August 22, 2017
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


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The Personal Retrospective Thing

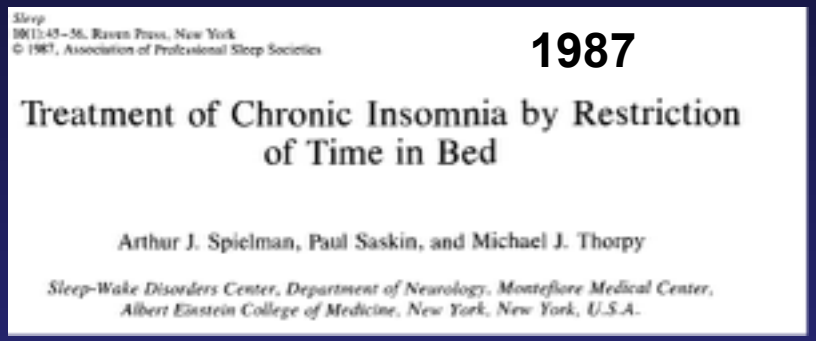
Allan Rechtschaffen

1974-1982

William Dement

1982-1992

Art Spielman



Jerry Yesavage

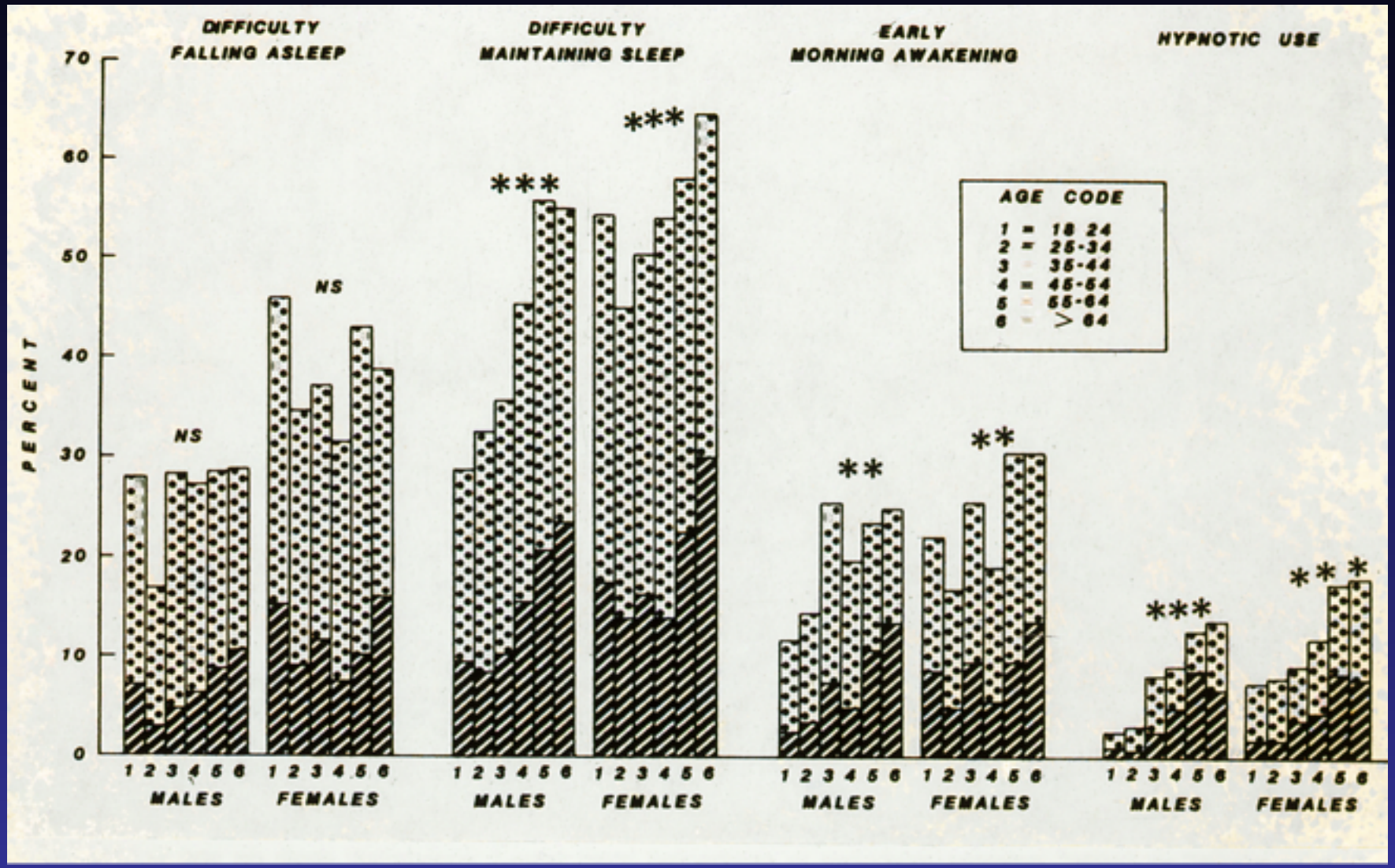
Leah Friedman

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 Voids[1]

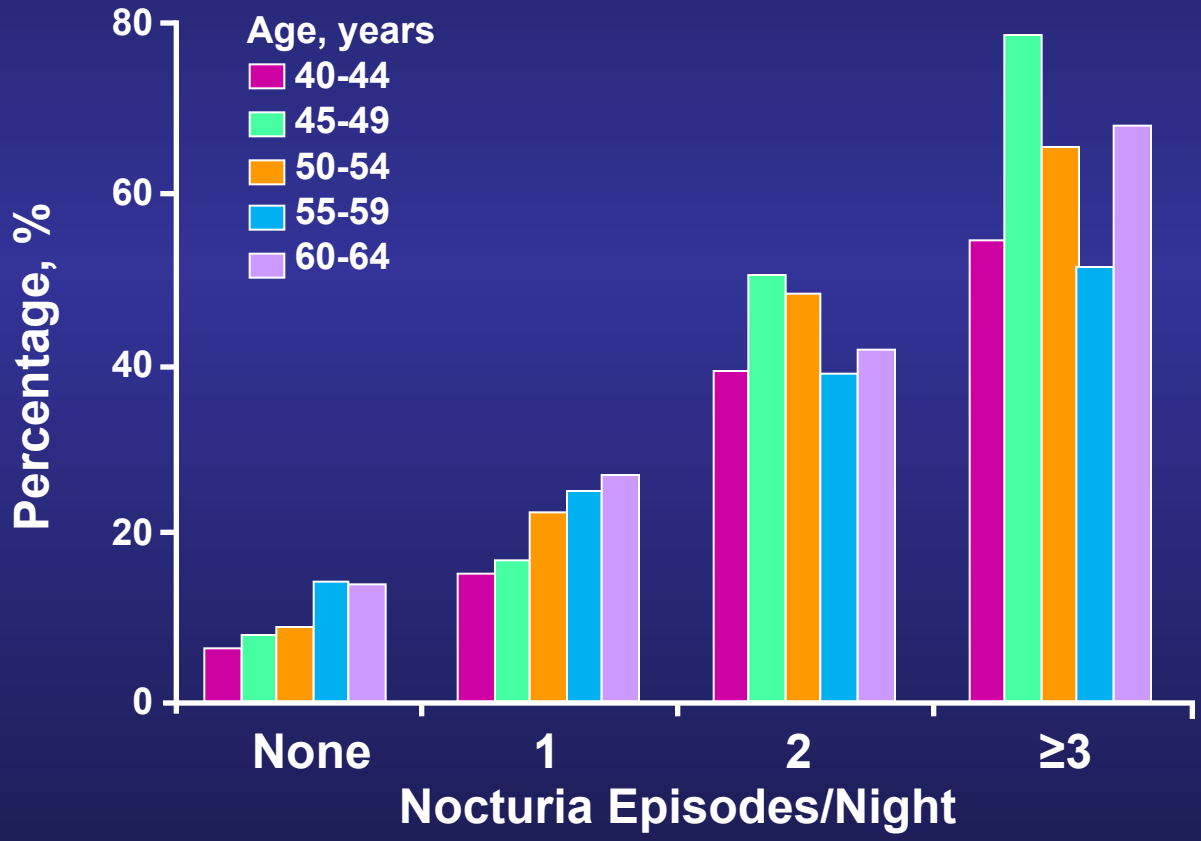
	Number of Voids			
	0	1	2	3+
Men[2]	89.9	91.3	78.3	75.5
Women[3]	79.9	75.4	56.8	43.6

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

[2, 3]p <.0001

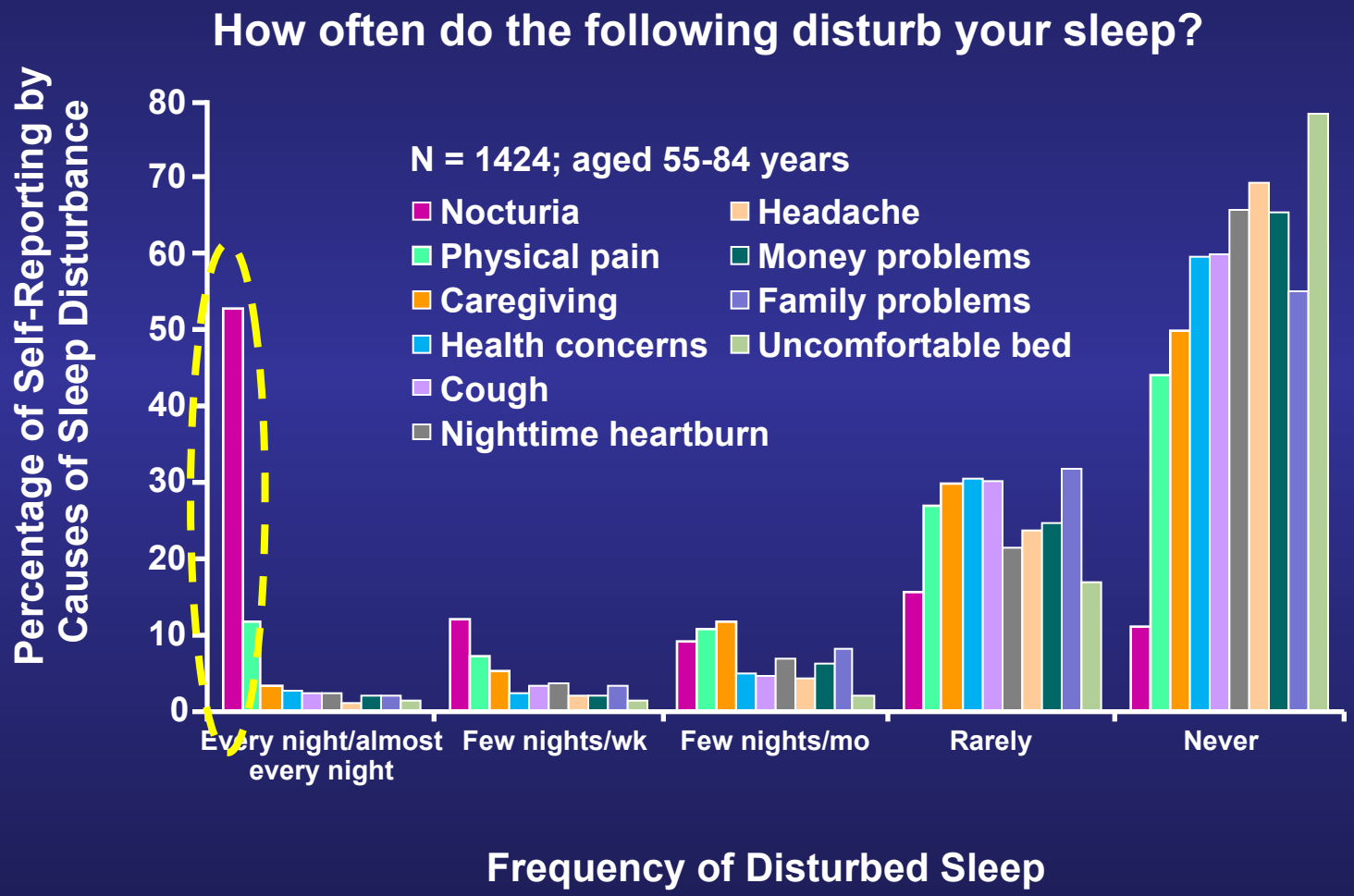
Nocturia Is a Widely Reported Cause of Poor Sleep

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



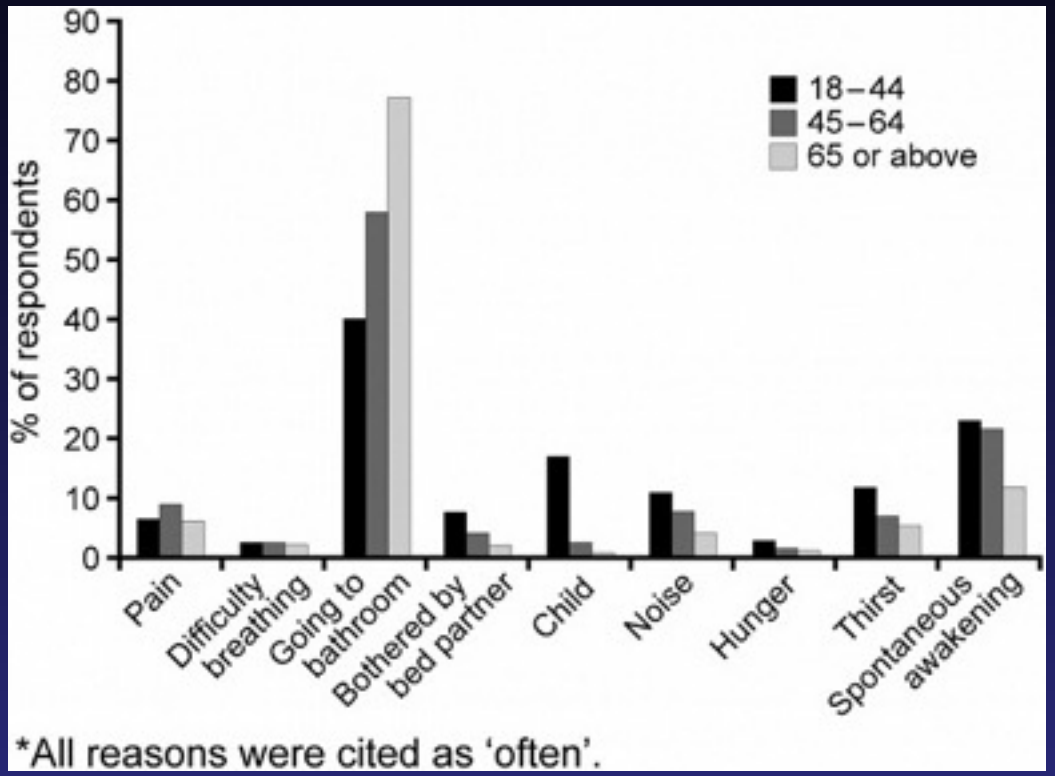
From: Asplund & Aberg, *Maturitas* 1996:24,73-81

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



Bliwise DL et al. *Sleep Med*. 2009;10(5):540-548.

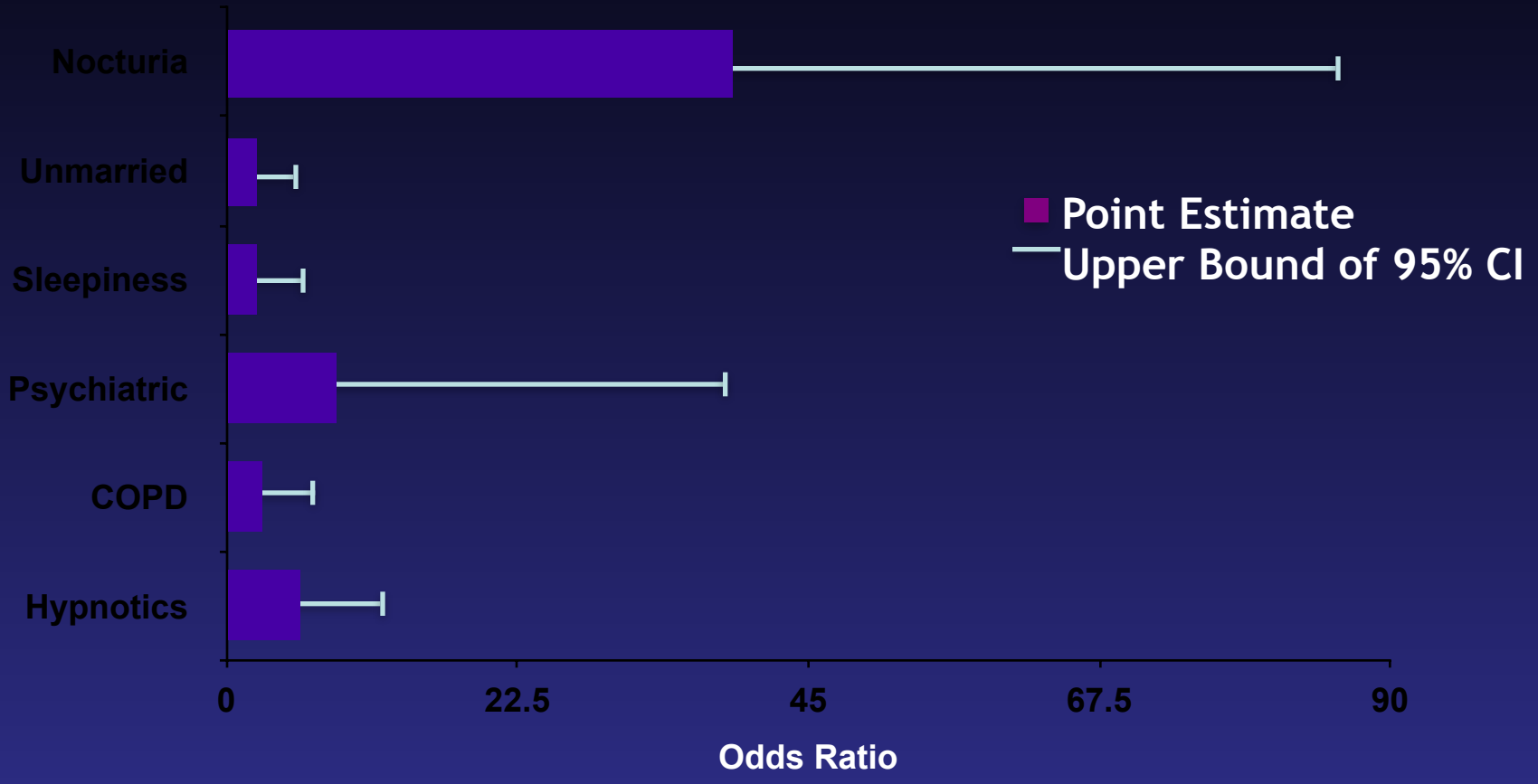
Nocturia as the Leading Cause of Disturbed Sleep across *All* Adult Age Groups(US population)



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

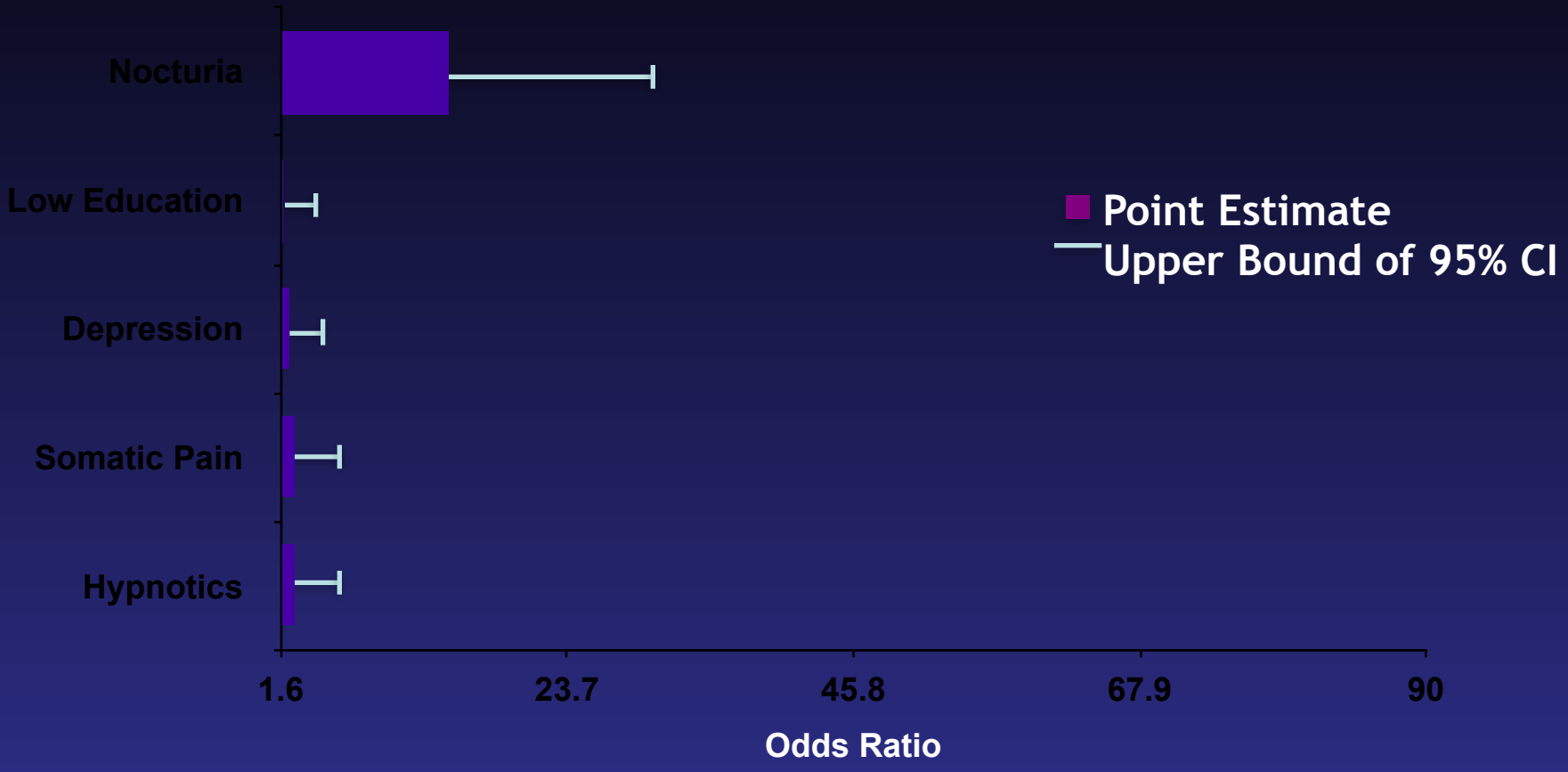
Multivariate Risk Factors for Insomnia in Elderly Taiwanese Men

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)

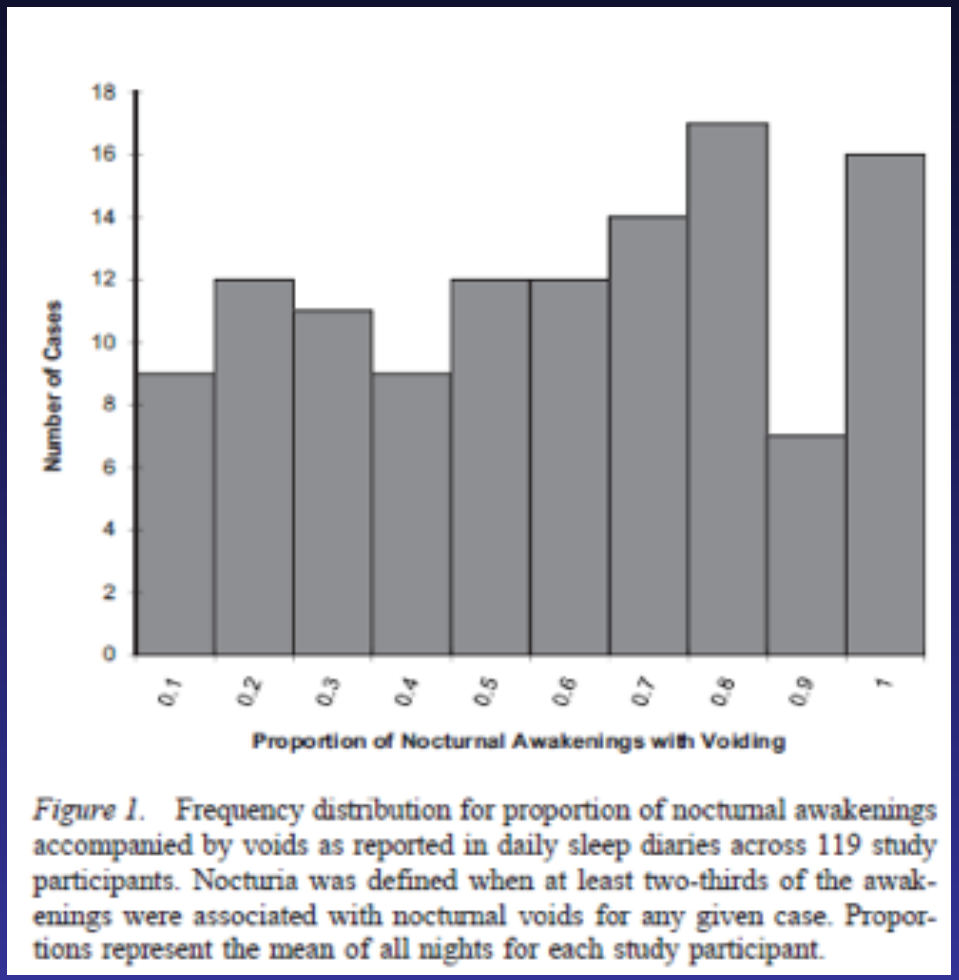
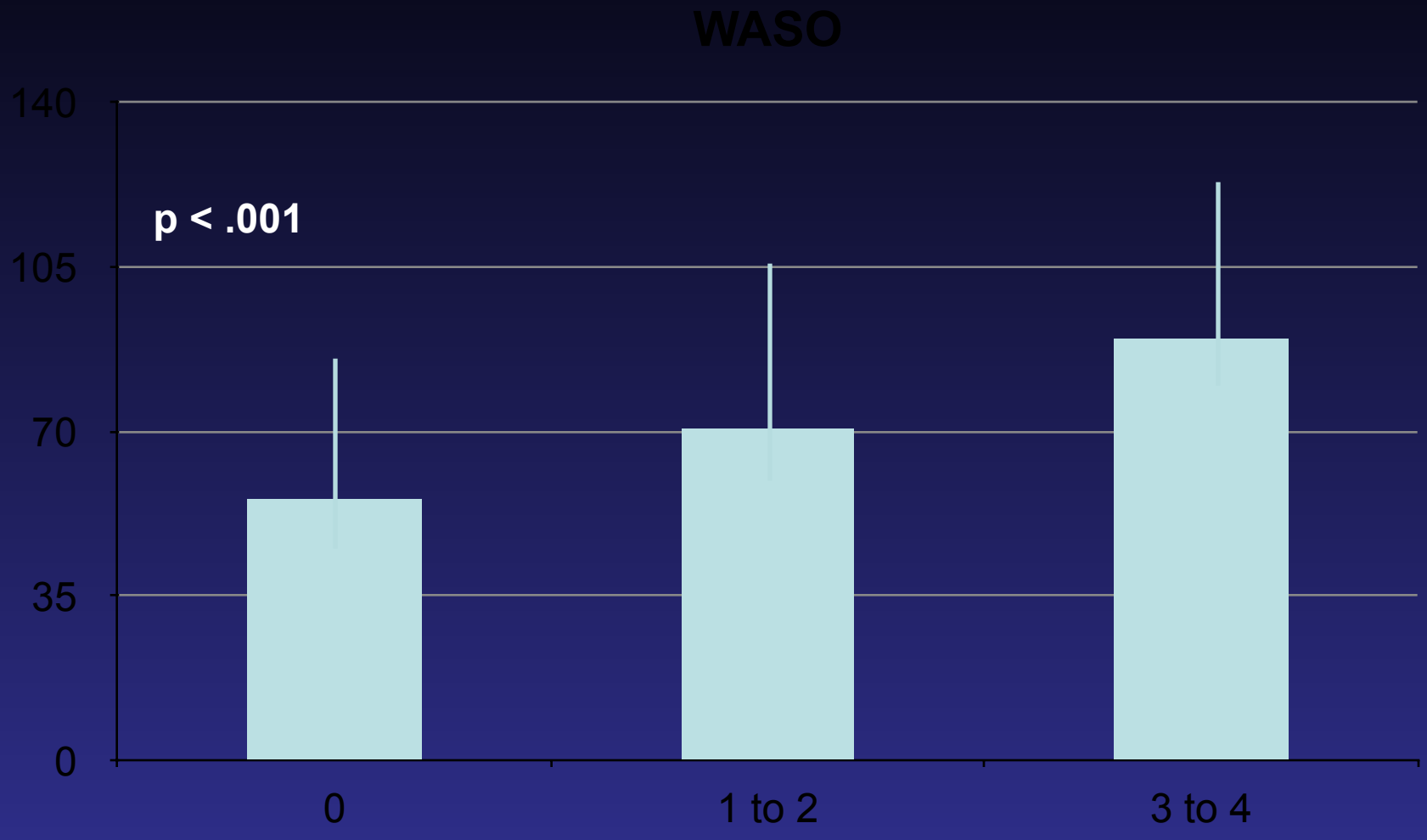


Figure 1. Frequency distribution for proportion of nocturnal awakenings accompanied by voids as reported in daily sleep diaries across 119 study participants. Nocturia was defined when at least two-thirds of the awakenings were associated with nocturnal voids for any given case. Proportions represent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

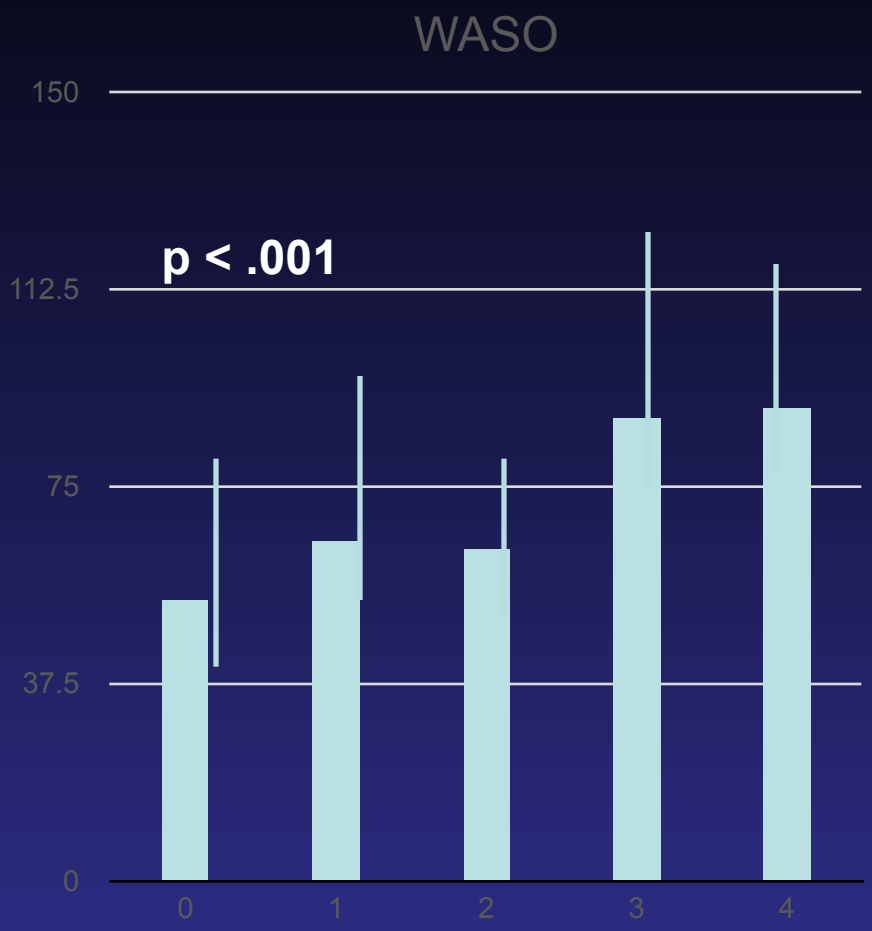
(Fung et al, *JAGS* 2017; in press)

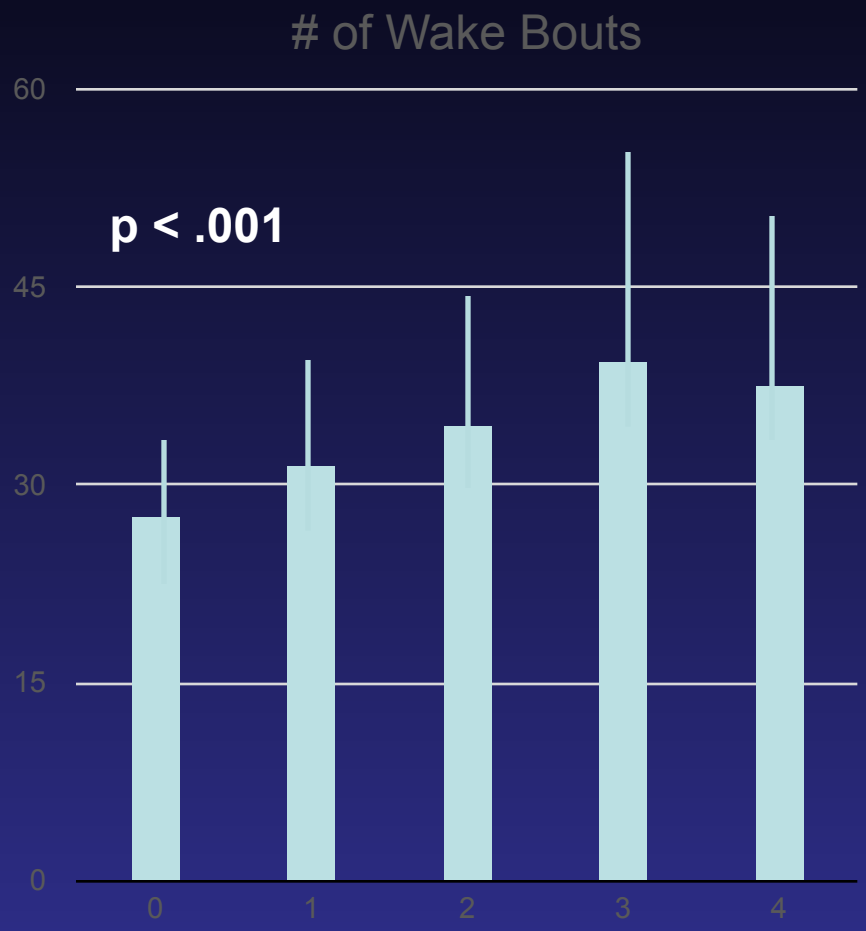


Actigraphic Measurements Confirm Higher WASO and Higher Number of Wake Bouts with Greater # of Voids

(n = 147; 1,774 individual nts)

(from Zeitzer et al, *JCSM* 2013; 9: 259-62)

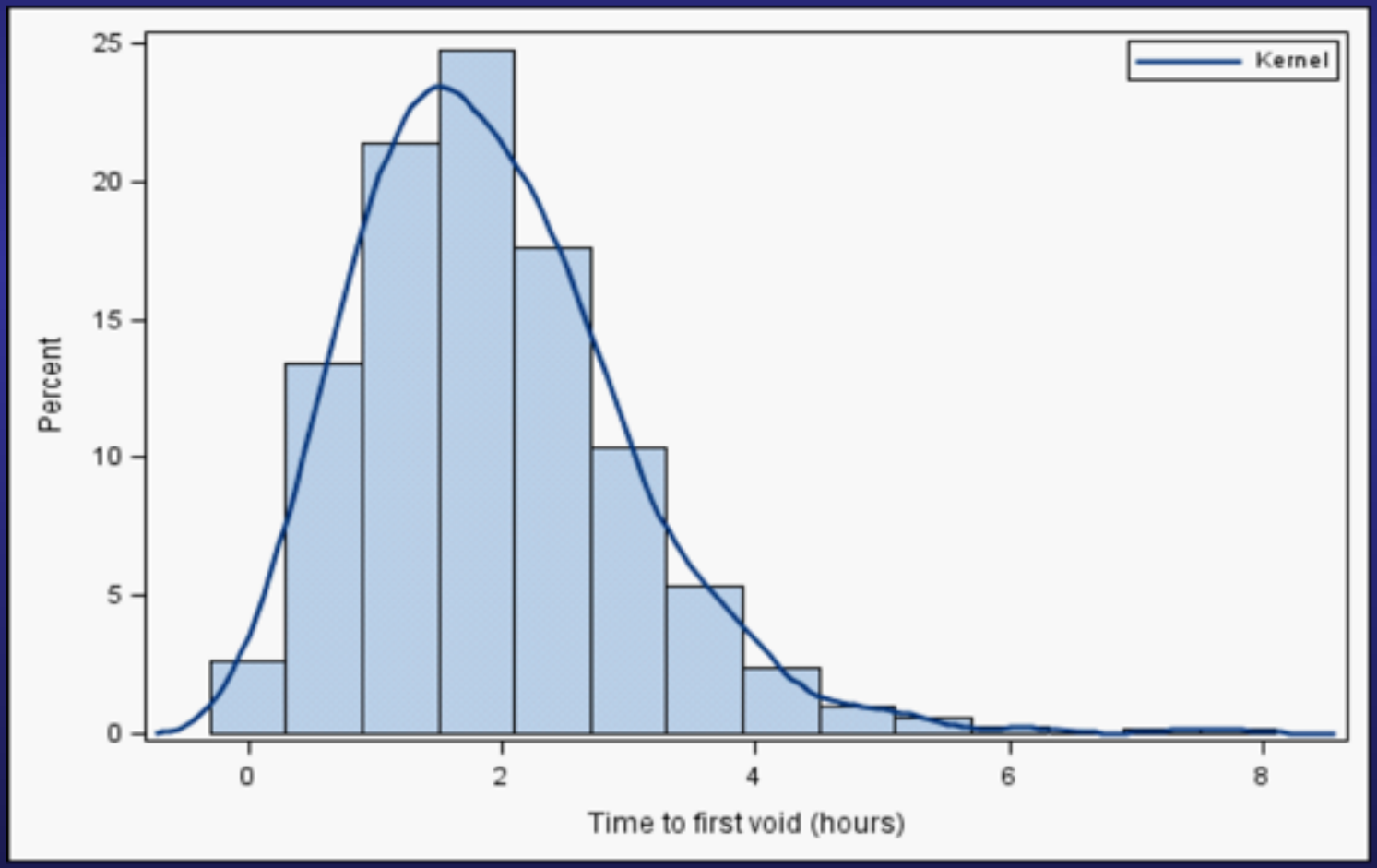




Number of Nocturnal Voids on Actigraphy Night

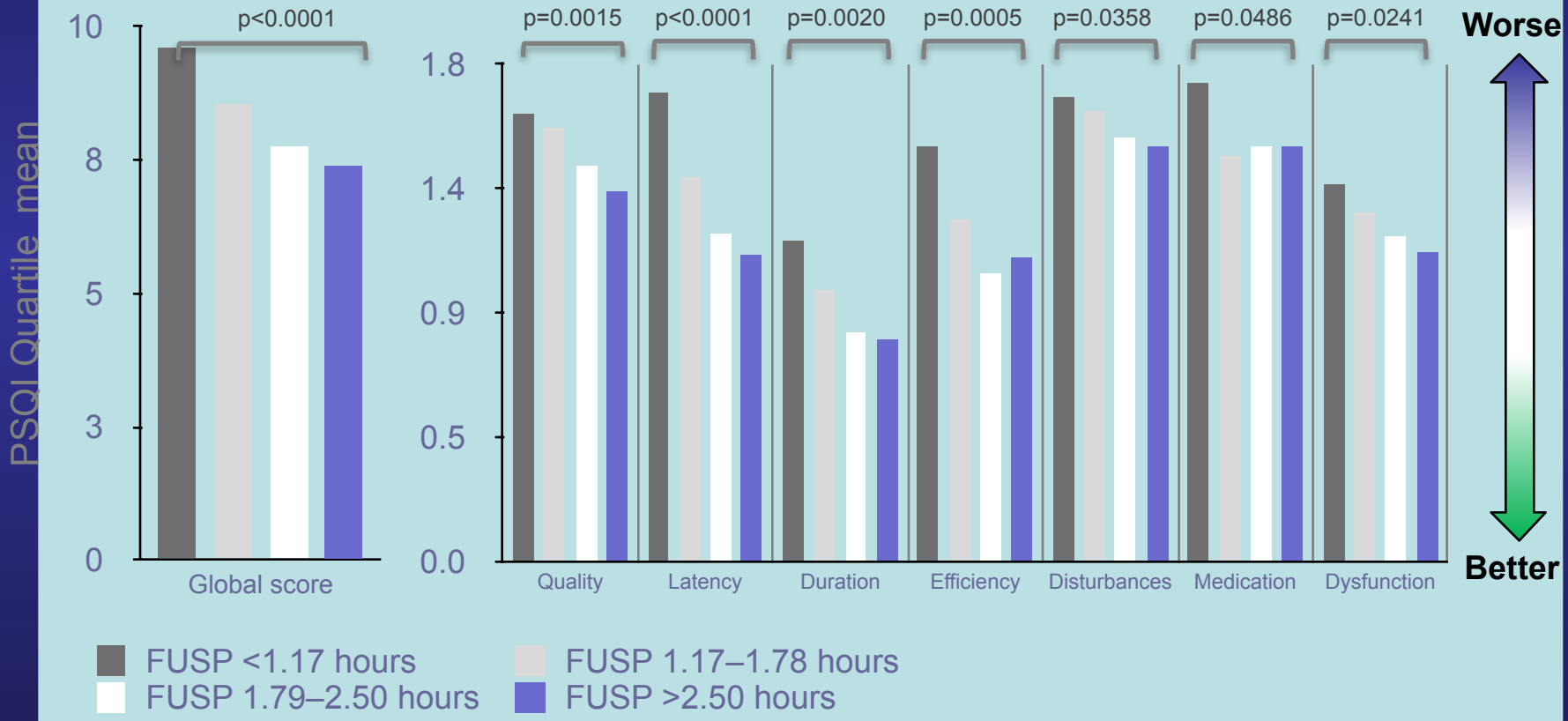
Frequency Distribution of Time to First Void (also called First Uninterrupted Sleep Period, FUSP) in Untreated Nocturia

(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

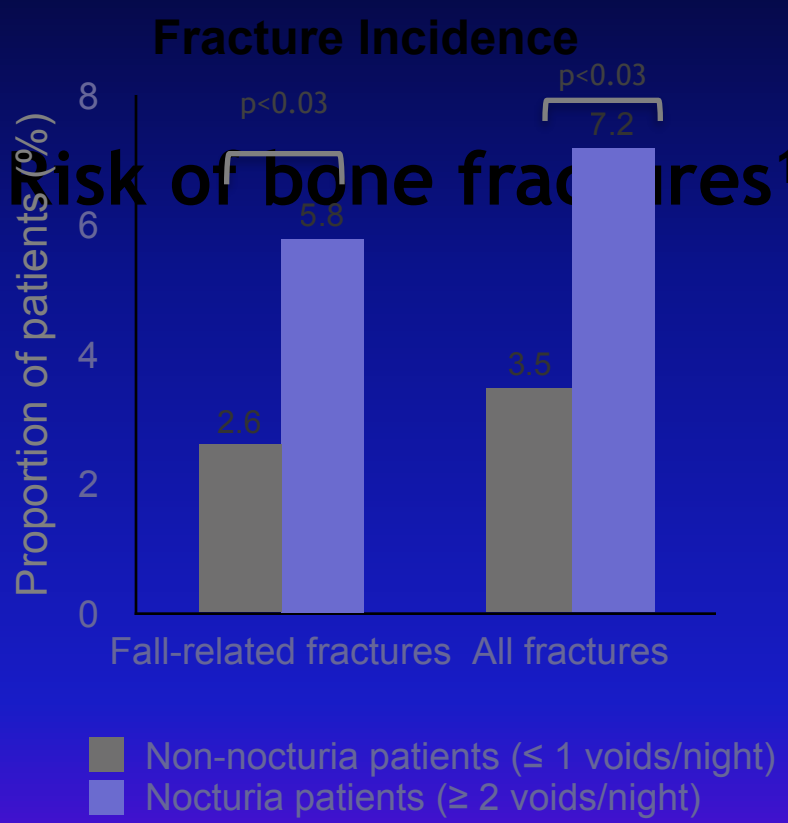
Nocturia

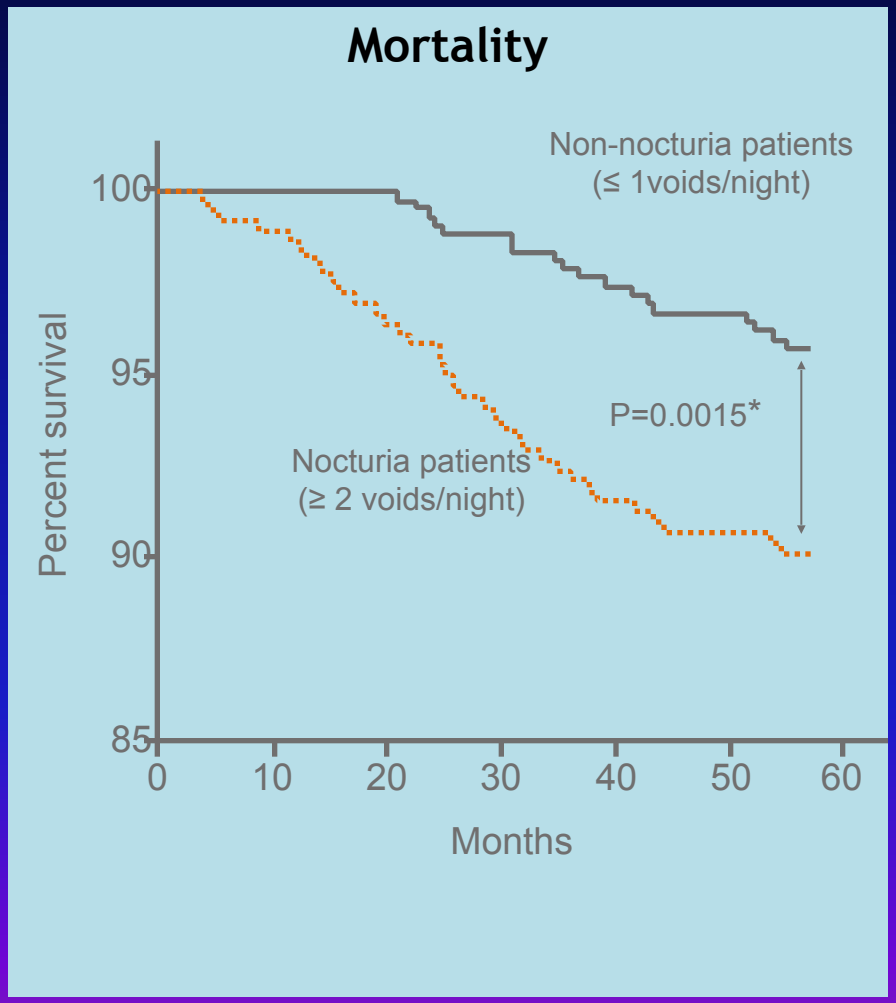
- Stewart et al, *JAGS* 1992; 40: 1217-20
- Asplund et al, *Arch Gerontol Geriatr* 1996; 43: 319-26
- Jensen et al *J Scand J Public Health* 2002; 30: 54-61

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

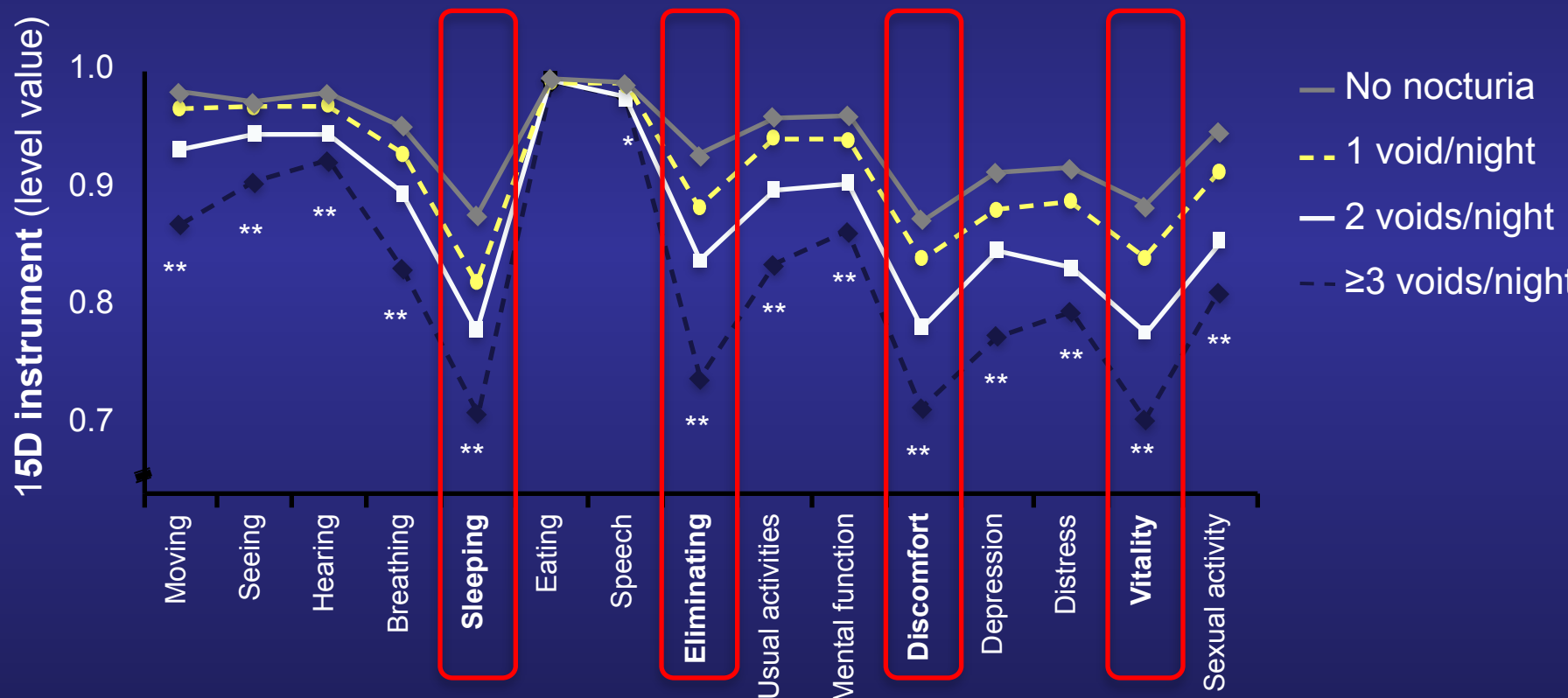
Nocturia Predicts Fall-related Fractures and Mortality in the Elderly





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)
Tikkinen 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."

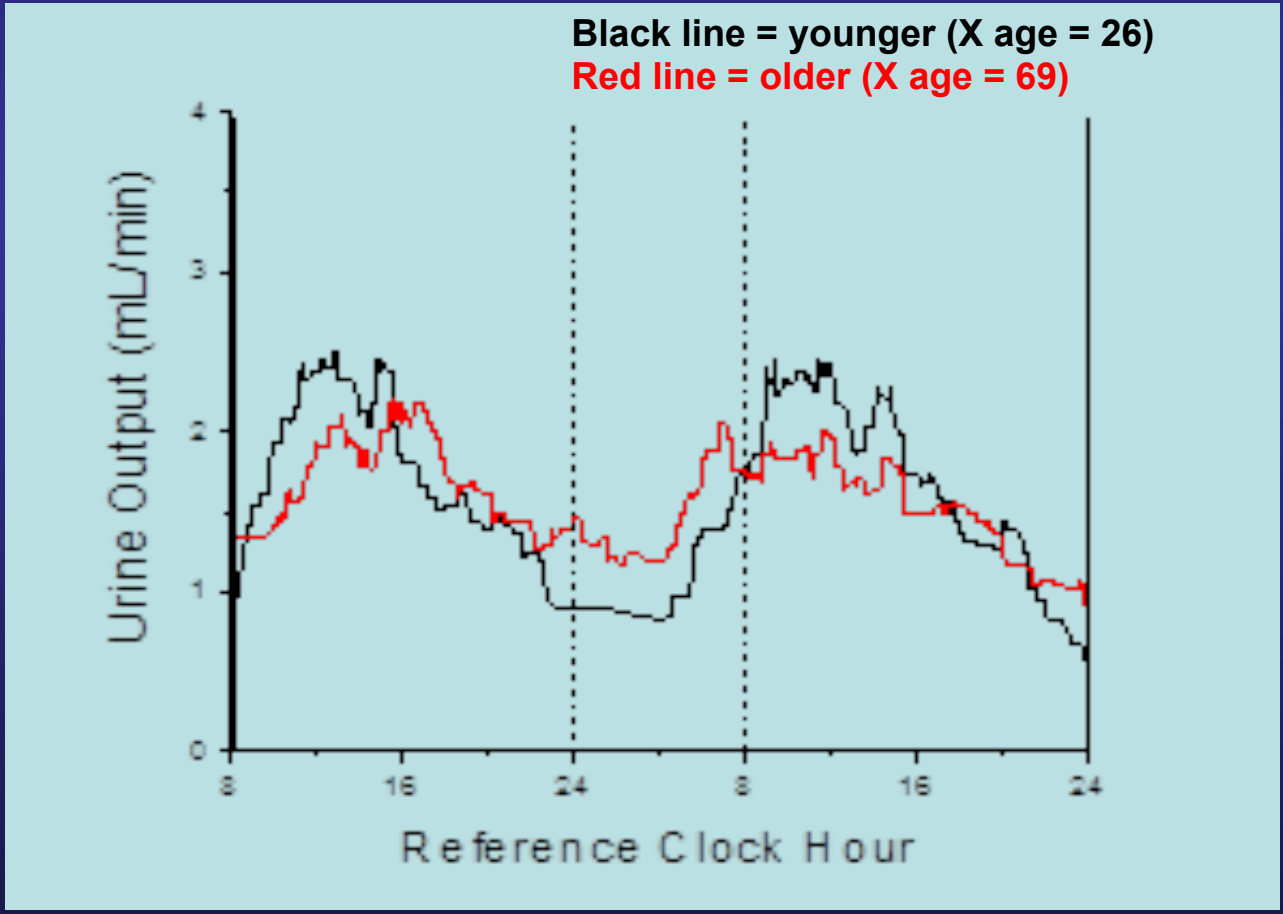
Weiss JP et al. *J Urol*. 2011;186(4):1358-1363.

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)

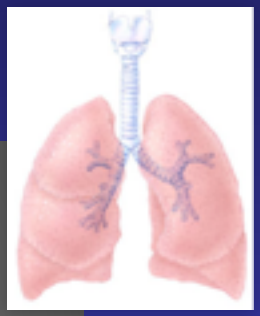
(from Duffy et al, *Current Aging Science* 2016: 9: 34-43

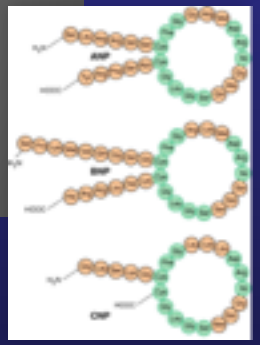


Pathophysiology of Nocturia in Sleep Apnea

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 (n=26)	10-24 (n=21)	25+ (n=11)	p
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

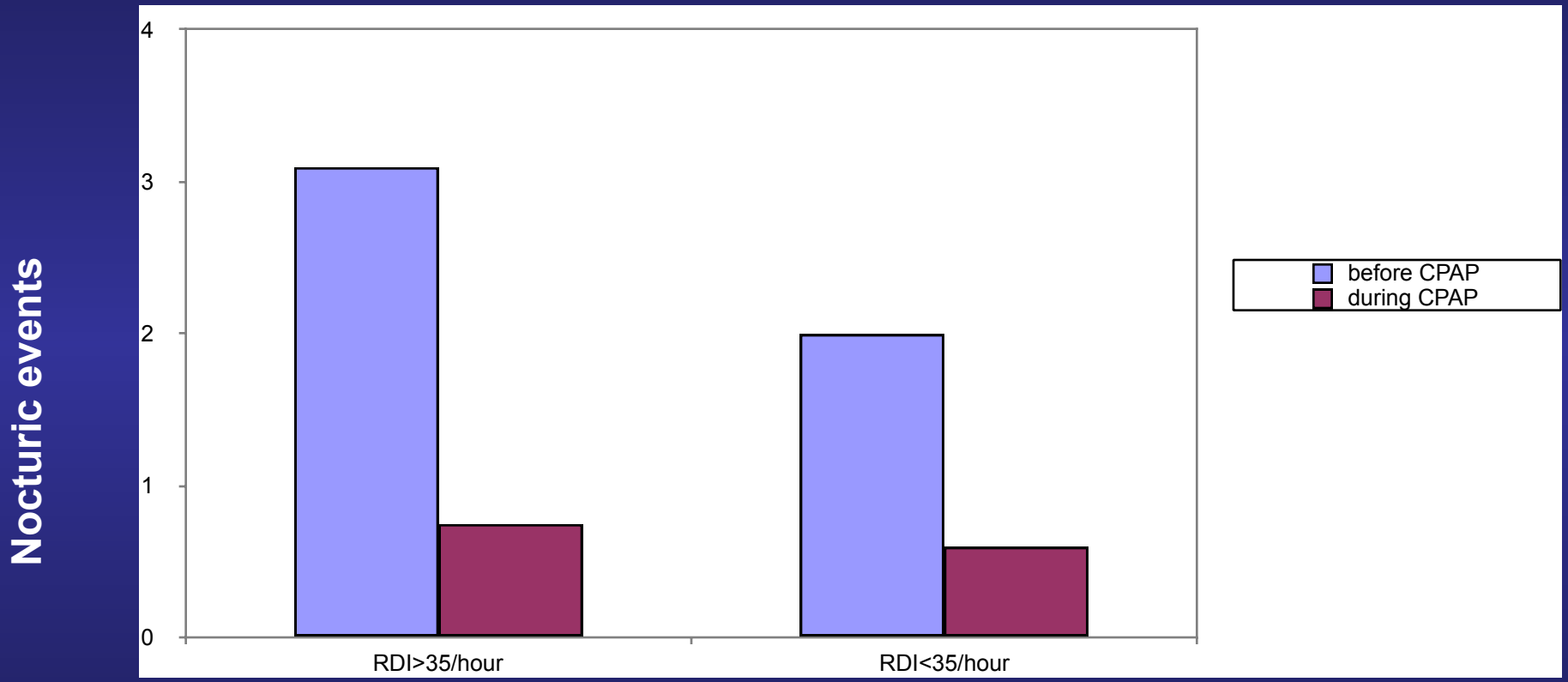
Polysomnographic (PSG) Measures and Nocturia*
Sleep Heart Health Study (n = 6342)

*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)
Sleep Duration	*365 (317, 404)*	*367 (322, 408)*	*.06*
Sleep	*82.8 (75.4,*	*85.1 (77.4,*	*< .0001*
WASO	*55.5 (34.0,*	*43.5 (26.5,*	*< .0001*
N1%	*4.6 (2.8, 7.2)*	*4.5 (2.8, 7.1)*	*.32*
N2%	*57.5 (49.3,*	*57.2 (49.3,*	*.30*
N3%	*16.7 (8.2,*	*17.0 (8.2,*	*.36*
REM%	*19.8 (15.4,*	*20.5 (16.5,*	*< .0001*
AHI > 15 (%)	*23.2*	*17.4*	*< .0001*

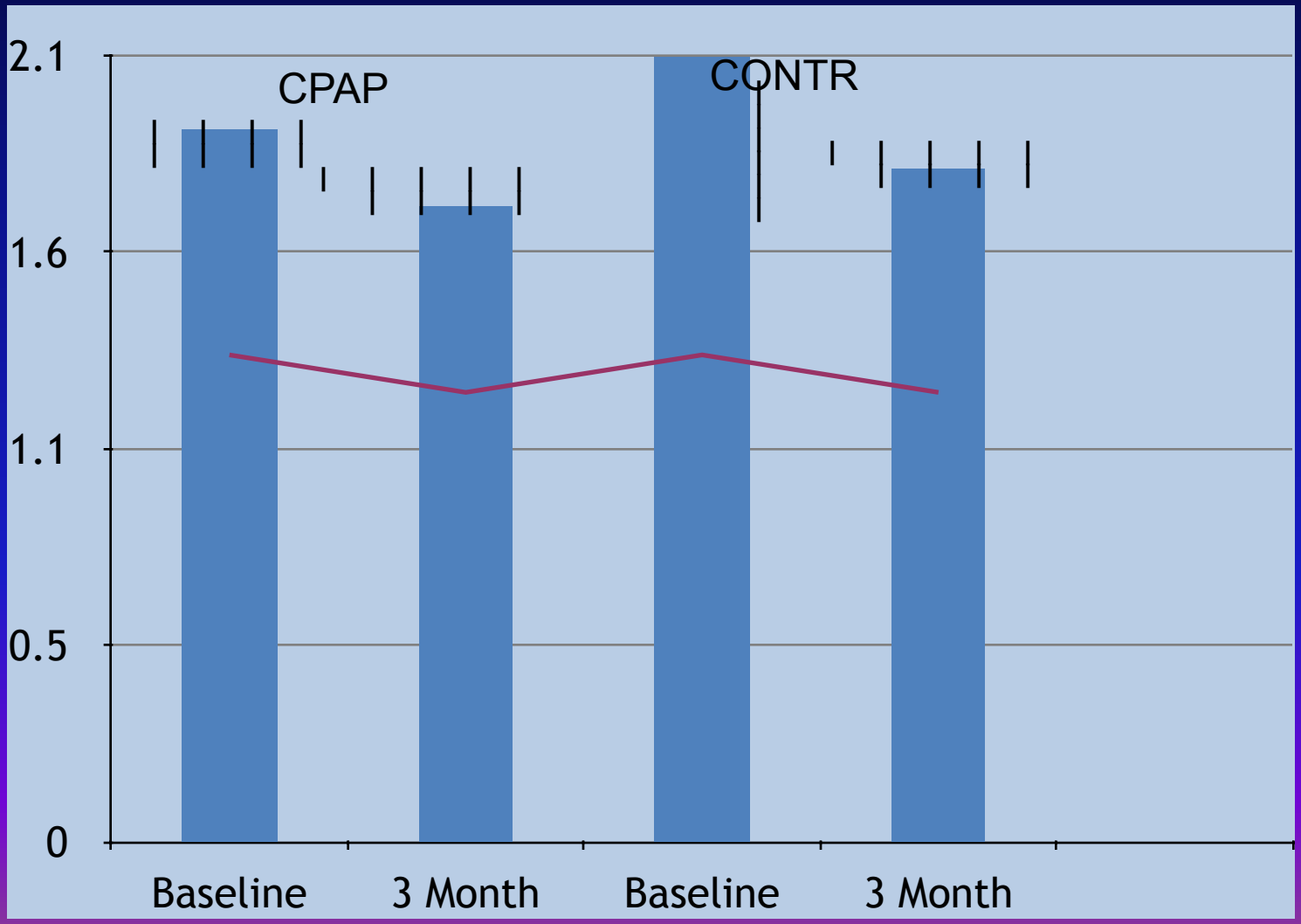
Nocturia Episodes Reduced by CPAP



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

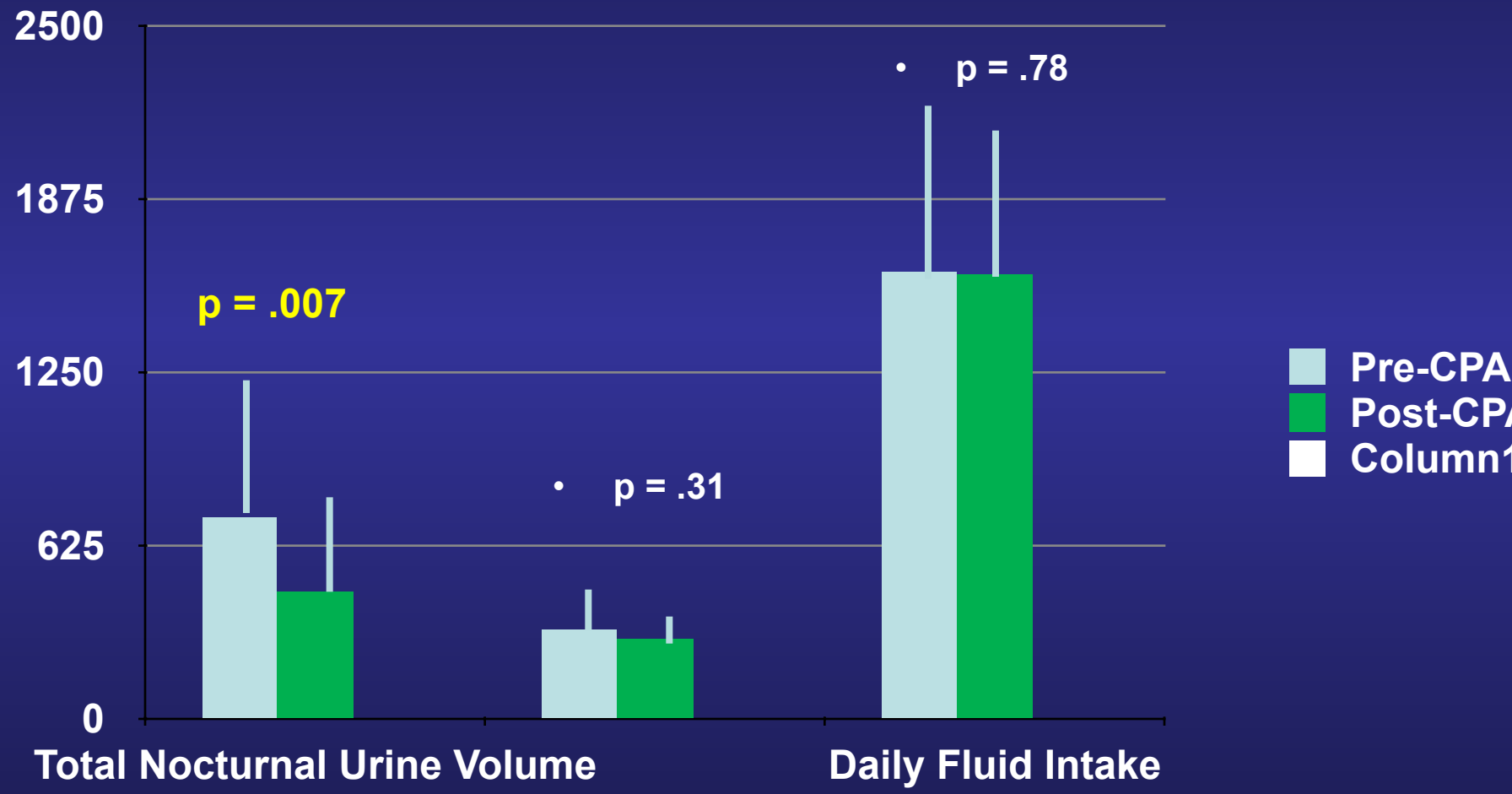
No Effect of CPAP on Nocturia: The PREDICT Trial

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



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?

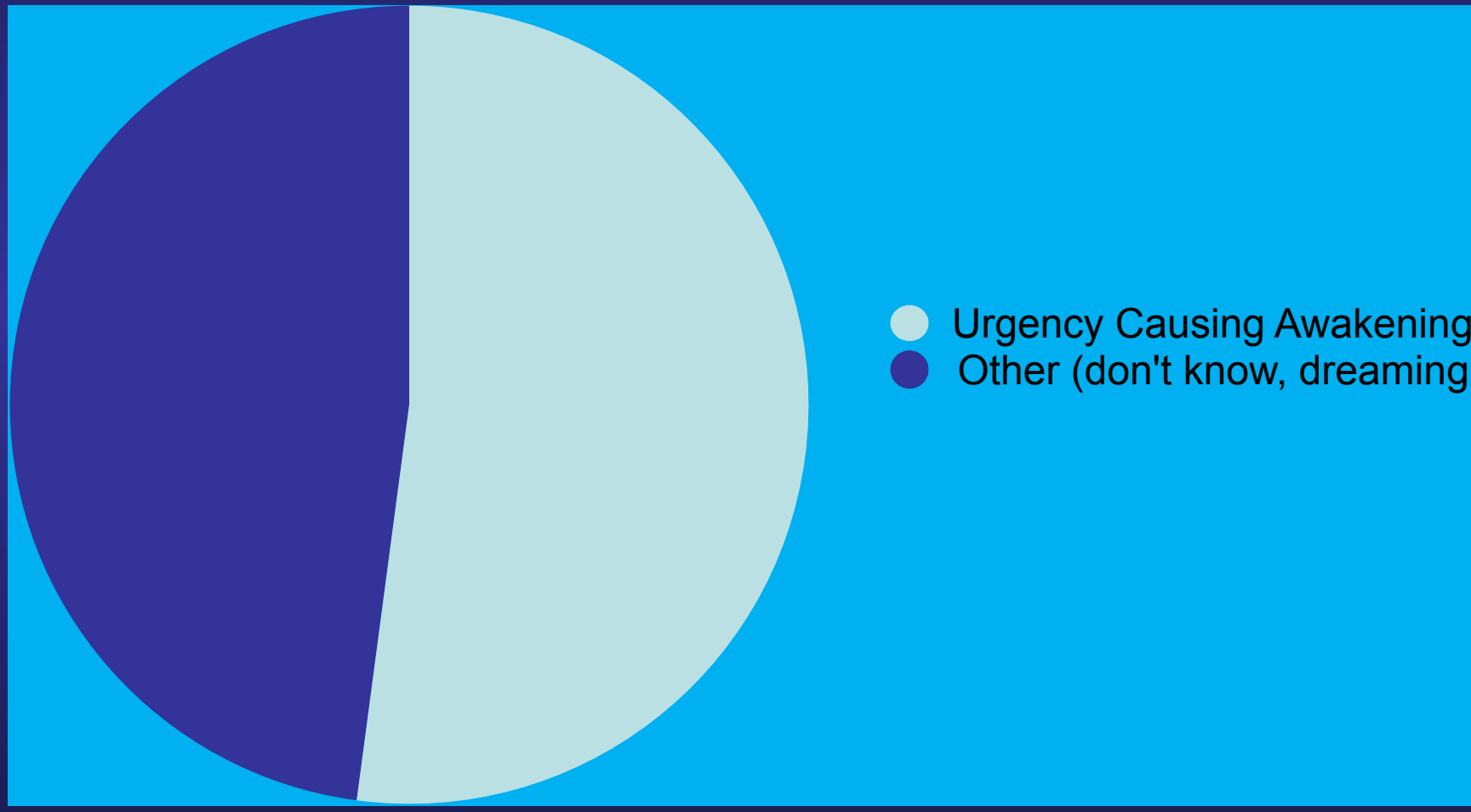
Chicken and Egg

- 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

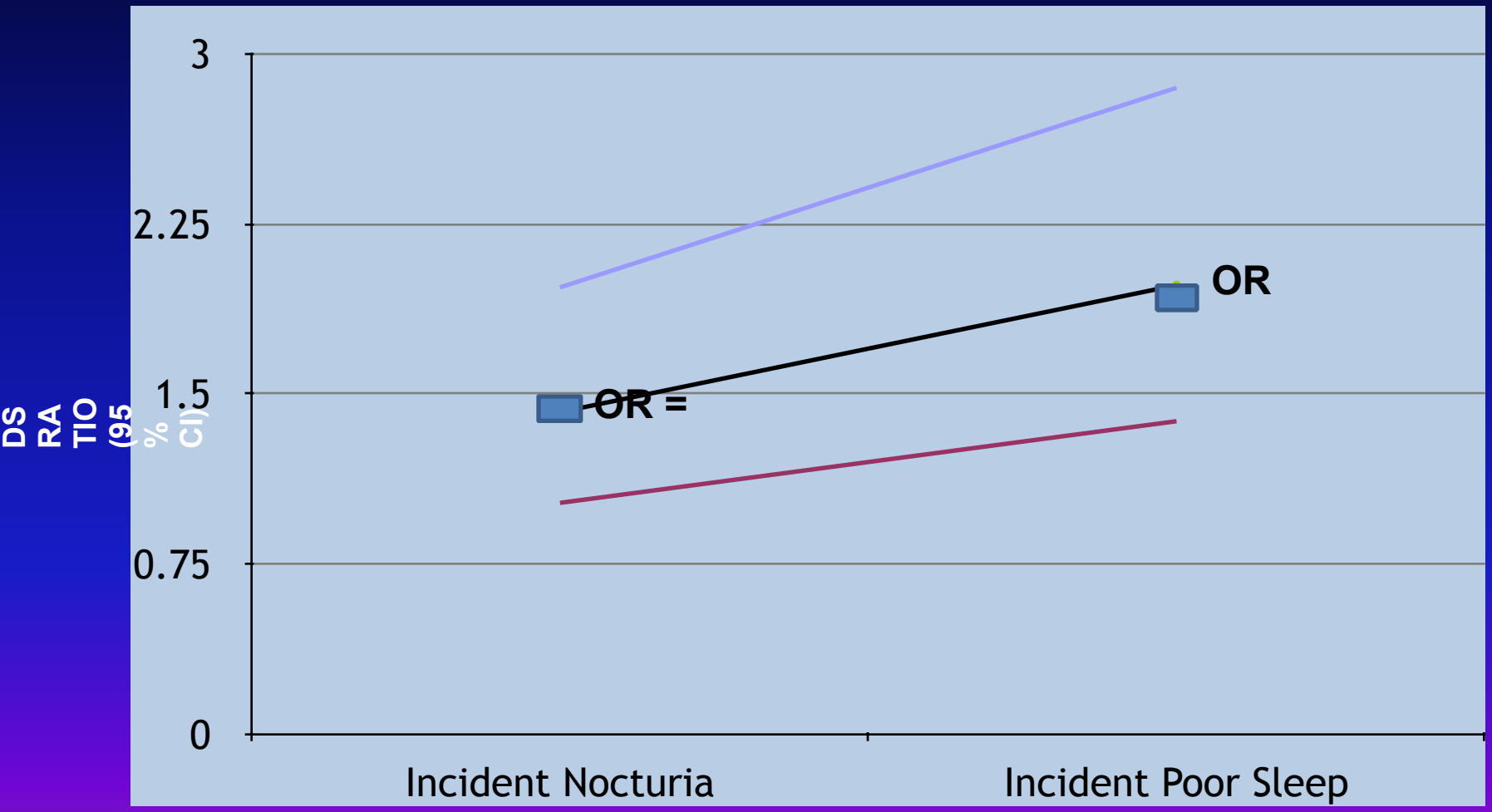
(Pressman et al, *Arch Int Med* 1996: 156: 545-60)



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 H20 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

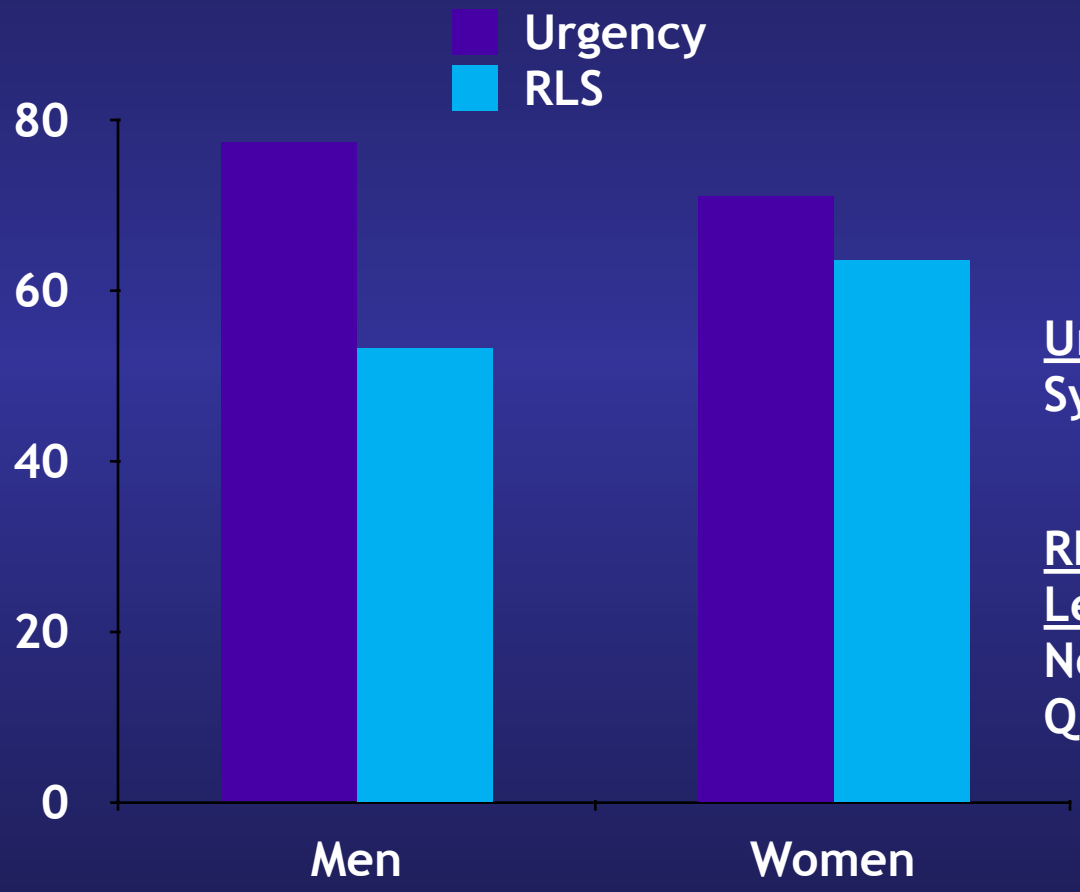
Wetness Episodes Can Begin During Apneic Events: Negative Pressure Breathing Causing Incontinence

(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



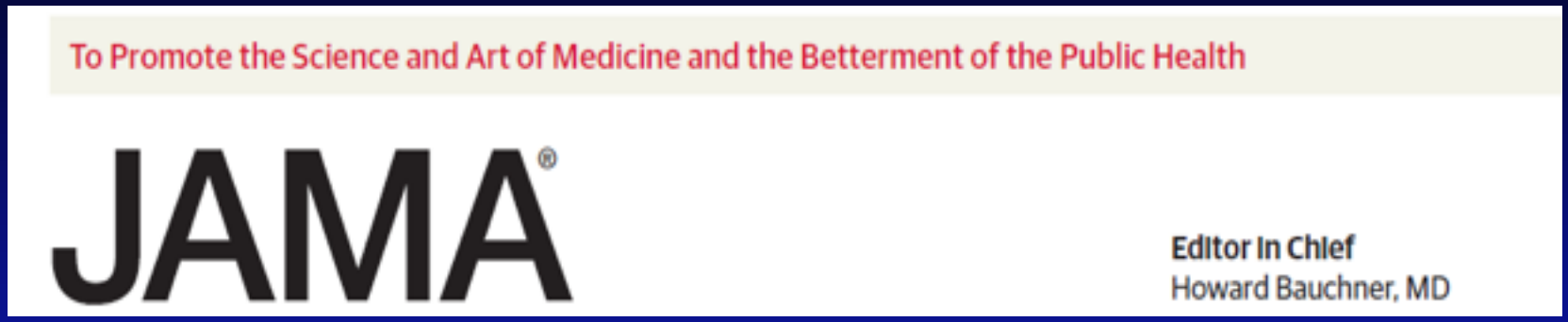
Urgency: Danish Symptom Score

RLS (Restless Legs Syndrome): Nordic Sleep Questionnaire

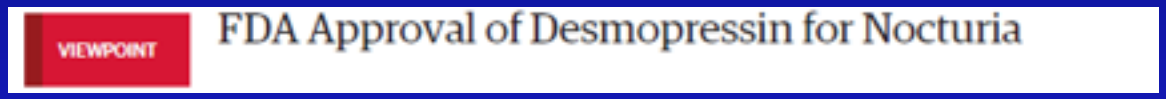
Tikkinen et al. *Am J Epidemiol*. 2009;170: 361-368.

Treatment Issues with Nocturia

Nocturia is in the News!



JAMA Online First **(April 06, 2017)**



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

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*

Bliwise et al, *Sleep Medicine* 2014; 15: 1276-8

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?

IPSS, international prostate symptom score.
Yoshimura et al. *Urology*.2003;614:786–790.

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

Open label, single-group design of a muscarinic antagonist

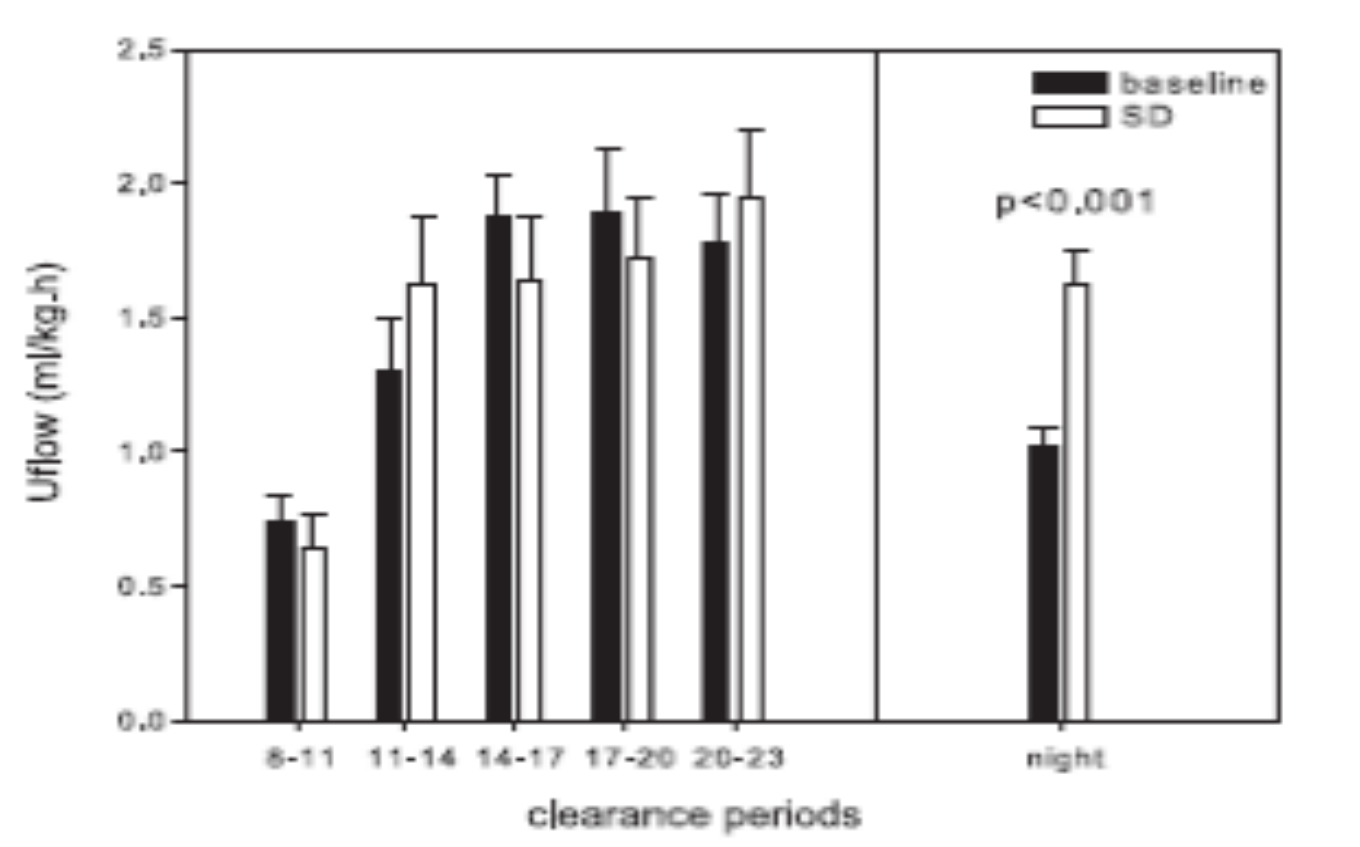
(Takao et al, *Urology* 2011: 78: 648-652)

	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 H_20 and Na intake controlled

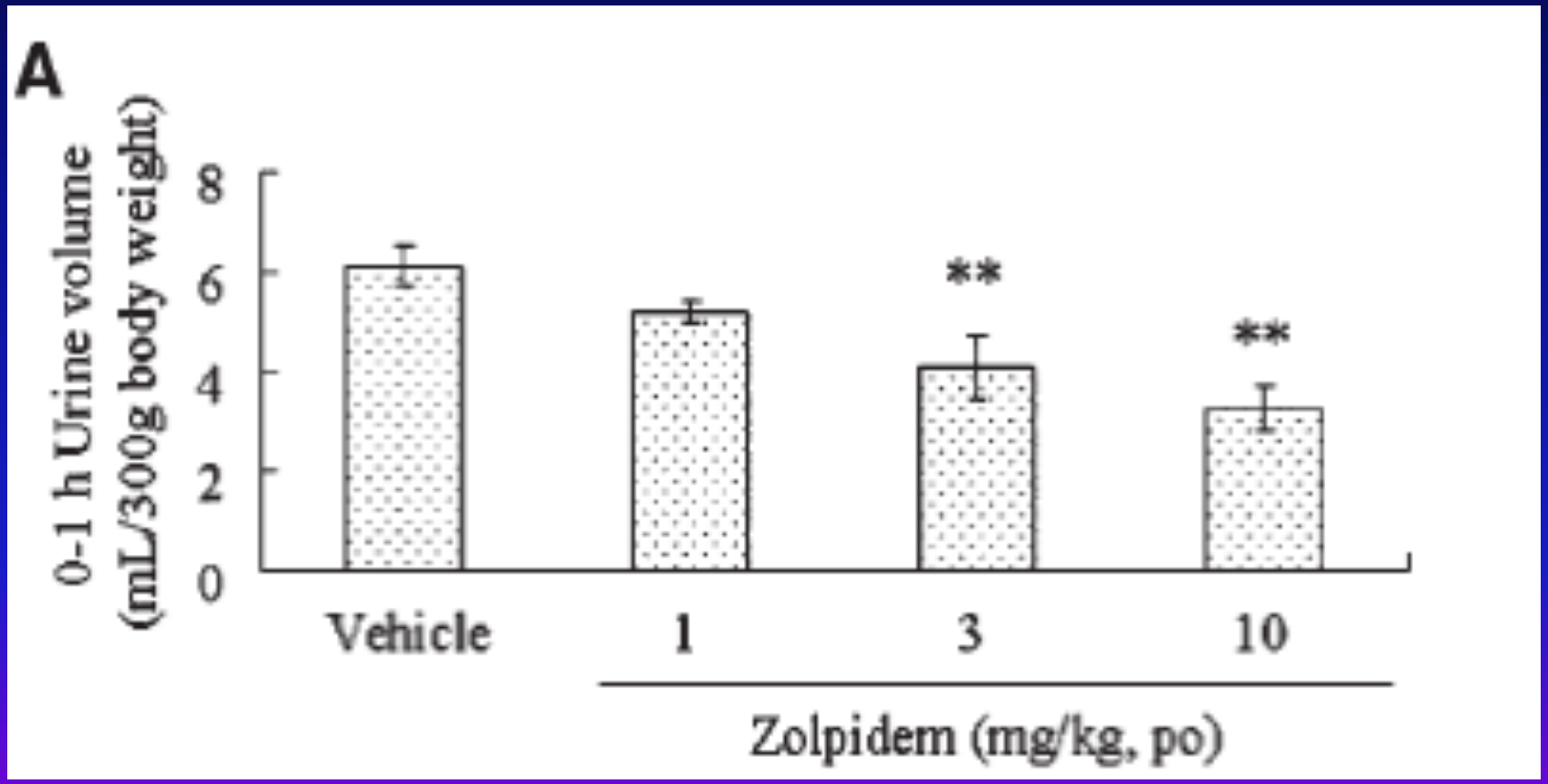
(Kamperis et al, *Am J Physiol Renal Physiol* 2010; 299: F404-11)



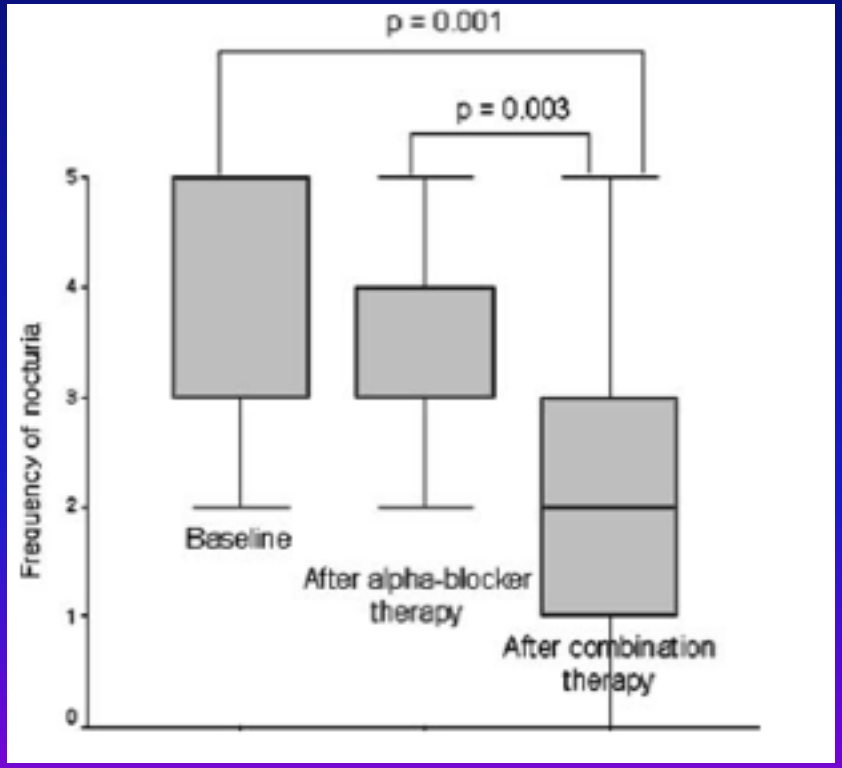
Water-loaded, wild-type rats show dose-dependent, zolpidem-induced decreases in urine volume the 1st hour after oral administration

An effect of sleep?

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



GABAergic Medication May Enhance Efficacy of Nocturia Rx

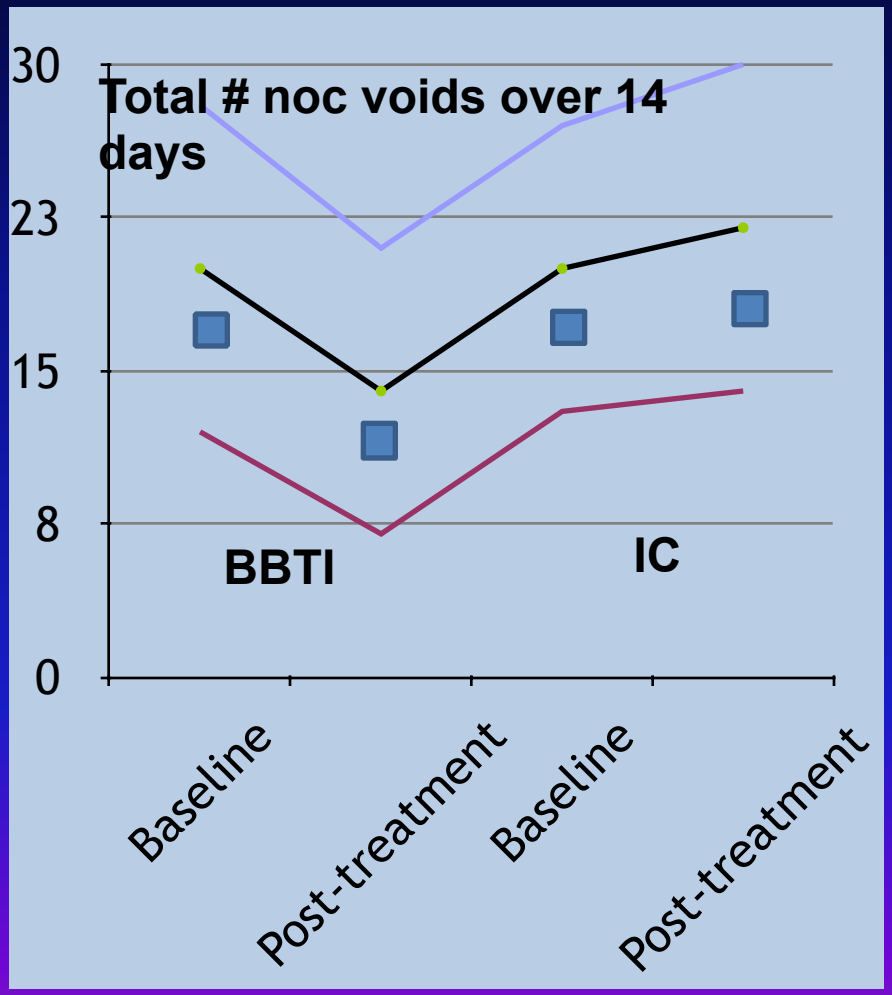


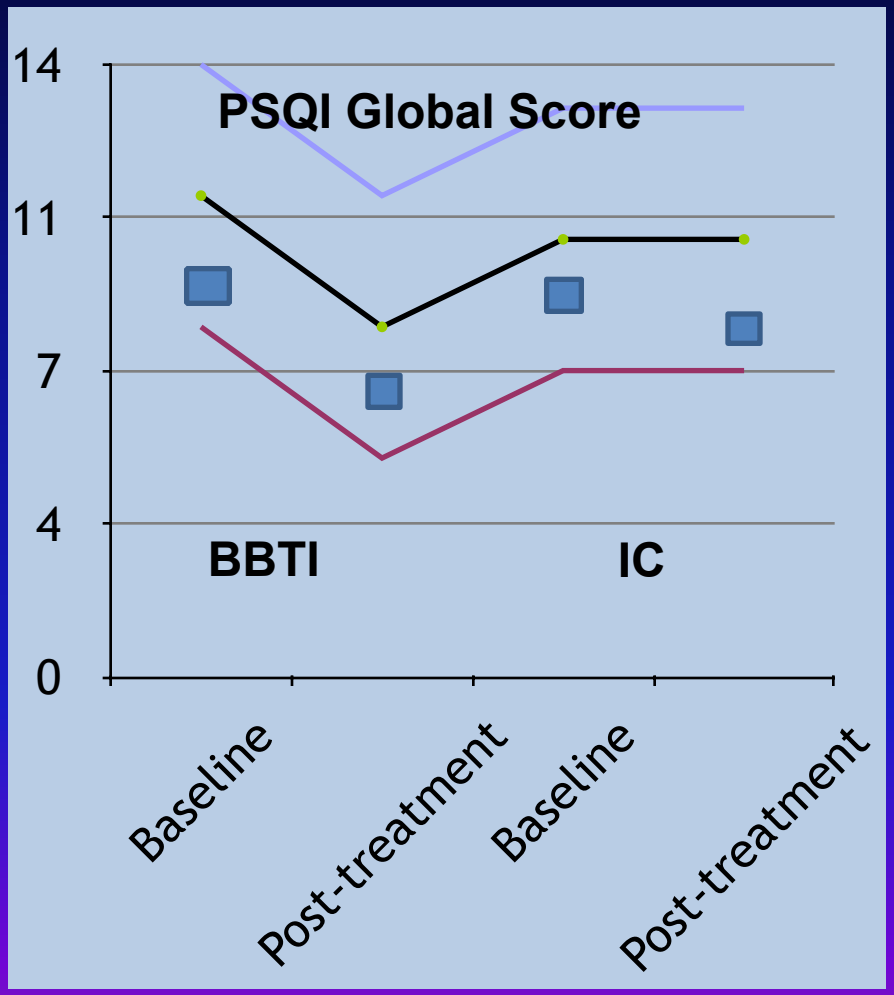
Song & Ku, *Int Urol Nephrol* 2007; 39: 1147-52

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

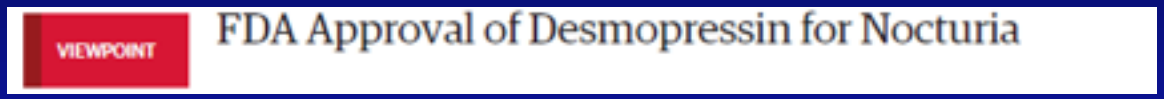
(Tyagi et al, *Sleep* 2014: 37: 681-7)

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

What about Desmopressin?

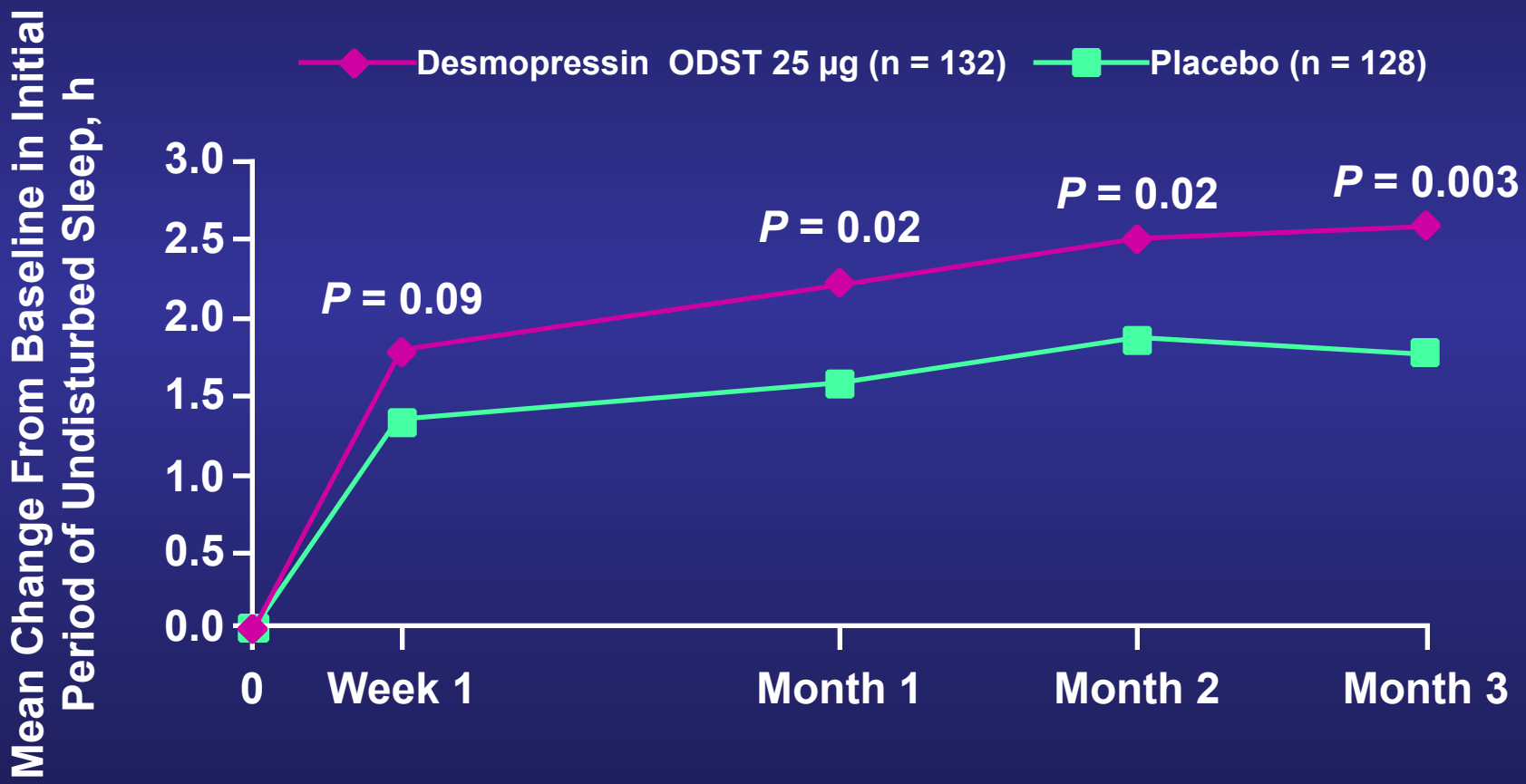
(trade names: Noctiva, Nocdurna)

JAMA **Online First (April 06, 2017)**



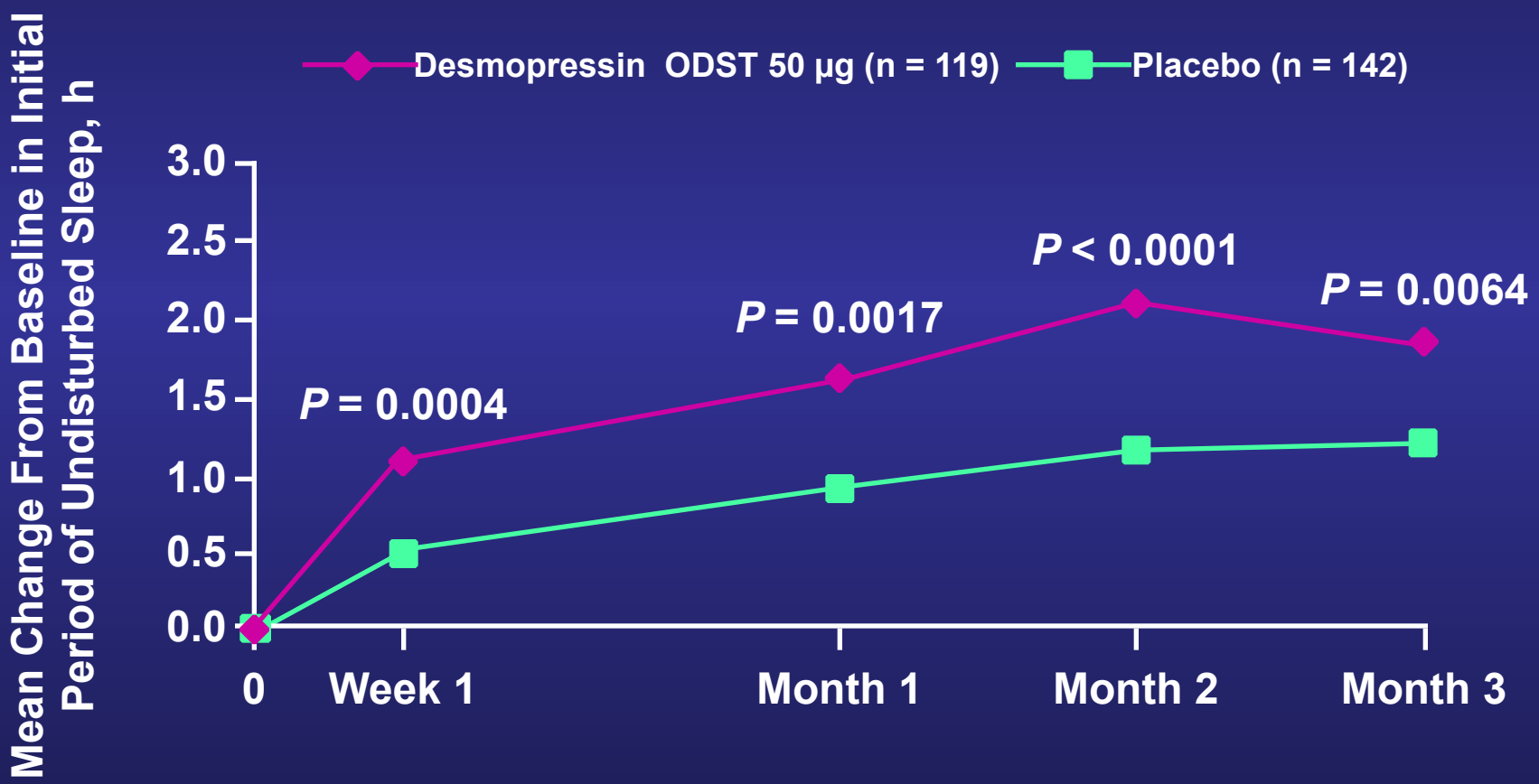
JAMA **2017; 317, 1518 (April 18, 2017)**

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



Sand PK et al. *J Urol.* 2013; 190:958-964.

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



Weiss JP et al. *J Urol*. 2013; 190:965-9729.

Baseline Subtracted Increments in FUSP with Oral Melt Formulation of Desmopressin Relative to Placebo: Average = 32-76 Mins [1-3]

Sedative-Hypnotic	Treatment Difference (Active − Placebo)
Eszopiclone (Lunesta)® 3mg[4]	*25.0*
Doxepin (Silenor)® 6mg[5]	*22.2*
Zolpidem-MR (Ambien-MR)®[6]	*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.
4. Zammit et al. *Curr Med Res Opin* 2004; 20: 1979-91.
5. Roth et al. *Sleep Med* 2010; 11: 843-7.
6. Roth et al. *Sleep Med* 2006; 7: 397-406.

Caudal-to-Rostral Fluid Shifts as Potentially Impacting Upper Airway Caliber

Could Fluid Retention Exacerbate Sleep Apnea?

BMES CrossMark

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

Azadeh Yadollahi,[1,2] B. Singh,[1] and T. Douglas Bradley[1,3,4]

Original Article

Overnight fluid shifts in subjects with and without obstructive sleep apnea

Respiratory Physiology & Neurobiology

ELSEVIER

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

Laura H. White[a,b], Shveta Motwani[a,b], Takatoshi Kasai[a,b], Dai Yumino[a,b], Vinoban Amirthalingam[a,b], T. Douglas Bradley[a,b,c,d,*]

ARTICLE INFO

ABSTRACT

New Research

Journal of Clinical Sleep Medicine

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

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

Thank you for your attention

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