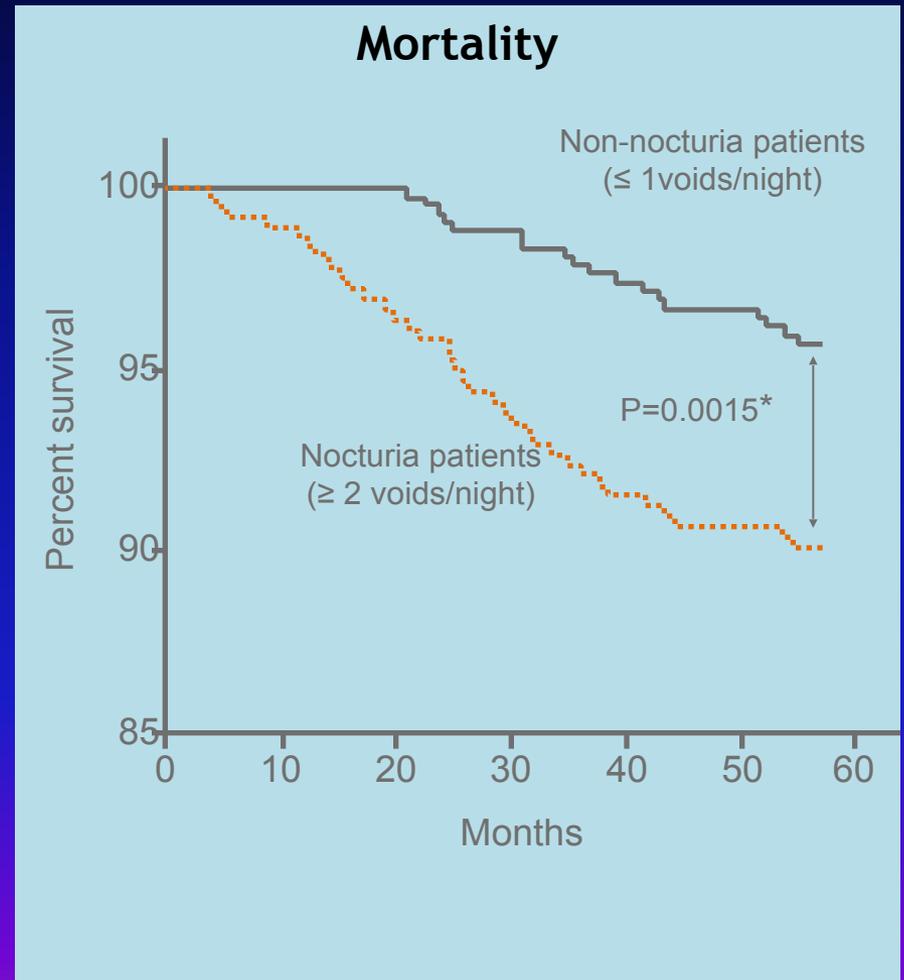
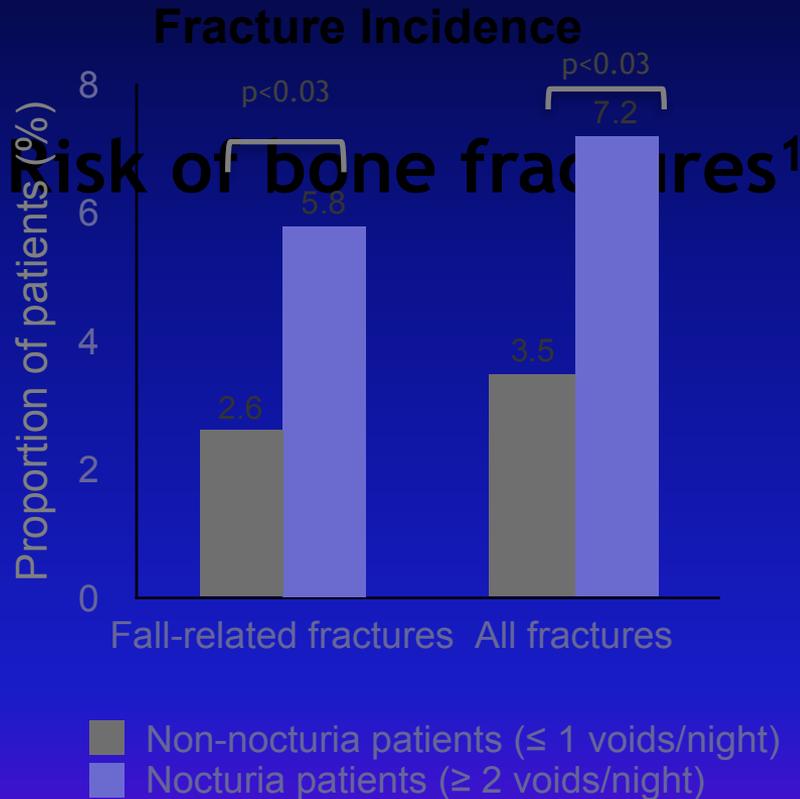
Nocturia

- 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

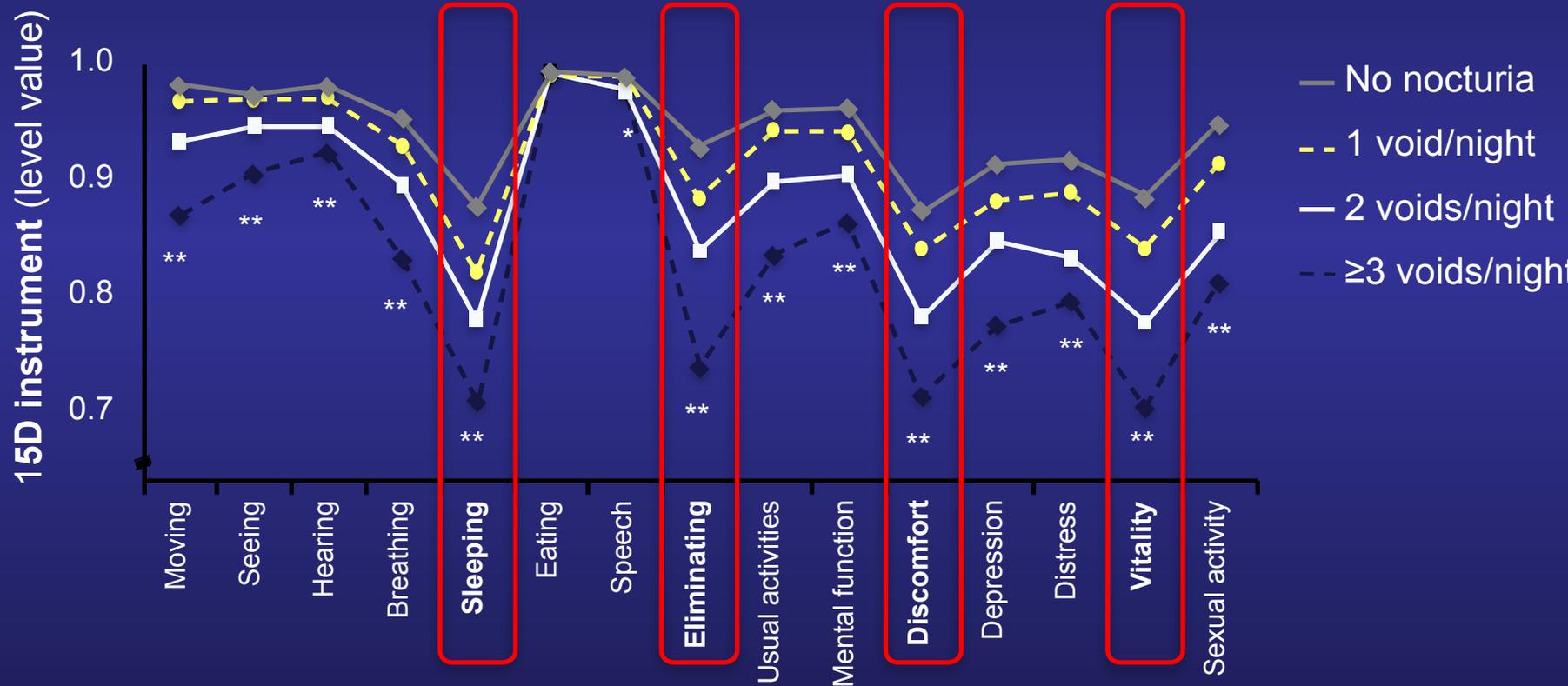
- Kutner et al, JAGS 1994; 42: 757-62
- Brown et al, JAGS 2000; 48: 721-5
- Wagner et al, Am J Manag Care 2002; 8: S598-607

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 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)

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

Mechanistic Issues Underlying the

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

Jeffrey P. Weiss,^{*,†} Philip E. V. van Kerrebroeck,[‡] Bjarke M. Klein[§]
and Jens Peter Nørgaard[§]

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

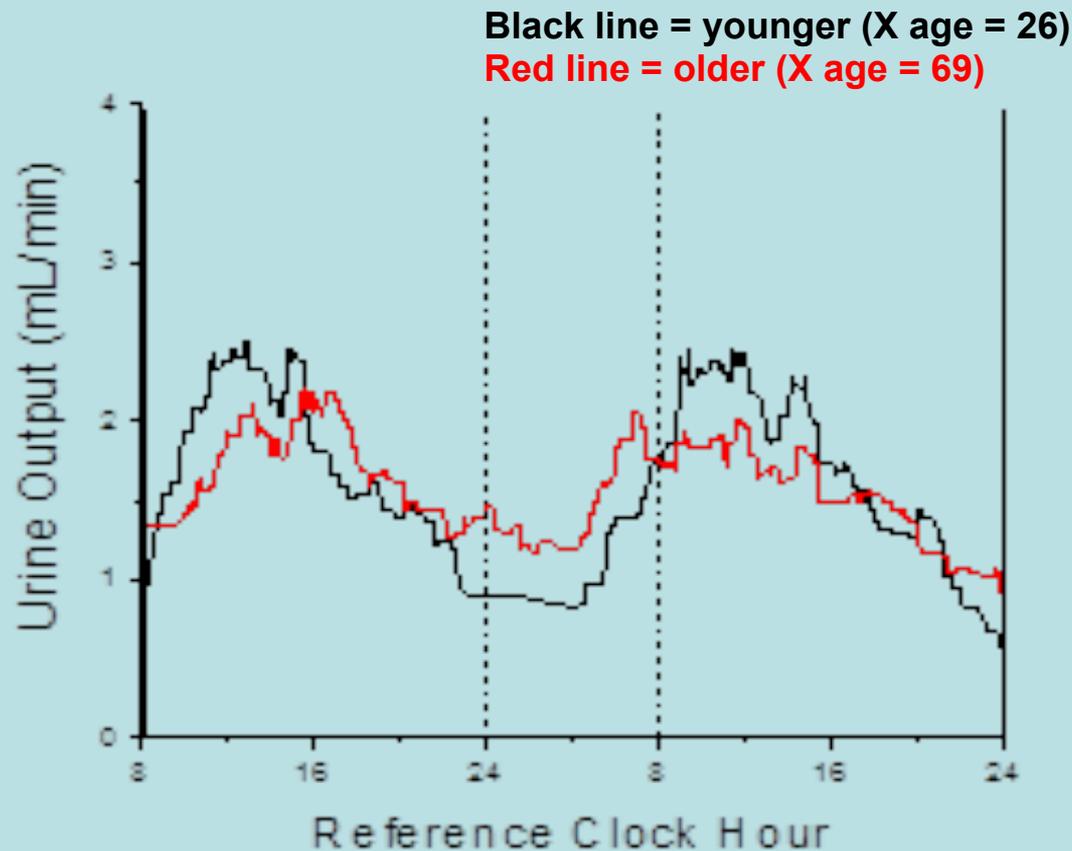
“...this study and others show that **NP (nightly urine overproduction) **is present in most patients with nocturia**, including those with persistent nocturia despite BPH and OAB therapy. This finding is consistent regardless of gender, age and ethnicity.”**

Chronobiology of Age Differences in Urine Production

Controlling for fluid and food intake, posture, sleep and lighting in the Constant Routine protocol

(Normal Subjects: c/o nocturia, sleep apnea)

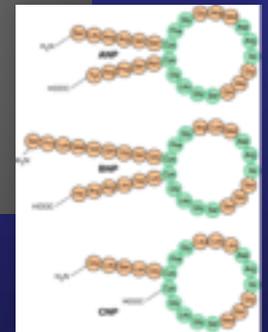
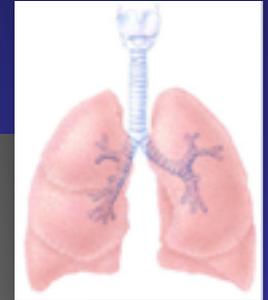
(from Duffy et al, *Current Aging Science* 2016: 9: 34-43)



Pathophysiology of Nocturia in Sleep Apnea

Obstructive sleep apnea

Intermittent occlusion of the airway →
Episodic, severe hypoxia →
Fluctuations in the intrathoracic pressure
Hypoxic pulmonary vasoconstriction →
Secretion of ANP →
Increased diuresis (natriuresis) →



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

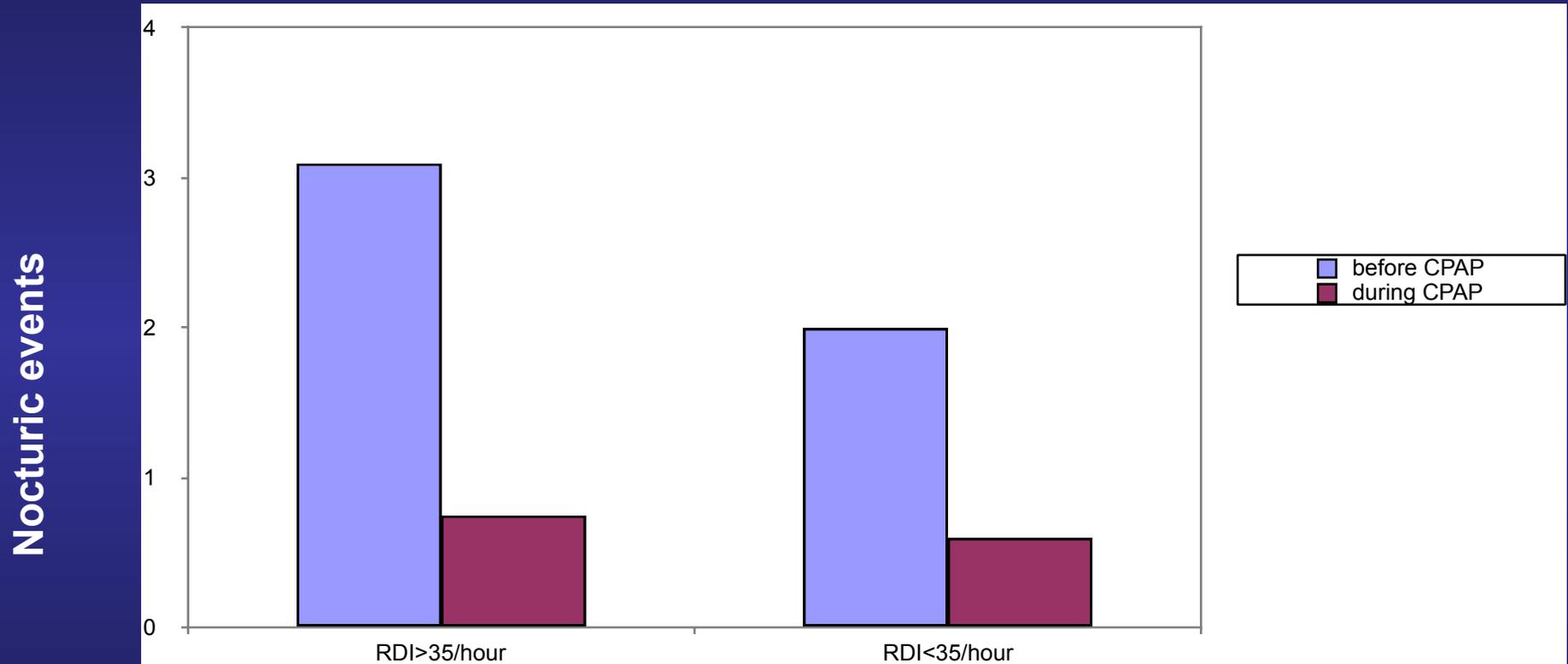
Polysomnographic (PSG) Measures and Nocturia^{*}

Sleep Heart Health Study (n = 6342)

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

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

Nocturia Episodes Reduced by CPAP

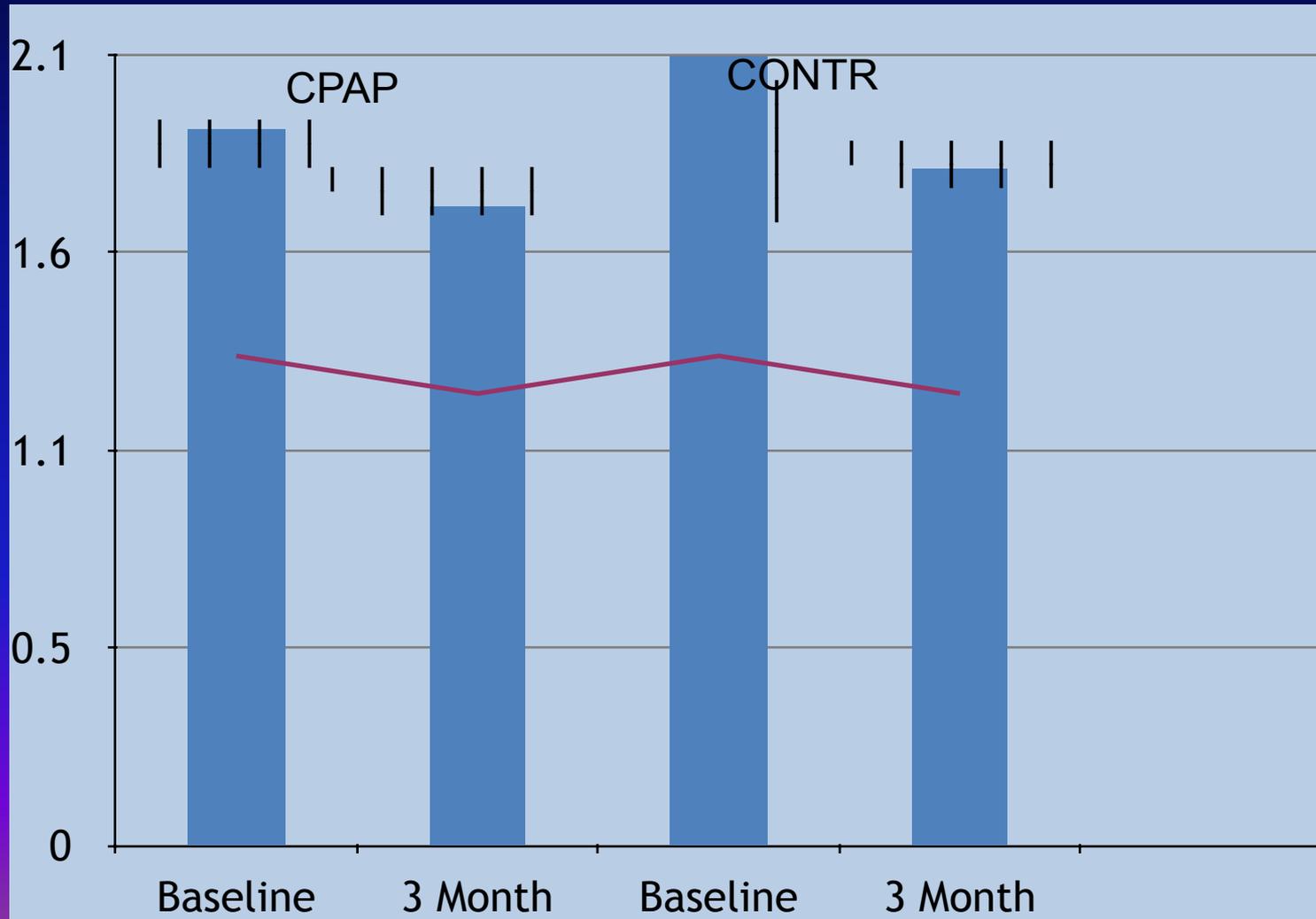


From: Margel et al, *Urology* 2006; 67:974-7.

No Effect of CPAP on Nocturia: The PREDICT Trial

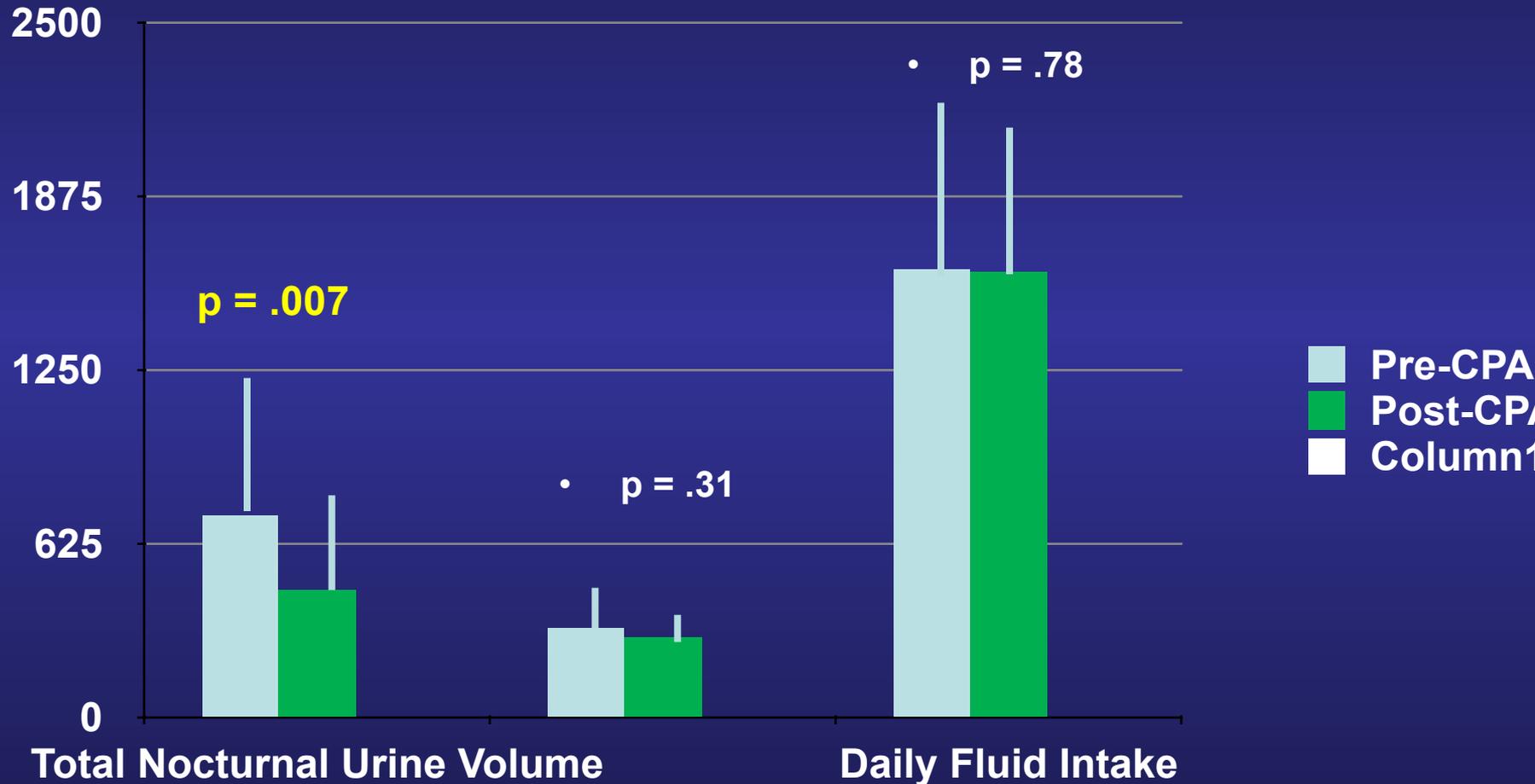
(McMillan et al, *Lancet Respir Med* 2014; 2: 804-12)

OF VOIDS

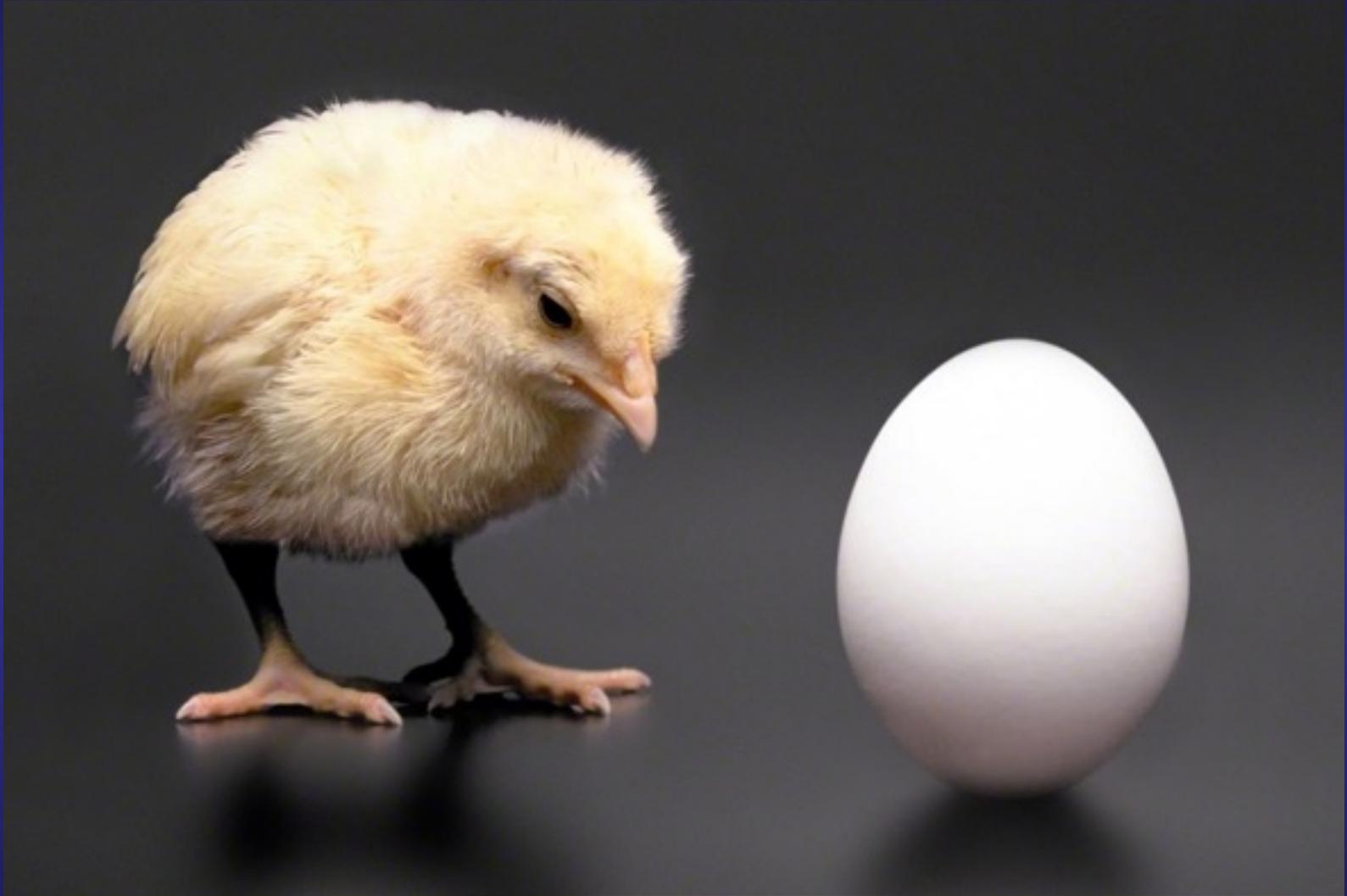


Nocturnal Urine Volume is Reduced by 3 Months of CPAP Usage

(Miyazato et al, *Neurourol Urodynam* 2017; 36: 376-9)



What About the Chicken and the Egg?



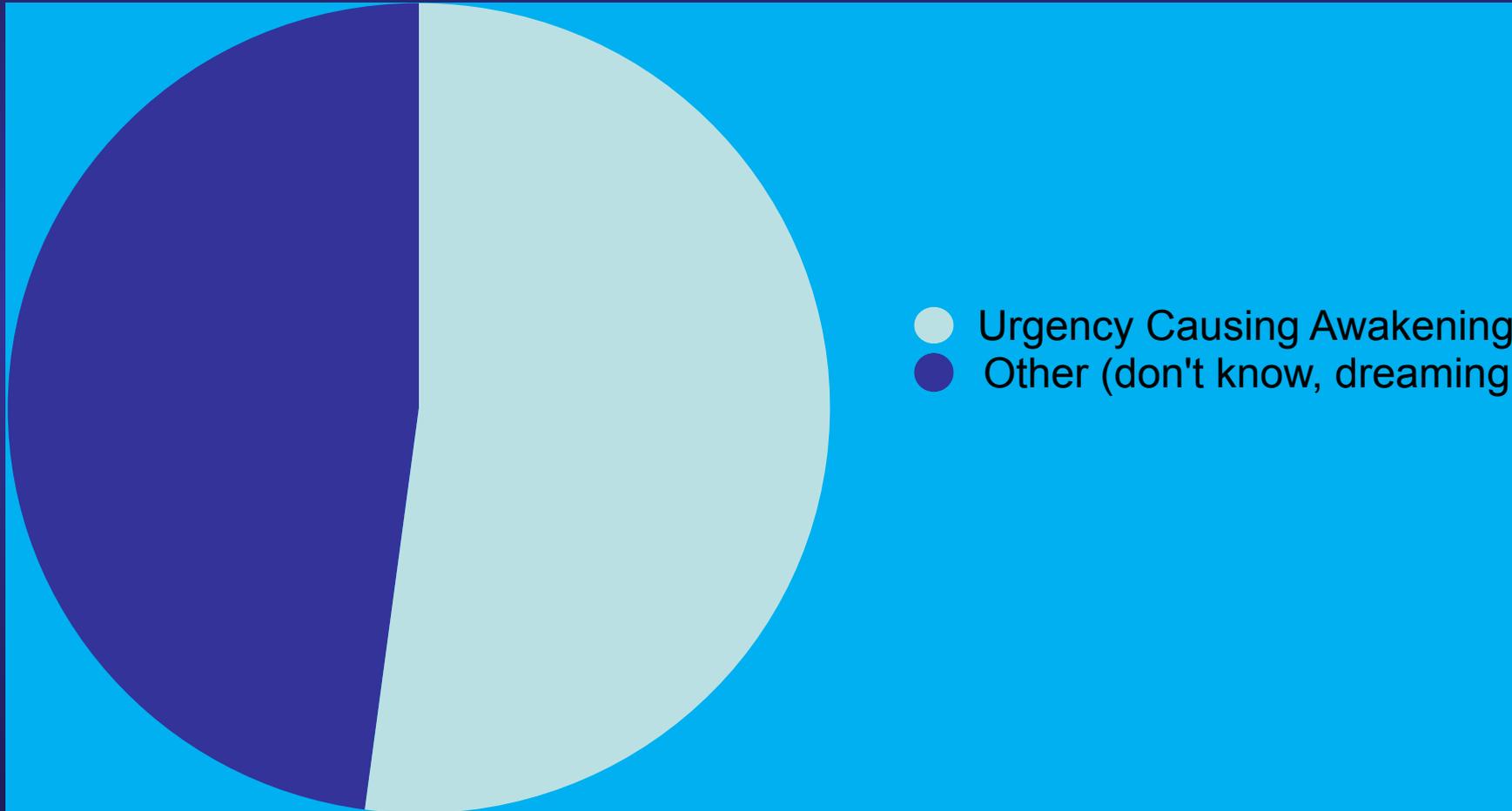
Chicken and Egg

- 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

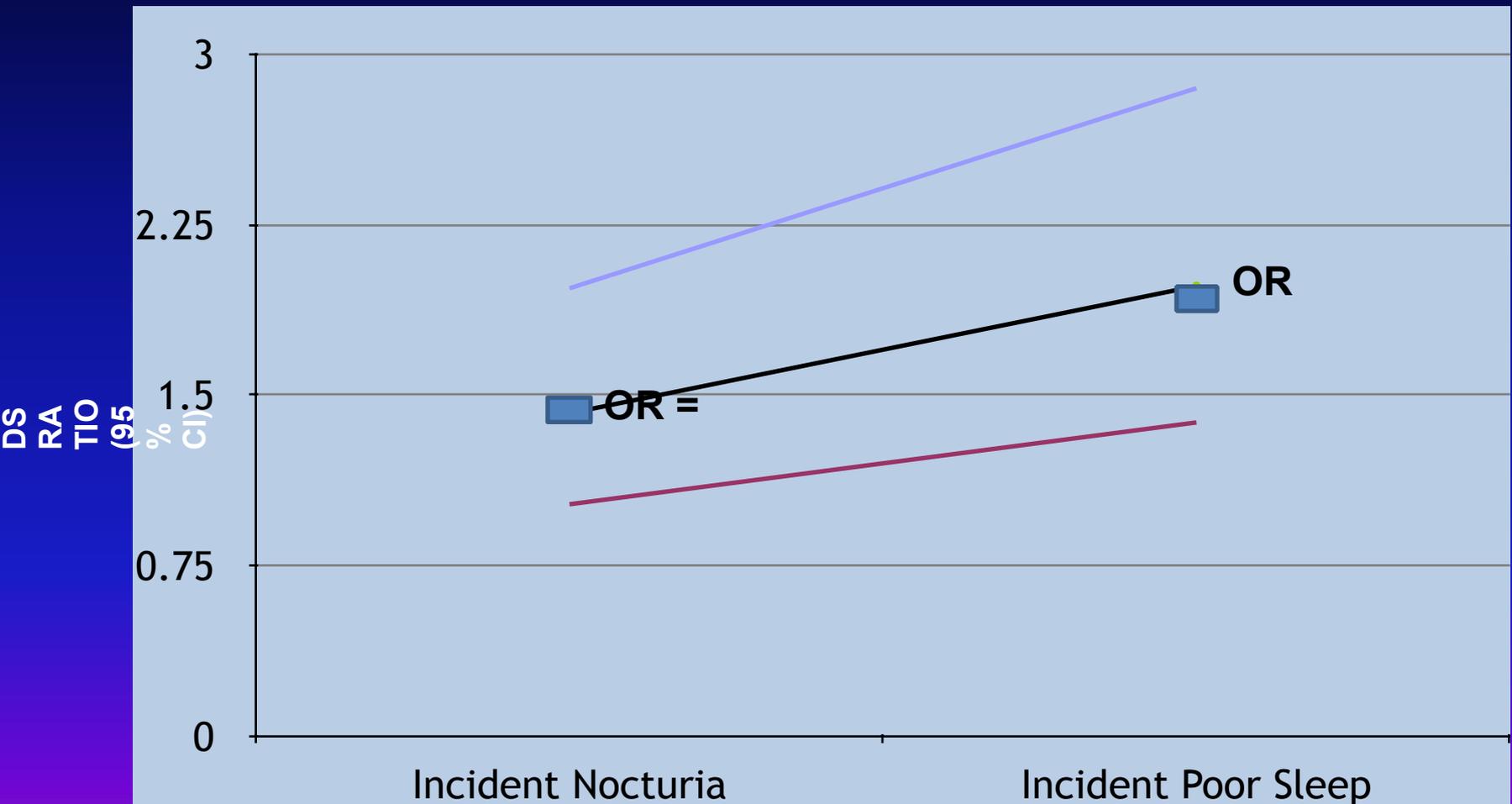
(Pressman et al, *Arch Int Med* 1996: 156: 545-60)



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)

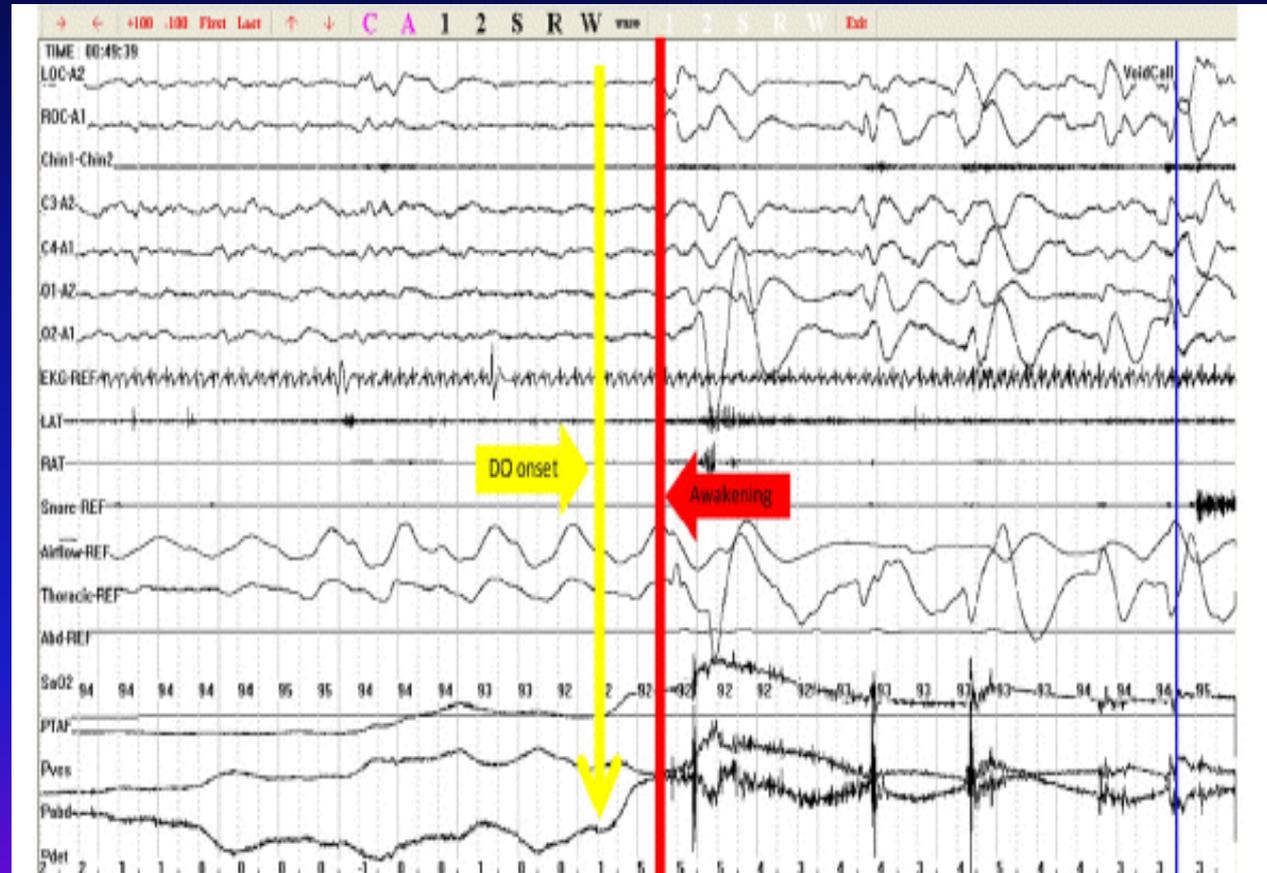


Controlling for baseline sleep (or nocturia) and controlling for age, sex, race, SES, diabetes, heart disease, alcohol, physical Activity, smoking, anti-depressants, sedative/hypnotics, stimulants

Proximate Causation (Part I): 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
 ≥ 2 cm H₂O for
 ≥ 1 sec



Pves: bladder pressure

Pabd: abdominal pressure

Pdet: detrusor pressure
(Pves - Pabd)



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

Proximate Causation (Part II)

Sleep Apnea and Incontinence in the Nursing Home

*Wetness Episodes Can Begin During Apneic Events:
Negative Pressure Breathing Causing Incontinence*

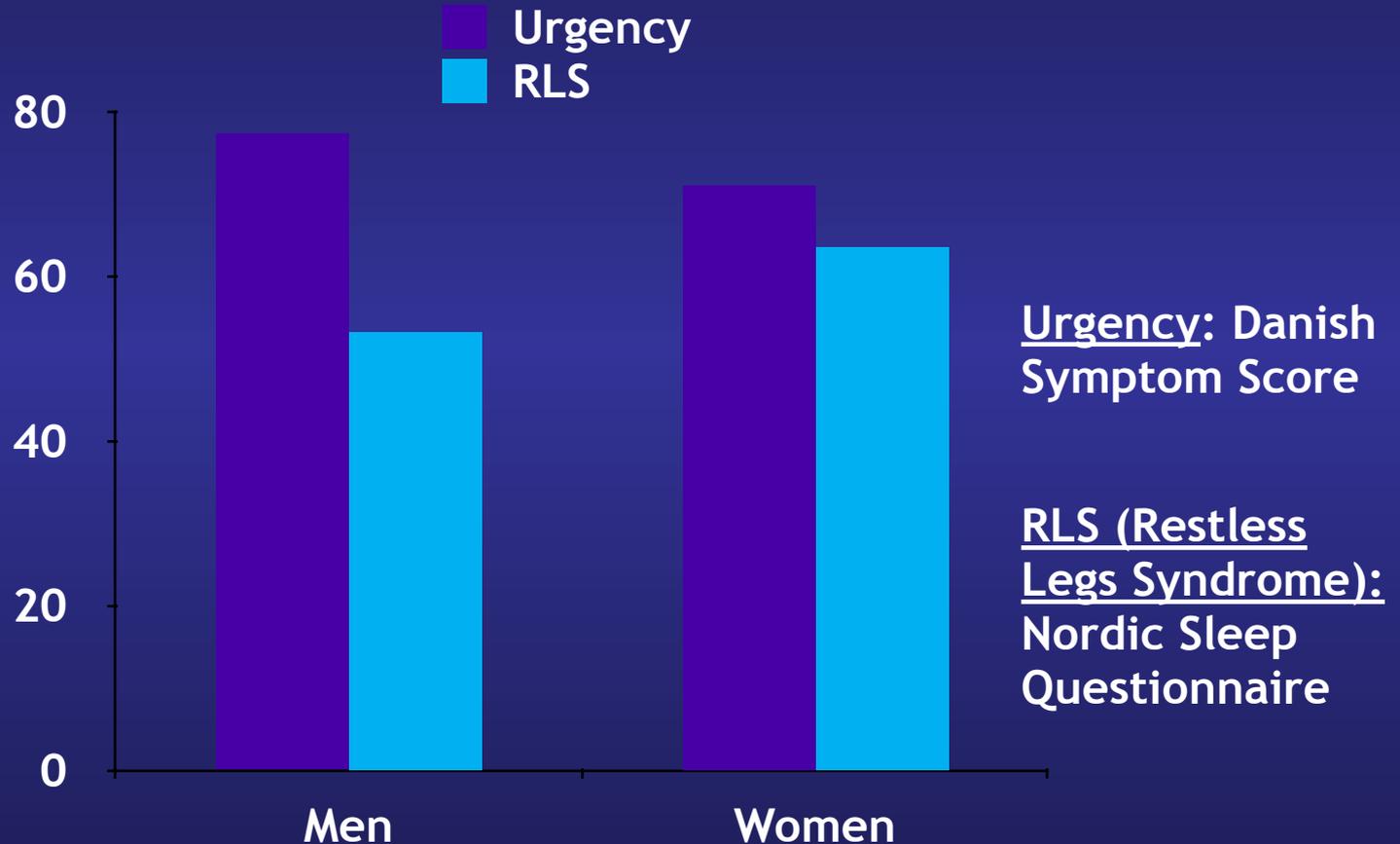


(Bliwise, Adelman & Ouslander, *Sleep* 2004;27:153-157)

Nocturia and Restless Legs

Attributable Fraction (%) of Nocturia Cases Eliminated If Exposure (i.e., Restless Legs) was Eliminated (Finland):

Awakening Because of Urge vs. Voiding When Awake



Treatment Issues with Nocturia

Nocturia is in the News!

To Promote the Science and Art of Medicine and the Betterment of the Public Health

JAMA[®]

Editor In Chief
Howard Bauchner, MD

JAMA Online First (April 06, 2017)

VIEWPOINT

FDA Approval of Desmopressin for Nocturia

JAMA 2017; 317, 1518 (April 18, 2017)

News From the Food and Drug Administration

Nocturnal Polyuria Drug Approved

Relief for Dust Mite Allergy

tions. Common adverse reactions included

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
<i>Global</i>	<i>607</i>	<i>-0.488</i>	<i>0.054</i>	<i><0.0001</i>
<i>Sleep Quality</i>	<i>633</i>	<i>-0.106</i>	<i>0.012</i>	<i><0.0001</i>
<i>Sleep Latency</i>	<i>609</i>	<i>-0.079</i>	<i>0.015</i>	<i><0.0001</i>
<i>Sleep Duration</i>	<i>632</i>	<i>-0.068</i>	<i>0.013</i>	<i><0.0001</i>
<i>Sleep Efficiency</i>	<i>632</i>	<i>-0.102</i>	<i>0.018</i>	<i><0.0001</i>
<i>Sleep Disturbances</i>	<i>634</i>	<i>-0.044</i>	<i>0.012</i>	<i>=0.0002</i>
<i>Sleep Medication</i>	<i>634</i>	<i>-0.016</i>	<i>0.016</i>	<i>=0.30</i>
<i>Daytime Dysfunction</i>	<i>634</i>	<i>-0.075</i>	<i>0.014</i>	<i><0.0001</i>

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 ≥ 2 score before TURP	Patients scoring ≥ 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?

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

Open label, single-group design of a muscarinic antagonist

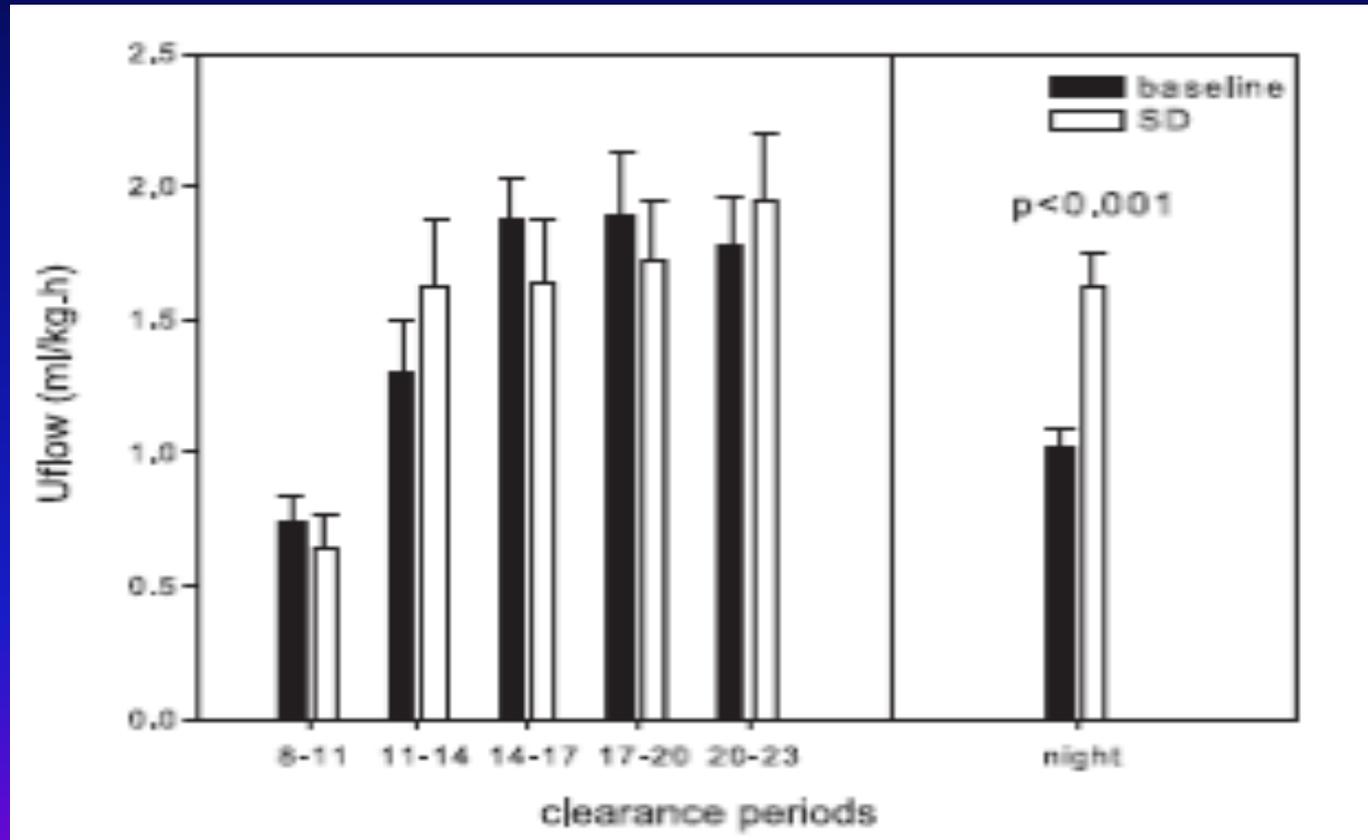
(Takao et al, *Urology* 2011; 78: 648-652)

	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	98.0 (40.0)	89.6 (35.5)	.096
NUMBER OF AWAKENINGS	30.8 (7.7)	29.6 (7.7)	.272

Sleep Deprivation in Humans Increases Urine Production

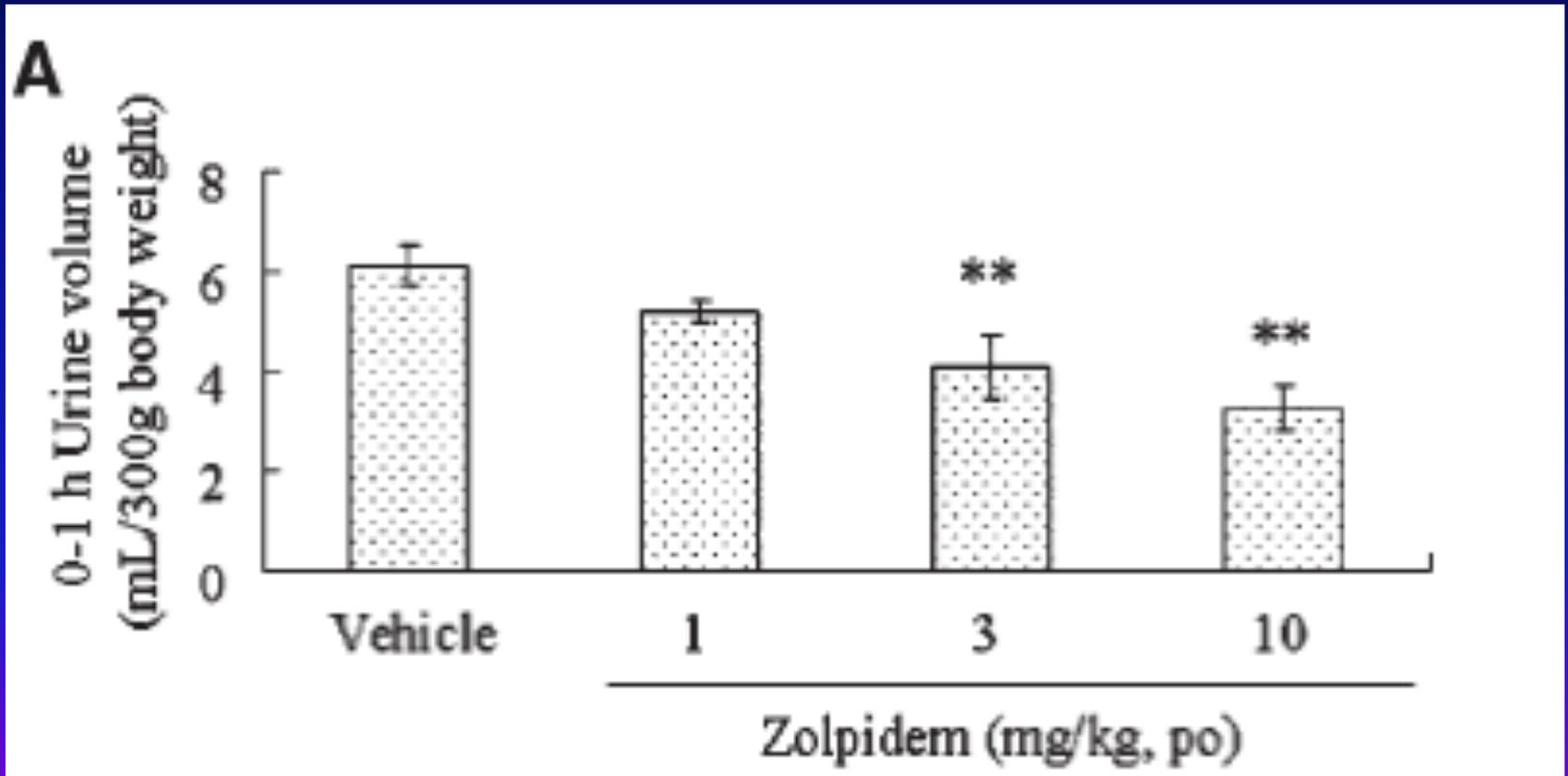
24 hrs sleep deprivation vs normal sleep with H₂O and Na intake controlled

(Kamperis et al, *Am J Physiol Renal Physiol* 2010; 299: F404-11)

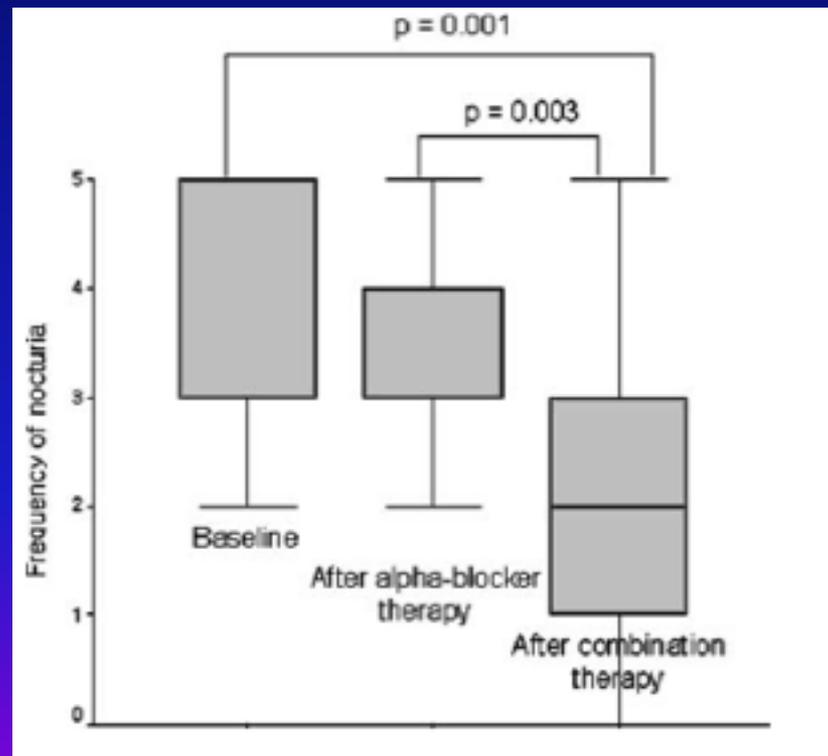


Water-loaded, wild-type rats show dose-dependent, zolpidem-induced decreases in urine volume the 1st hour after oral administration
An effect of sleep?

(Yokoyama et al, *NeuroUrol Urodynam* 2010; 29: 587-91)



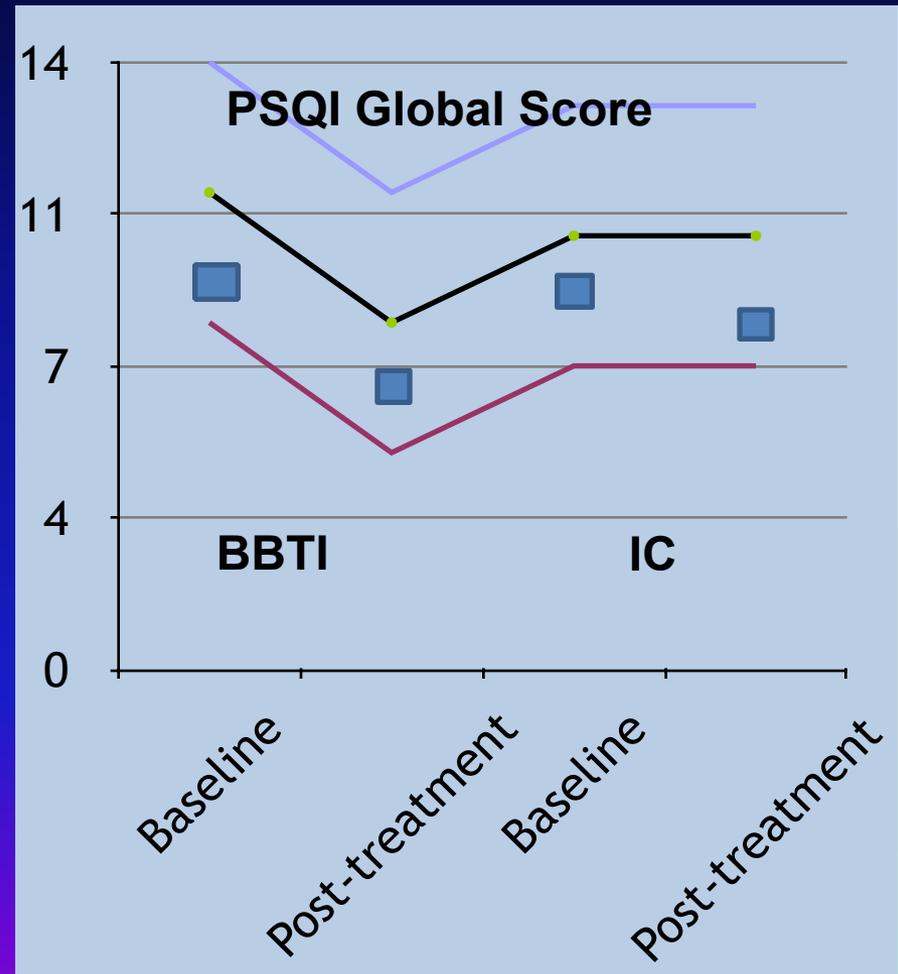
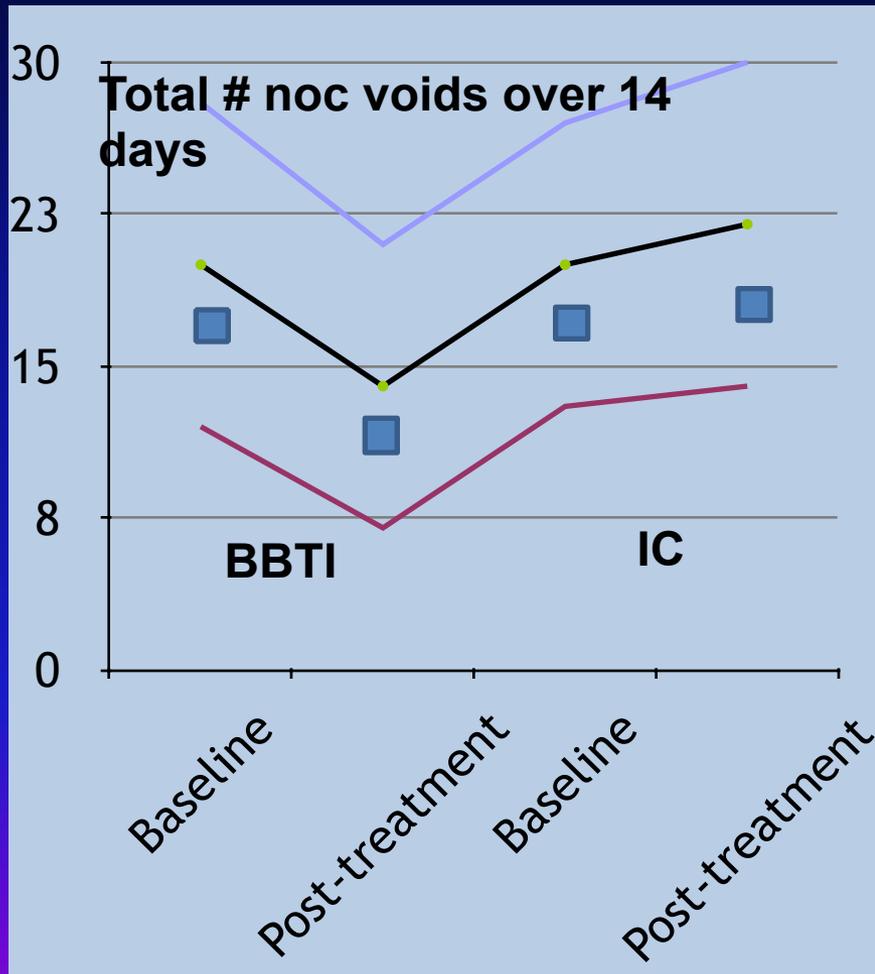
GABAergic Medication May Enhance Efficacy of Nocturia Rx



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)



Nocturia Moderates Relative Effect Sizes (d) for Treatment Efficacy in Behavioral Insomnia Treatment:

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

Sleep Efficiency (SE) (in mins) and PSQI Global Score

(Tyagi et al, *Sleep* 2014: 37: 681-7)

	Nocturia Pre/Post- Baseline Adjusted Group Differences	No Nocturia Pre/Post- Baseline Adjusted Group Differences	Nocturia (Cohen's d)	No Nocturia (Cohen's d)
<i>SE (%) (self-</i>	2.16 (4.13)	6.72 (1.64)	0.25	0.71
<i>SE (%) (actigraphy</i>	3.48 (1.91)	2.59 (1.57)	0.43	0.55
<i>PSQI Global</i>	-2.27 (0.92)	-3.41 (0.72)	0.53	0.82

What about Desmopressin?

(trade names: Noctiva, Nocdurna)

JAMA Online First (April 06, 2017)

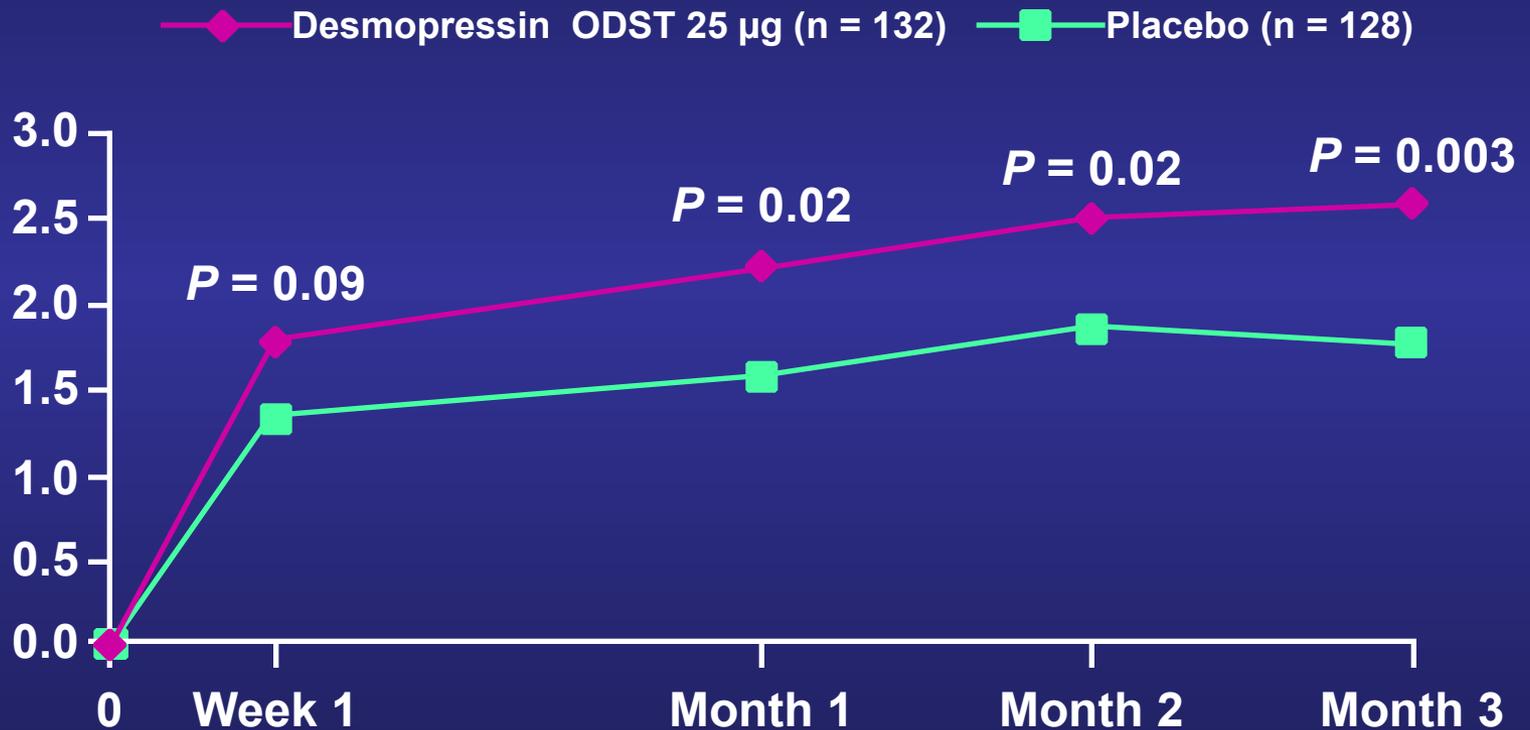


JAMA 2017; 317, 1518 (April 18, 2017)



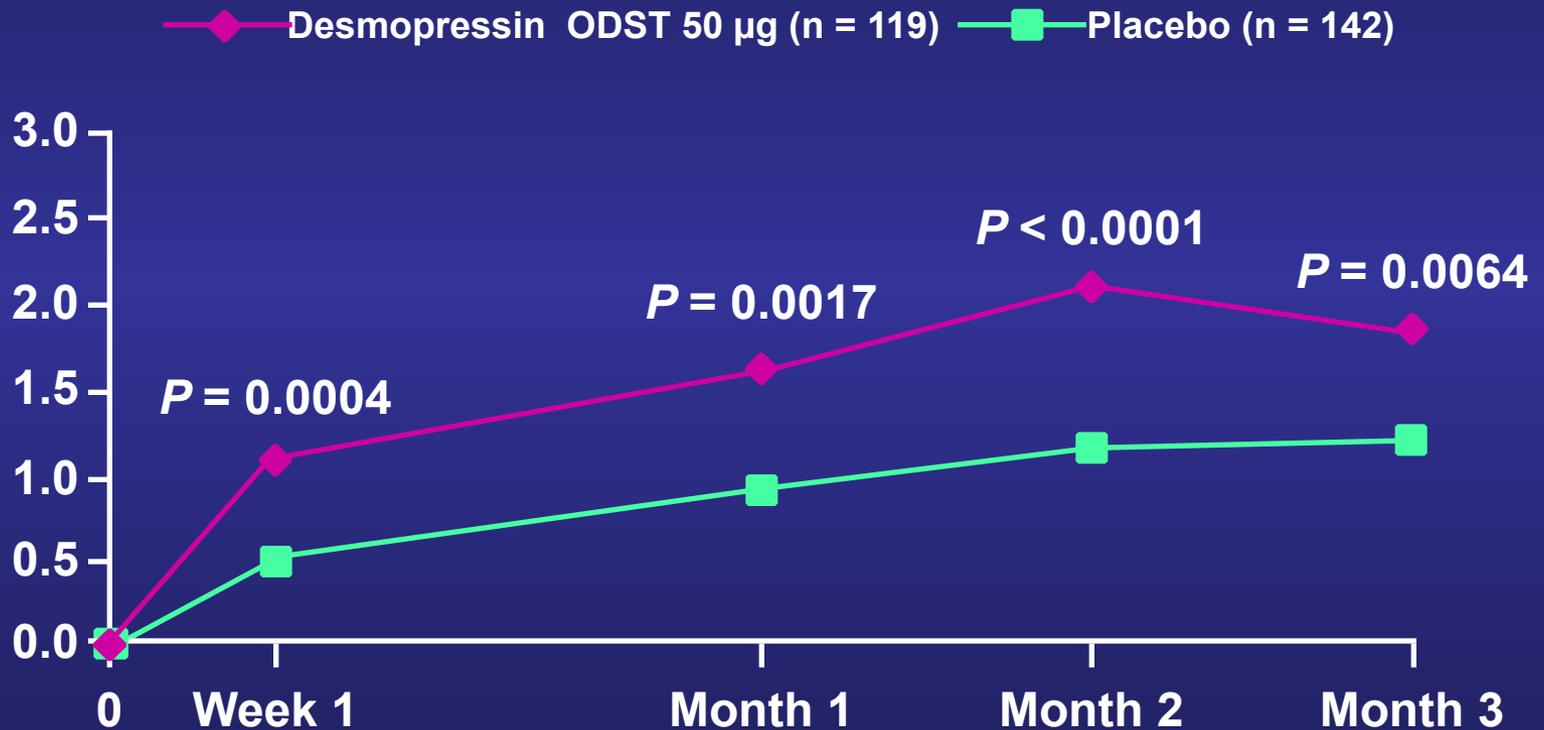
Increase in FUSP With Desmopressin Melt (25 µg) in Women Over 3 Months' Nightly Administration

Mean Change From Baseline in Initial Period of Undisturbed Sleep, h



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

Mean Change From Baseline in Initial Period of Undisturbed Sleep, h



**Baseline Subtracted Increments in FUSP with Oral Melt Formulation of Desmopressin Relative to Placebo:
Average = 32-76 Mins¹⁻³**

Sedative-Hypnotic	Treatment Difference (Average - Placebo)
<i>Eszopiclone (Lunesta)[®] 3mg⁴</i>	25.0
<i>Doxepin (Silenor)[®] 6mg⁵</i>	22.2
<i>Zolpidem-MR (Ambien-MR)^{®6}</i>	16.0

1. Weiss et al. *Neurourol Urodyn* 2012; 31: 441-7
2. Weiss et al. *J Urol* 2013; 190: 965-72.
3. Sand et al. *J Urol* 2013; 190: 958-64.
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Caudal-to-Rostral Fluid Shifts as Potentially Impacting Upper Airway Caliber

Could Fluid Retention Exacerbate Sleep Apnea?

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Investigating the Dynamics of Supine Fluid Redistribution Within Multiple Body Segments Between Men and Women

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Effect of rostral fluid shift on pharyngeal resistance in men with and without obstructive sleep apnea

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ABSTRACT

Background: Obstructive sleep apnea (OSA) relates to overnight rostral fluid shift, possibly because fluid accumulation around the pharynx increases pharyngeal resistance (R_{ph}). We hypothesized that R_{ph} will increase more in men with than without OSA in response to rostral fluid redistribution.

Methods: Seventeen men with, and 12 without OSA were randomized to lower body positive pressure (LBPP) for 15-min or control, then crossed over; leg fluid volume (LFV) and R_{ph} were measured before and after each period.

Results: LBPP displaced similar amounts of fluid from the legs in both groups. However, compared to the non-OSA group, R_{ph} increased significantly more during LBPP in the OSA group (-0.58 ± 2.87 vs. 2.32 ± 2.84 cmH₂O/L, $p=0.016$). Change in R_{ph} during LBPP correlated directly with baseline R_{ph} in the OSA group, but inversely in the non-OSA group.

Conclusions: OSA patients have increased susceptibility to pharyngeal obstruction in response to rostral fluid redistribution, which could predispose to pharyngeal collapse during sleep.

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Original Article

Overnight fluid shifts in subjects with and without obstructive sleep apnea

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Objective: To investigate the characteristics of baseline body fluid content and overnight fluid shifts between non-obstructive sleep apnea (non-OSA) and obstructive sleep apnea (OSA) subjects.

Methods: A non-controlled study was performed between February 2013 and January 2014, with 14 (12 OSA and 2 non-OSA) participants enrolled in this study. Polysomnographic parameters and results of body fluid were compared between the two groups.

Results: There were no differences in age, weight, and body mass index (BMI) between groups. Compared with the non-OSA group, OSA group had significantly higher snore comorbidity (1°C) and fluid volume shift in the leg, OSA patients had higher left and right leg fluid volume than non-OSA patients. There were significant correlations between apnoea-hypopnoea index and baseline fluid volume in both legs as well as the increase in overnight change in both legs fluid volume. The increase in 1°C was also significantly correlated with the increase in overnight change in both legs fluid volume, but not with the change in head and neck fluid volume. There were significant correlations between change in 1°C and increased fluid shifts in head and neck regions.

Conclusions: OSA patients had a higher baseline fluid content in both legs as compared with non-OSA patients, which may be the major factor with respect to fluid shifts in OSA patients. The increase in head and neck fluid volume did not directly correlate with the severity of OSA.

Keywords: Obstructive sleep apnea (OSA), fluid shifts, body composition analysis

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NEW RESEARCH

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Influence of Rostral Fluid Shift on Upper Airway Size and Mucosal Water Content

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Study Objective: Fluid displacement from the legs during increased lower body positive pressure (LBPP) may narrow the upper airway (UA) in association with rostral fluid accumulation that may contribute to the pathogenesis of obstructive sleep apnea (OSA). The aim of this study was to test the hypothesis that rostral fluid displacement from the legs causes a greater decrease in UA cross-sectional area (UA-CSA) and a greater increase in UA mucosal water content (UA-MWC) and internal jugular venous volume (IJV) in subjects with OSA than in those without OSA.

Methods: Subjects underwent baseline assessment of leg fluid volume (LFV) measured by bio-electrical impedance, as well as UA-CSA and UA-MWC by magnetic resonance imaging. They were then randomly assigned to a 20-min period either with or without application of lower body positive pressure (LBPP) of 40 mm Hg, followed by a 15-min post-LBPP period, after which they crossed over to the other arm of the study. Measurements of LFV, UA-MWC, and UA-CSA were repeated after each arm of the study.

Results: In 12 subjects without sleep apnea, UA-CSA increased and UA-MWC decreased significantly, whereas in 12 subjects with OSA, UA-CSA decreased and UA-MWC increased significantly in response to LBPP. The changes in UA-CSA and UA-MWC in response to LBPP differed significantly between the 2 groups ($p=0.008$ and $p<0.001$, respectively), despite similar changes in LFV and IJV.

Conclusions: Our results suggest that rostral fluid shift may contribute to the pathogenesis of OSA at least partly through narrowing of the UA due to translocation of fluid into the UA mucosa.

Keywords: Fluid displacement, lower body positive pressure, obstructive sleep apnea, upper airway cross-sectional area, upper airway mucosal water

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SCIENTIFIC INVESTIGATIONS

SUMMARY

- **Epidemiology (Prevalence, Outcomes)**
- **Mechanistic Issues involving Circadian Rhythms and Features of Sleep (including sleep apnea)**
- **Chicken and Egg Problem**
- **Treatments for Nocturia**

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