Sleep, Circadian Rhythms and Metabolism

Kenneth P. Wright Jr., PHD
Professor
Department of Integrative Physiology, University of Colorado Boulder
Division of Endocrinology, Metabolism and Diabetes
University of Colorado Anschutz Medical Campus
Kenneth.wright@Colorado.edu

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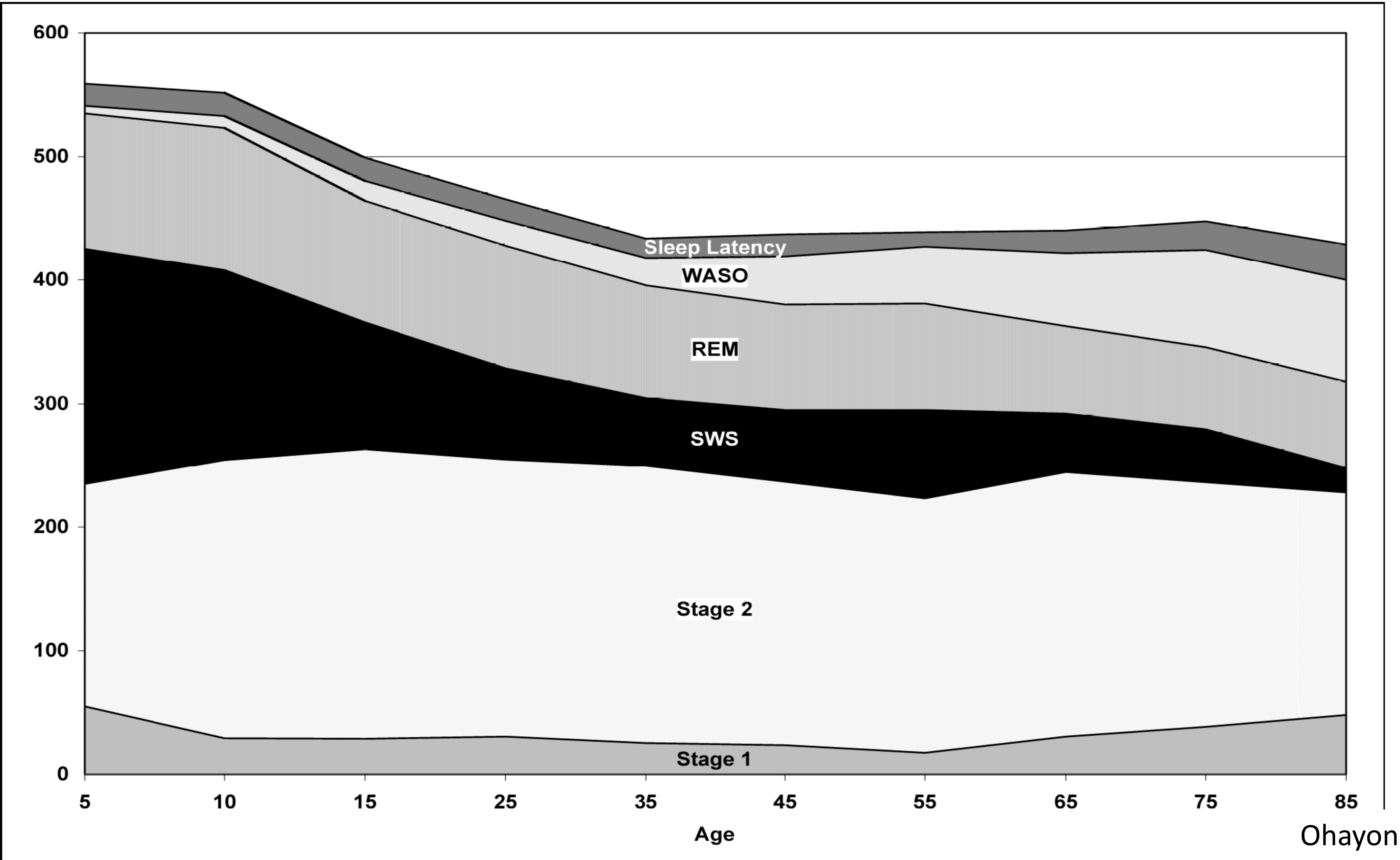
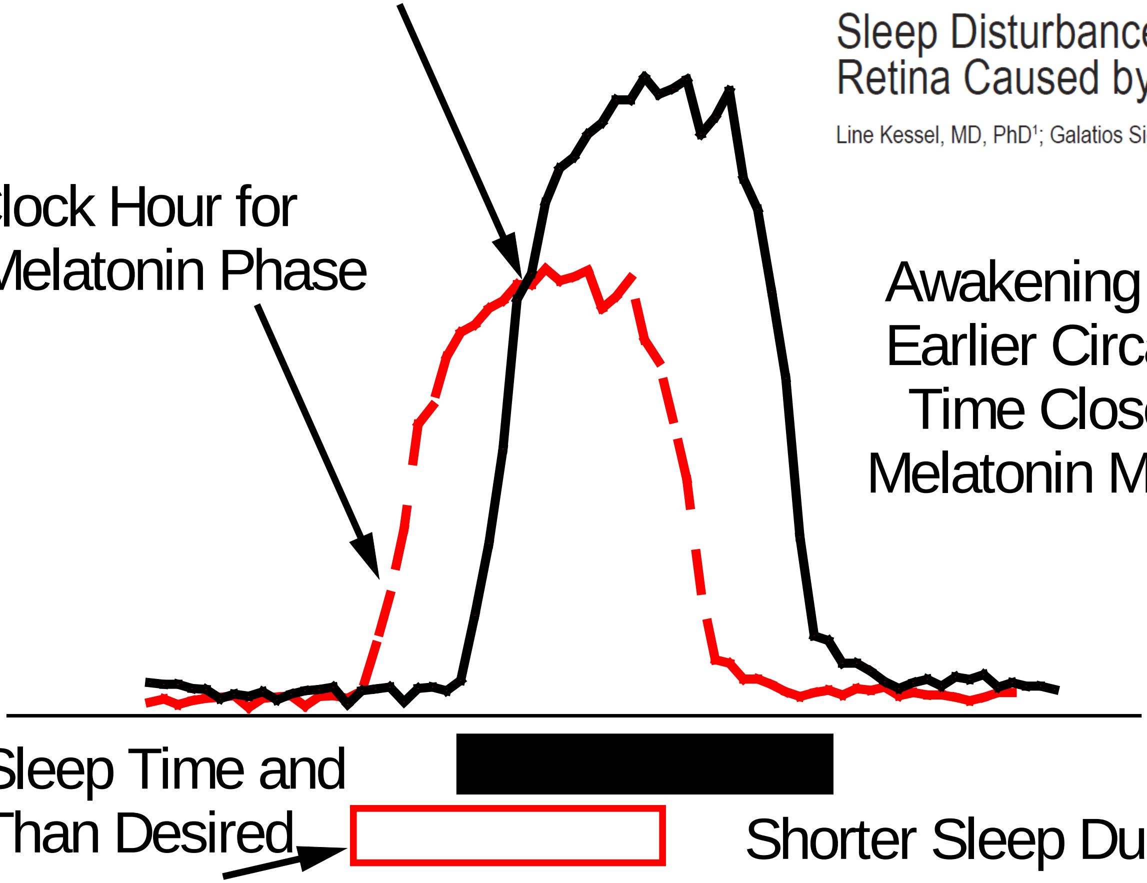
- Other financial relationships: Consulting fees from or served as a paid member of scientific advisory boards for NIH (Sleep Disorders Research Advisory Board - National Heart, Lung and Blood Institute) and Torvec Inc.
- Conflicts of interest: Speaker/educational consultant honorarium fees from Associated Professional Sleep Societies and American College of Chest Physicians

Sleep Changes Across the Human Lifespan



Ohayon et al. *SLEEP*, 2004

Sleep Timing and Circadian Changes in Older Adults



SLEEP DISTURBANCES AND LENS YELLOWING

DOI: 10.5665/SLEEP.1242

Sleep Disturbances Are Related to Decreased Transmission of Blue Light to the Retina Caused by Lens Yellowing

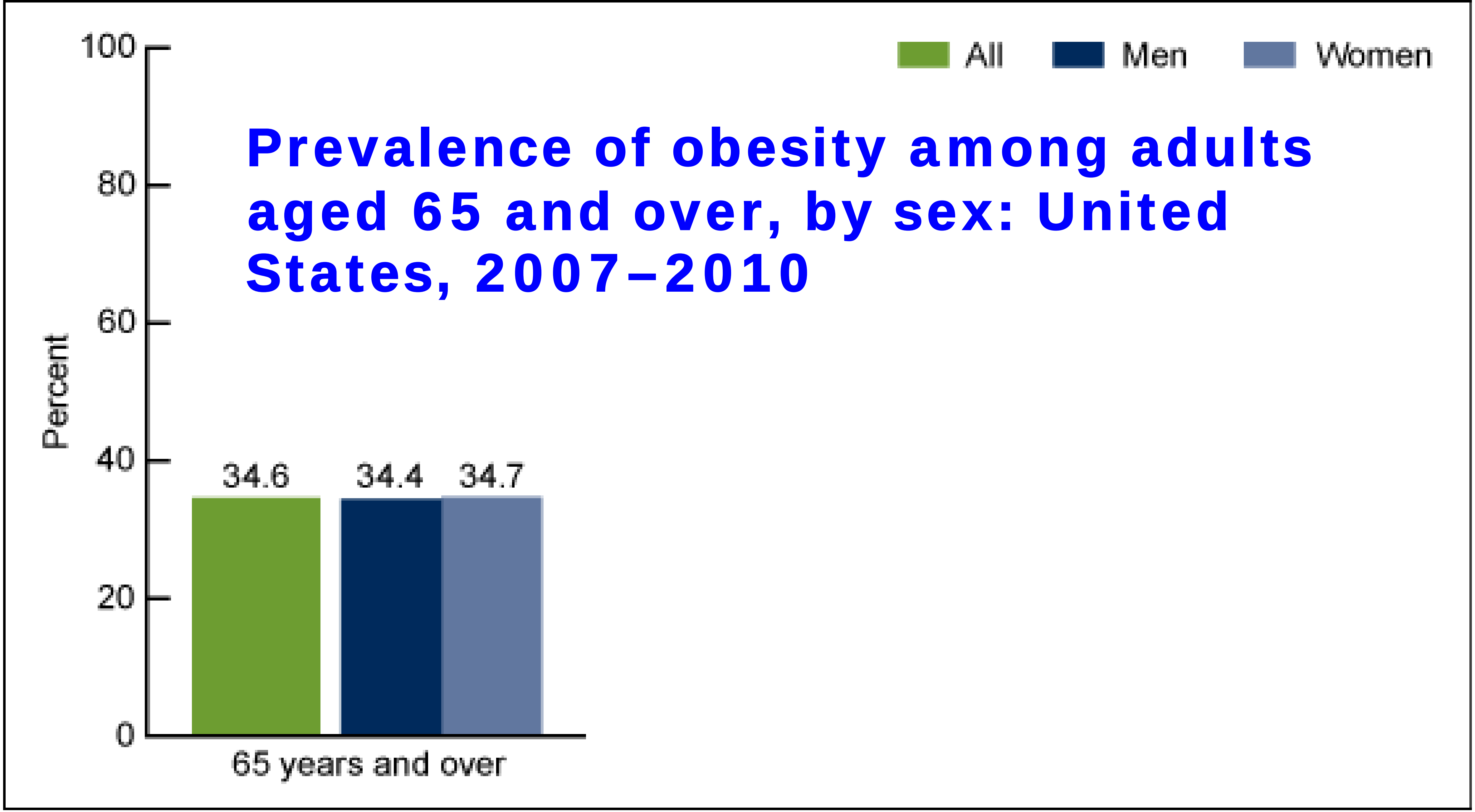
Line Kessel, MD, PhD[1]; Galatios Siganos, MSc[2]; Torben Jørgensen, MD, DMSci[2,3]; Michael Larsen, MD, DMSci[1]

Wright & Frey (2008) Age Related Changes in Sleep and Circadian Physiology: From Brain Mechanisms to Sleep Behavior. In A.Y. Avidan, and C. Alessi: *Geriatric Sleep Disorders*.

1) significance - Metabolic dysregulation and disease

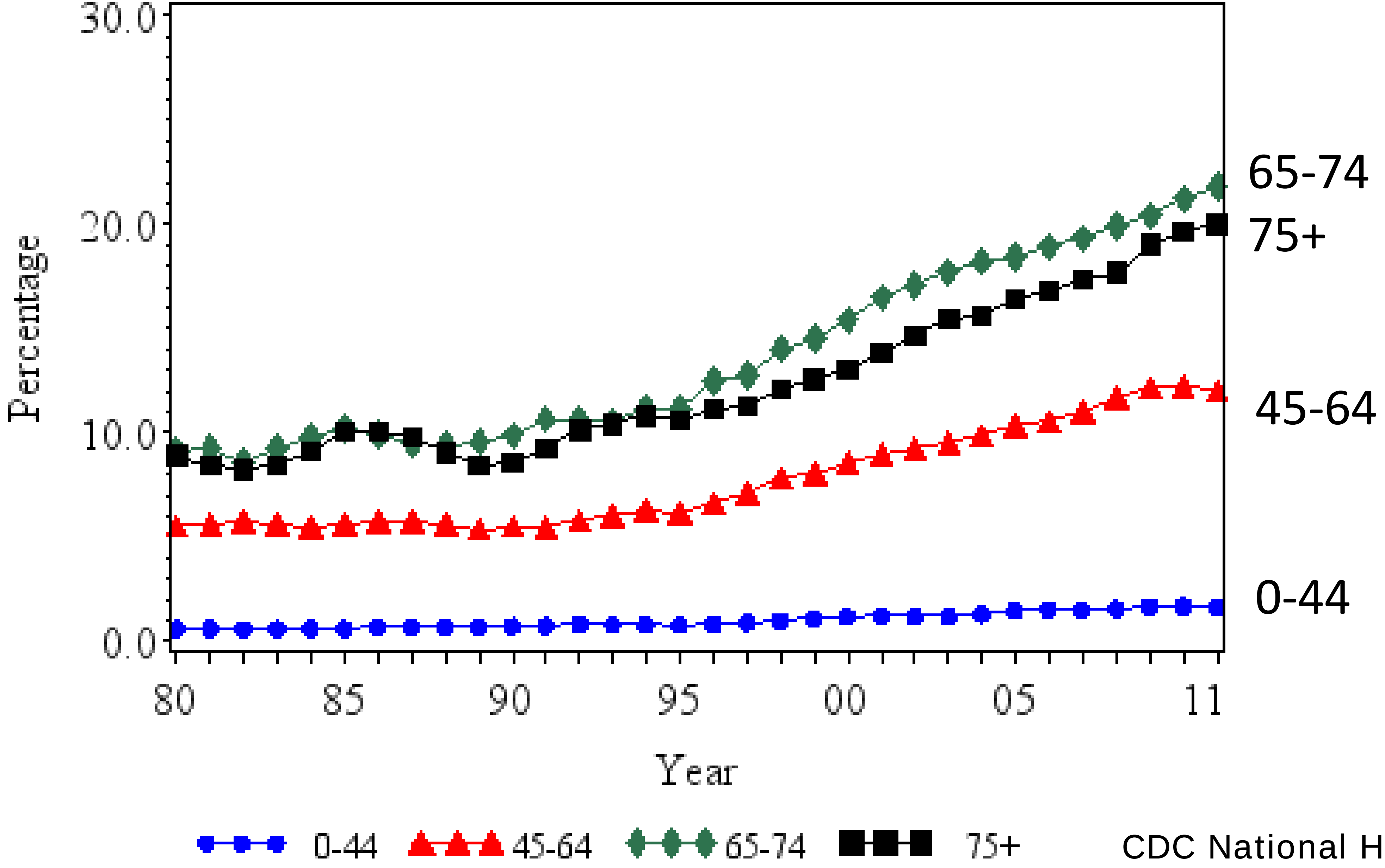
- Prevalence of chronic metabolic disorders such as obesity and type 2 diabetes has increased rapidly over the past 30 years reaching world-wide epidemic proportions

Prevalence of obesity among adults aged 65 and over, by sex: United States, 2007–2010



CDC/NCHS, National Health and Nutrition Examination Survey, 2007–2010

Rate per 100 of Civilian, Noninstitutionalized Population with Diagnosed Diabetes, by Age, United States, 1980–2011



CDC National Health Interview Survey

1) significance - Metabolic dysregulation and disease

- Prevalence of chronic metabolic disorders such as obesity and type 2 diabetes has increased rapidly over the past 30 years reaching world-wide epidemic proportions
- Obesity, diabetes and the metabolic syndrome have large economic and qualilty of life burdens
- Healthy People 2020 goals are to reduce the prevalence of obesity and diabetes

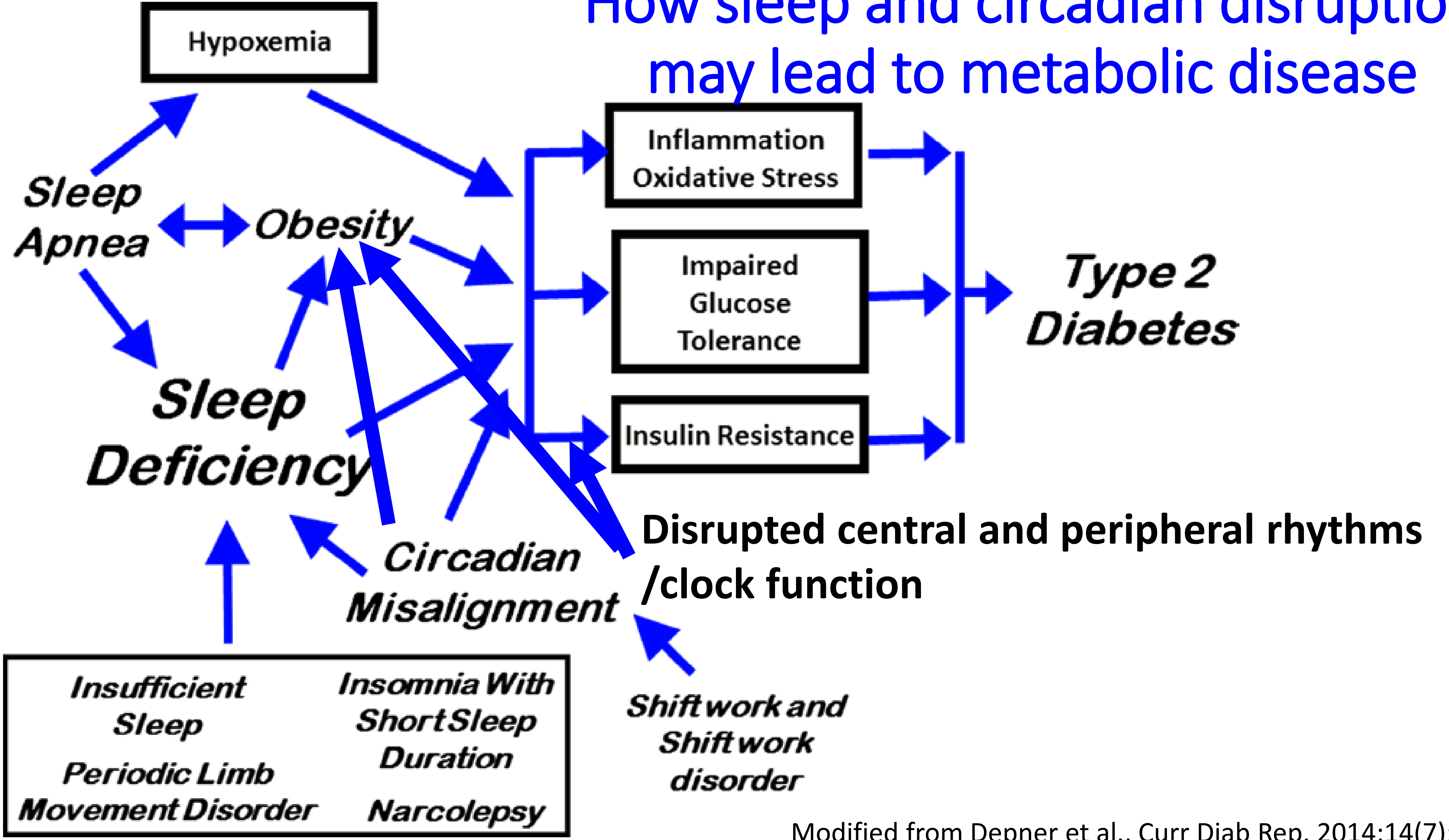
Overweight and obesity substantially raise the risk for

- Cardiovascular diseases
- Hypertension
- Hyperlipidemia
- Osteoarthritis
- Sleep apnea
- Depression
- Diabetes
- Cancer
- Urinary Incontinence

Diabetes substantially raises the risk for

- Heart disease and stroke
- Kidney damage
- Blindness
- Neuropathy
- Urinary Incontinence
- also evidence for Wernicke-Korsakoff syndrome - delirium

How sleep and circadian disruption may lead to metabolic disease



Modified from Depner et al., Curr Diab Rep. 2014;14(7):507.

2) State-of-the Art Knowledge

Do age related changes in sleep and circadian rhythms contribute to metabolic dysregulation and disease

- Sleep disorders – yes
- Short (and sometimes long) sleep duration – yes ?
- Sleep architecture / fragmentation – yes ?
- Sleep and circadian timing – yes
- Circadian misalignment/shift work - ?

Journal of Psychosomatic Research 56 (2004) 497–502

Sleep disturbances and chronic disease in older adults Results of the 2003 National Sleep Foundation *Sleep in America* Survey

Daniel Foley[a,*], Sonia Ancoli-Israel[b], Patricia Britz[c], James Walsh[d]

- 1506 community dwelling 55-84 years old; phone survey
- Obesity and diabetes, were associated with sleep-related problems such as breathing pauses, snoring, daytime sleepiness, restless legs.

International Journal of Obesity (2008) 32, 1825–1834

0307-0565/08 $32.00
www.nature.com/ijo

ORIGINAL ARTICLE

The association between sleep duration and obesity in older adults

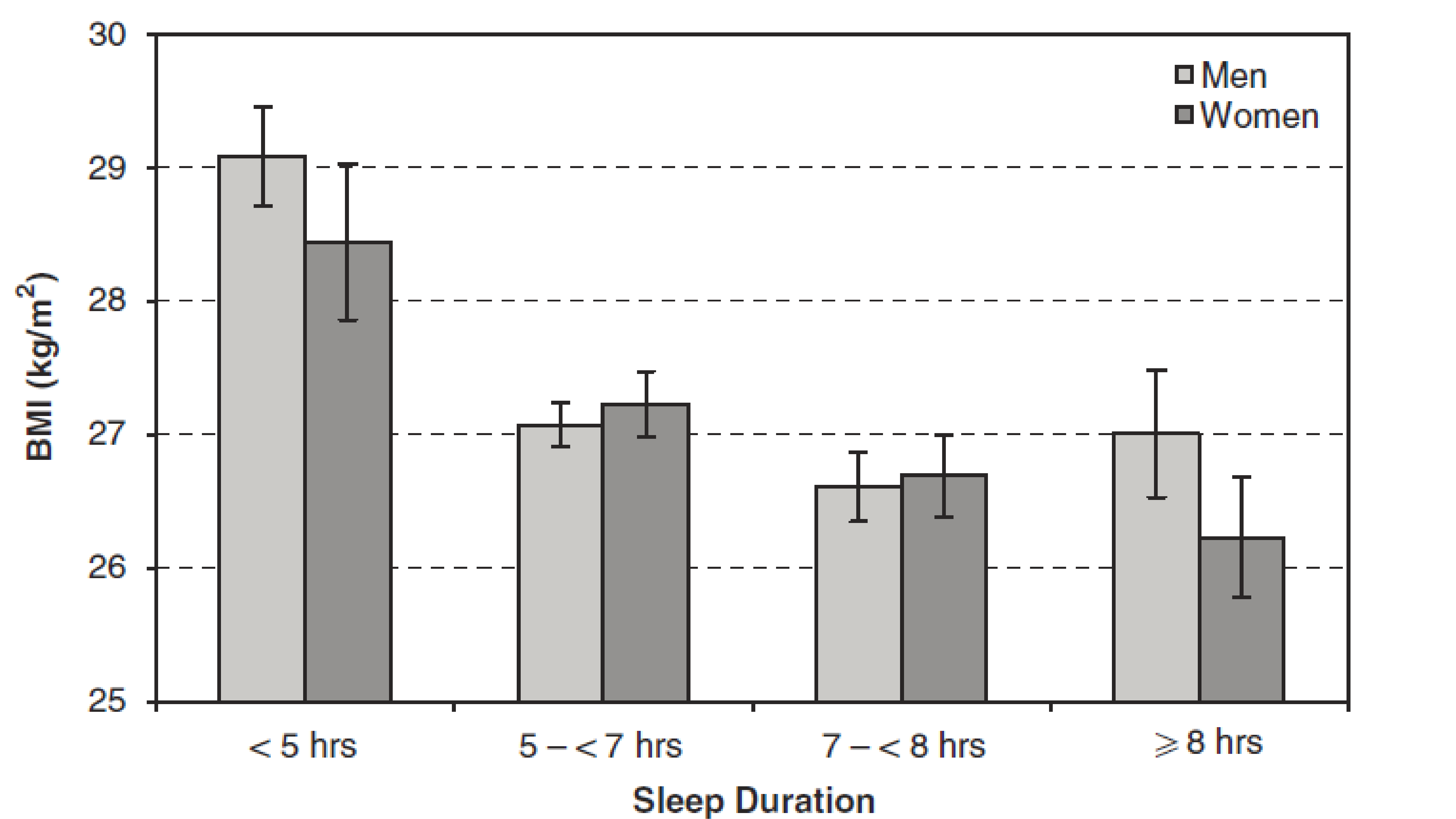
SR Patel[1], T Blackwell[2], S Redline[1], S Ancoli-Israel[3], JA Cauley[4], TA Hillier[5], CE Lewis[6], ES Orwoll[7], ML Stefanick[2], BC Taylor[8], K Yaffe[9] and KL Stone[2] for the Osteoporotic Fractures in Men and the Study of Osteoporotic Fractures Research Groups

Wrist actigraphy

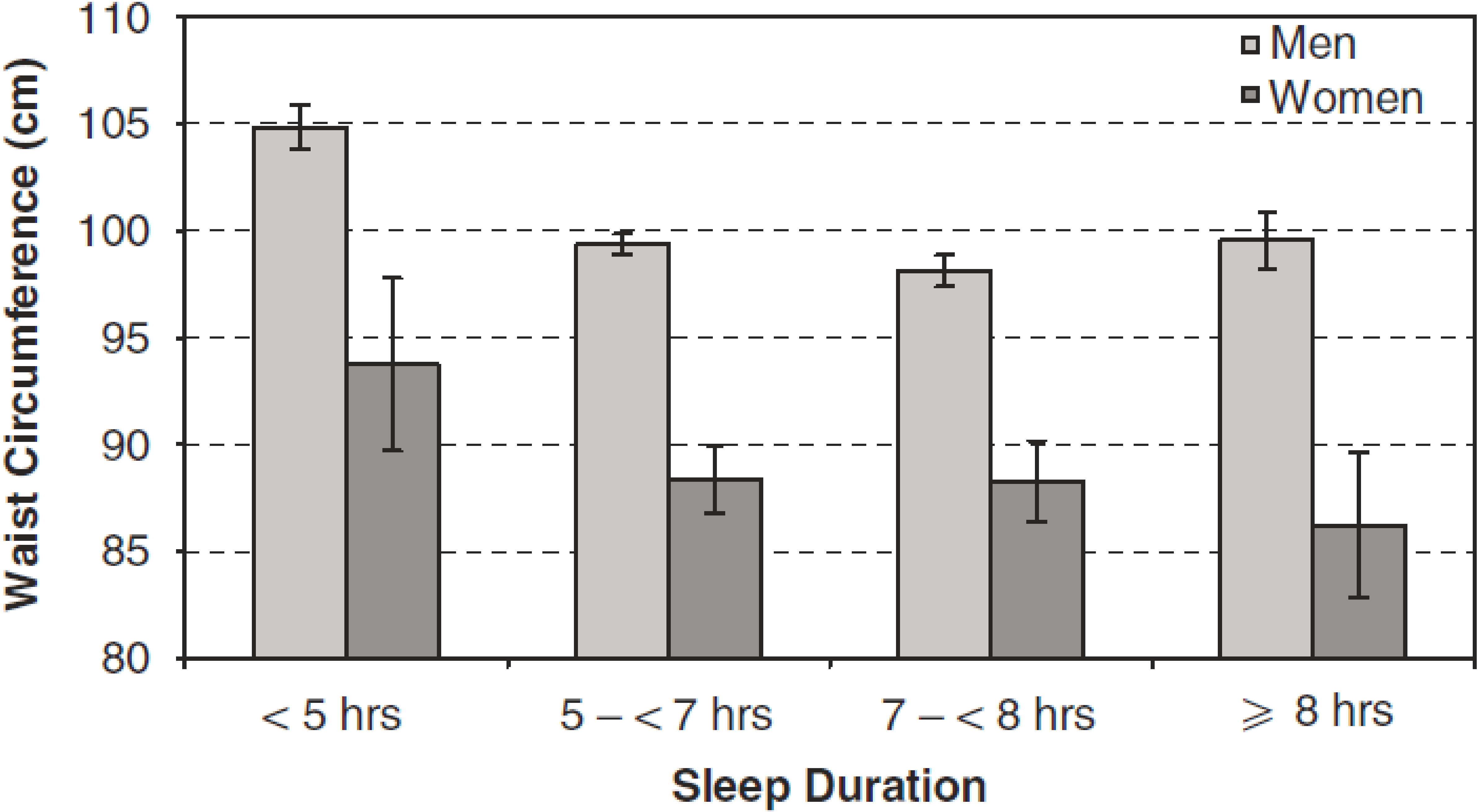
5.2 (0.9 SD) nights in 3055 men (age: 67–96 years) participating in the Osteoporotic Fractures in Men Study (MrOS)

4.1 (0.8 SD) nights in 3052 women (age: 70–99 years) participating in the Study of Osteoporotic Fractures (SOF)

Subgroup of 2862 men and 455 women also underwent PSG for OSA



30
29
28
27
26
25
BMI (kg/m2)
Men
Women
< 5 hrs
5 – < 7 hrs
7 – < 8 hrs
≥ 8 hrs
Sleep Duration


110
105
100
95
90
85
80
Waist Circumference (cm)
Men
Women
< 5 hrs
5 – < 7 hrs
7 – < 8 hrs
≥ 8 hrs
Sleep Duration

International Journal of Obesity (2014) **38,** 1159–1164

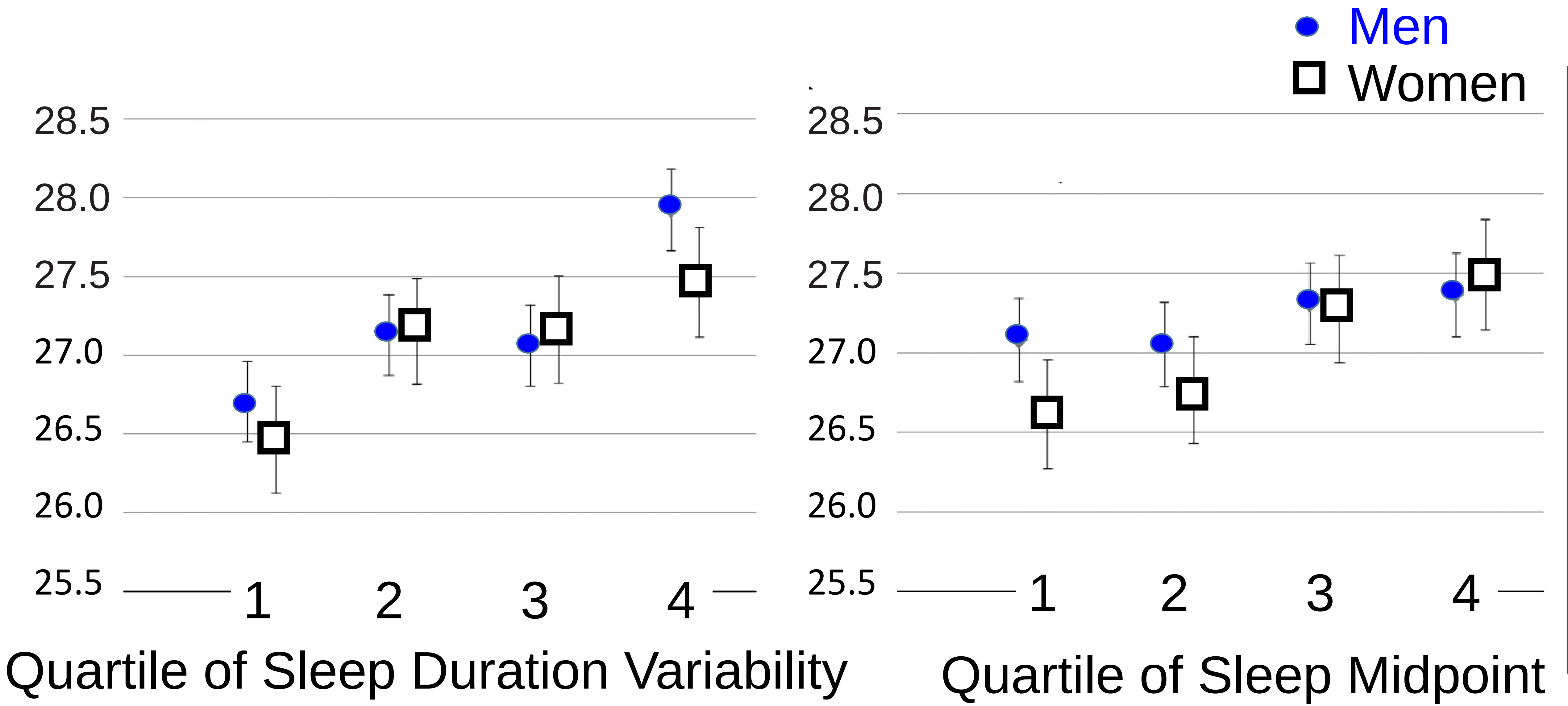
www.nature.com/ijo

ORIGINAL ARTICLE

The association between sleep patterns and obesity in older adults

SR Patel[1], AL Hayes[2], T Blackwell[3], DS Evans[3], S Ancoli-Israel[4], YK Wing[5] and KL Stone[3] for the Osteoporotic Fractures in Men (MrOS) and the Study of Osteoporotic Fractures (SOF) Research Groups

3053 men (mean age 76.4 years) and 2985 women (mean age 83.5 years) mean 5.2 and 4.1 actigraphic sleep data days



Journal of Aging and Health
22(8) 1235–1255

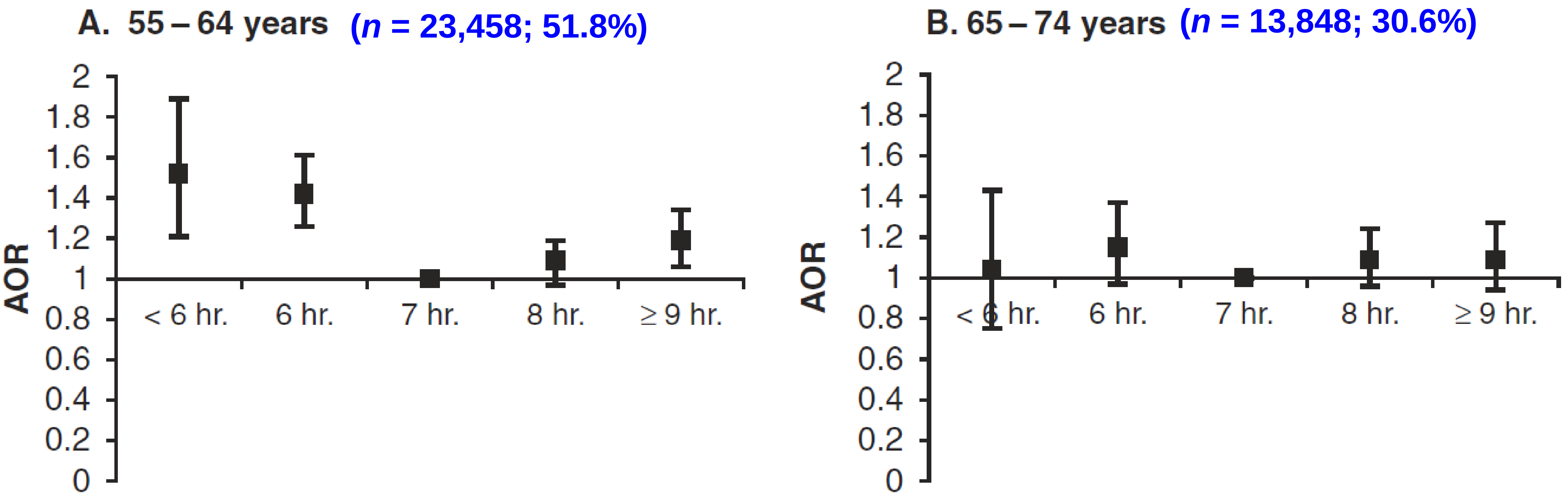
DOI: 10.1177/0898264310372780
http://jah.sagepub.com

Is Sleep Duration Associated With Obesity in Older Australian Adults?

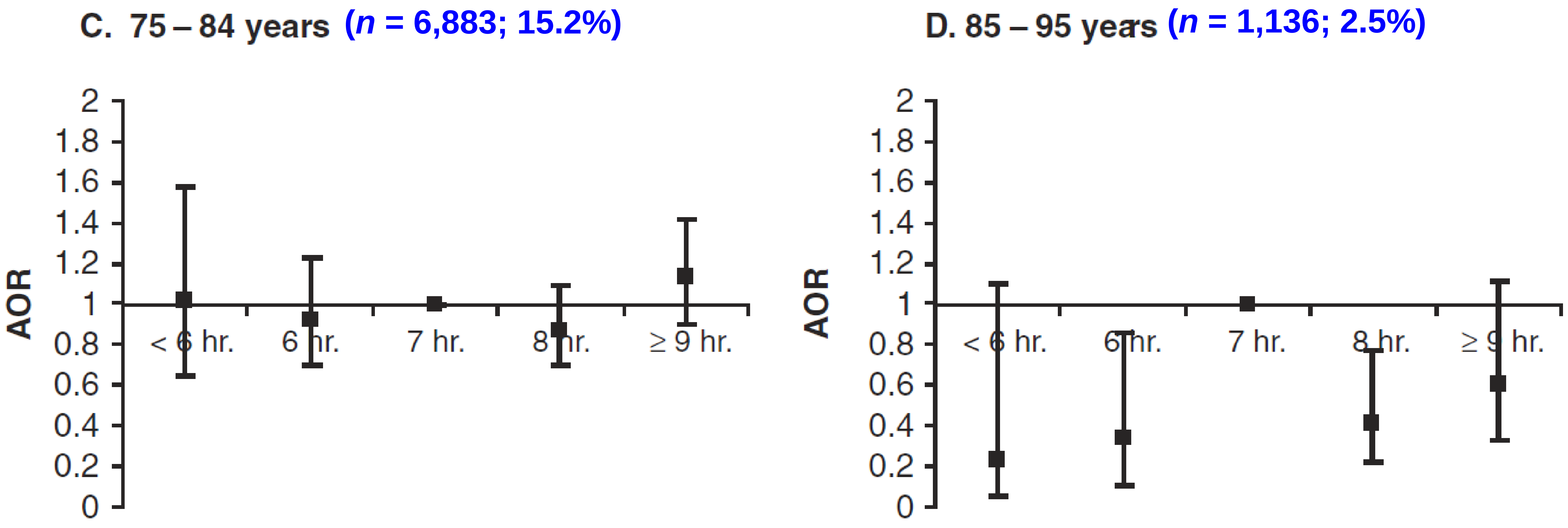
Christopher A. Magee, PhD[1],
Peter Caputi, PhD[1], and
Don C. Iverson, PhD[1]

Table 3. Relationship Between Sleep Duration and Obesity for the Entire Sample (n = 45,325)—Results From the Adjusted and Unadjusted Models

	Overweight		Obese		p value
Model 1					
Sleep category					<.001
<6 hr	0.93	0.81-1.07	1.47*	1.26-1.71	
6 hr	1.00	0.93-1.08	1.33*	1.22-1.45	
7 hr	ref		ref		
8 hr	0.97	0.92-1.02	1.05	0.99-1.12	
≥9 hr	1.01	0.95-1.07	1.22*	1.13-1.32	



A. 55 – 64 years
(n = 23,458; 51.8%)
B. 65 – 74 years
(n = 13,848; 30.6%)
AOR
2
1.8
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
< 6 hr.
6 hr.
7 hr.
8 hr.
≥ 9 hr.


C. 75 – 84 years (n = 6,883; 15.2%)
D. 85 – 95 years (n = 1,136; 2.5%)
AOR
2
1.8
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
< 6 hr.
6 hr.
7 hr.
8 hr.
≥ 9 hr.

Diabetes Care 29:657–661, 2006

Sleep Duration as a Risk Factor for the Development of Type 2 Diabetes

H. Klar Yaggi, MD, MPH[1,2]
Andre B. Araujo, PhD[3]
John B. McKinlay, PhD[3]

N=1567, Massachusetts Male Aging Study without diabetes at baseline (1987–1989; aged 40-70) were followed until 2004 for development of diabetes

Sleep duration	a. Age adjusted
≤5 h	2.60 (1.28–5.27)
6 h	1.93 (1.06–3.50)
7 h	1.00
8 h	1.40 (0.78–2.53)
>8 h	3.63 (1.79–7.38)

Basic Research

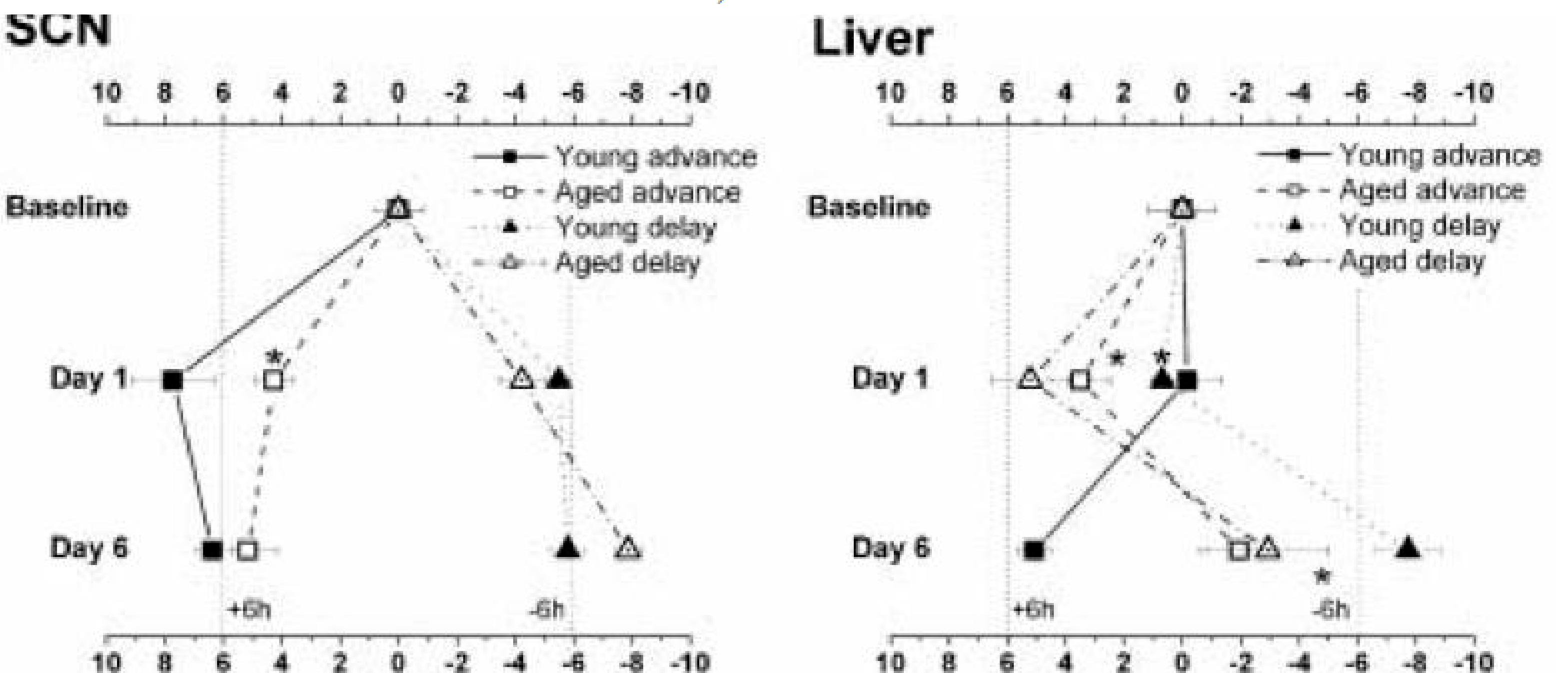
Neurobiology of Aging 29 (2008) 471–477

NEUROBIOLOGY OF AGING

www.elsevier.com/locate/neuaging

Resetting of central and peripheral circadian oscillators in aged rats

Alec J. Davidson [1], Shin Yamazaki [2], Deanna M. Arble [3], Michael Menaker, Gene D. Block *



RESEARCH COMMUNICATION GENES & DEVELOPMENT 20:1868–1873 © 2006

Early aging and age-related pathologies in mice deficient in BMAL1, the core component of the circadian clock

Roman V. Kondratov,[1,4] Anna A. Kondratova,[2] Victoria Y. Gorbacheva,[1] Olena V. Vykhovanets,[1] and Marina P. Antoch[1,3]

[1]Department of Cancer Biology, Lerner Research Institute, Cleveland Clinic Foundation, Cleveland, Ohio 44195, USA; [2]Department of Molecular Genetics, Lerner Research Institute, Cleveland Clinic Foundation, Cleveland, Ohio 44195, USA

Mice deficient in the circadian transcription factor BMAL1

Reduced lifespan
Display various symptoms of premature aging

- **Sarcopenia**
- **Cataracts**
- **Less subcutaneous fat**
- **Organ shrinkage**
- **Increased oxidative stress**
- **Diabetes** (Marcheva et al Nature 2010)

Aging Cell

Aging and sleep deprivation induce the unfolded protein response in the pancreas: implications for metabolism

1.Nirinjini Naidoo[1,2,*], James G. Davis[3,4], Jingxu Zhu[2], Maya Yabumoto[2],
2.Kristan Singletary[2], Marishka Brown[2], Raymond Galante[2], Beamon Agarwal[3,4,†] and Joseph A. Baur[3,4,*]

Volume 13, Issue 1, pages 131–141, February 2014

- **Adaptive arm of the unfolded protein response in pancreatic cells**
  - **Upregulated during SD in young mice**
  - **Reduced in older mice**
- **Maladaptive arm (pro-apoptotic) upregulated in older mice**

3) knowledge gaps

- Mechanisms by which sleep deficiency and circadian disruption contribute to metabolic dysregulation and disease in older adults
  - Age related changes in sleep structure (e.g., slow wave sleep, sleep fragmentation), sleep duration, untreated sleep disorders
  - Age related changes in circadian timing, circadian amplitude, disrupted central and peripheral clocks
  - Vulnerable time for development of metabolic dis (young adult, middle-age, older age)

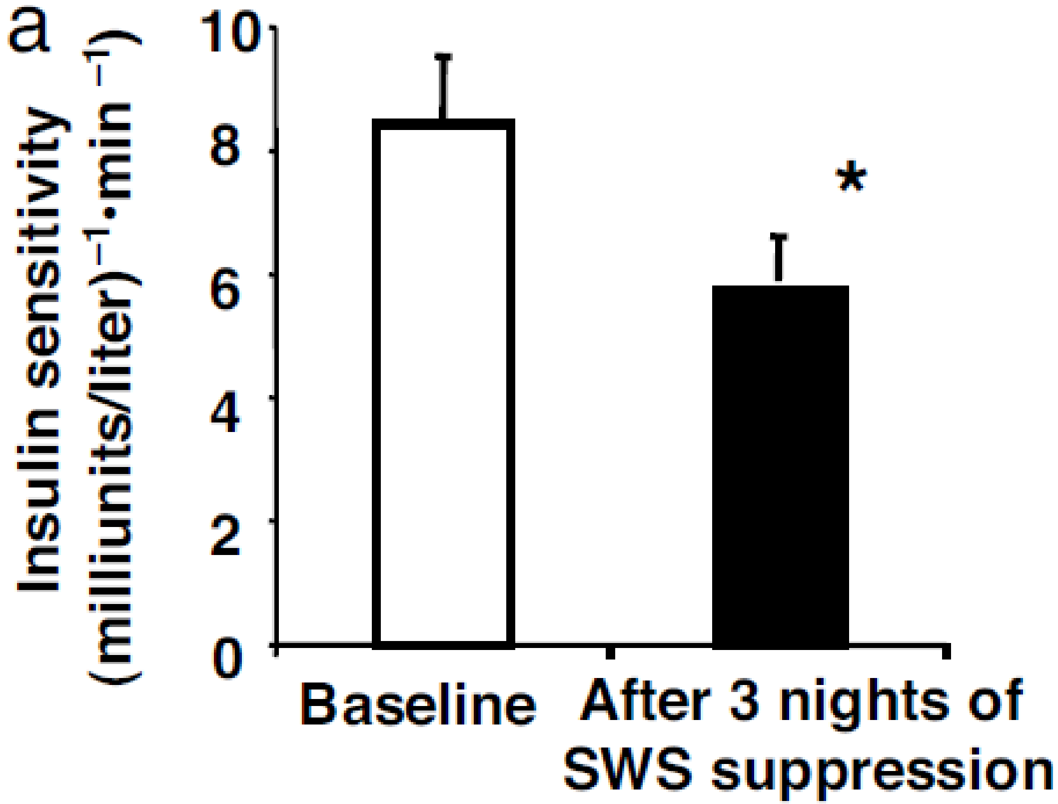
3) knowledge gaps

- Sex differences?
  - Menopause
  - Sleep disorders
  - Health behaviors
- Bi-directional effects (metabolic disorders impacting sleep and circadian)
- Sleep and circadian countermeasure/treatments to treat age related metabolic dysregulation
  - When is it optimal or too late to intervene to prevent versus manage disease

Slow-wave sleep and the risk of type 2 diabetes in humans

Esra Tasali*, Rachel Leproult, David A. Ehrmann, and Eve Van Cauter

1044–1049 | PNAS | January 22, 2008 | vol. 105 | no. 3



Do age related changes in sleep structure contribute to metabolic dysregulation?

Hormone Research

Horm Res 1998;49:147–152

Eve Van Cauter
Laurence Plat
Rachel Leproult
Georges Copinschi

Department of Medicine,
University of Chicago, Ill., USA;

Alterations of Circadian Rhythmicity and Sleep in Aging: Endocrine Consequences

Total growth hormone in older men reduced to 30% of levels in young men

Higher Plasma IGF-1 Levels Are Associated With Increased Delta Sleep in Healthy Older Men

Patricia N. Prinz, Karen E. Moe, Eric M. Dulberg, Lawrence H. Larsen, Michael V. Vitiello, Bert Toivola and George R. Merriam

J Gerontol A Biol Sci Med Sci(1995) 50A (4): M222-M226.

Age-adjusted IGF levels in healthy senior men co-vary significantly with SWS

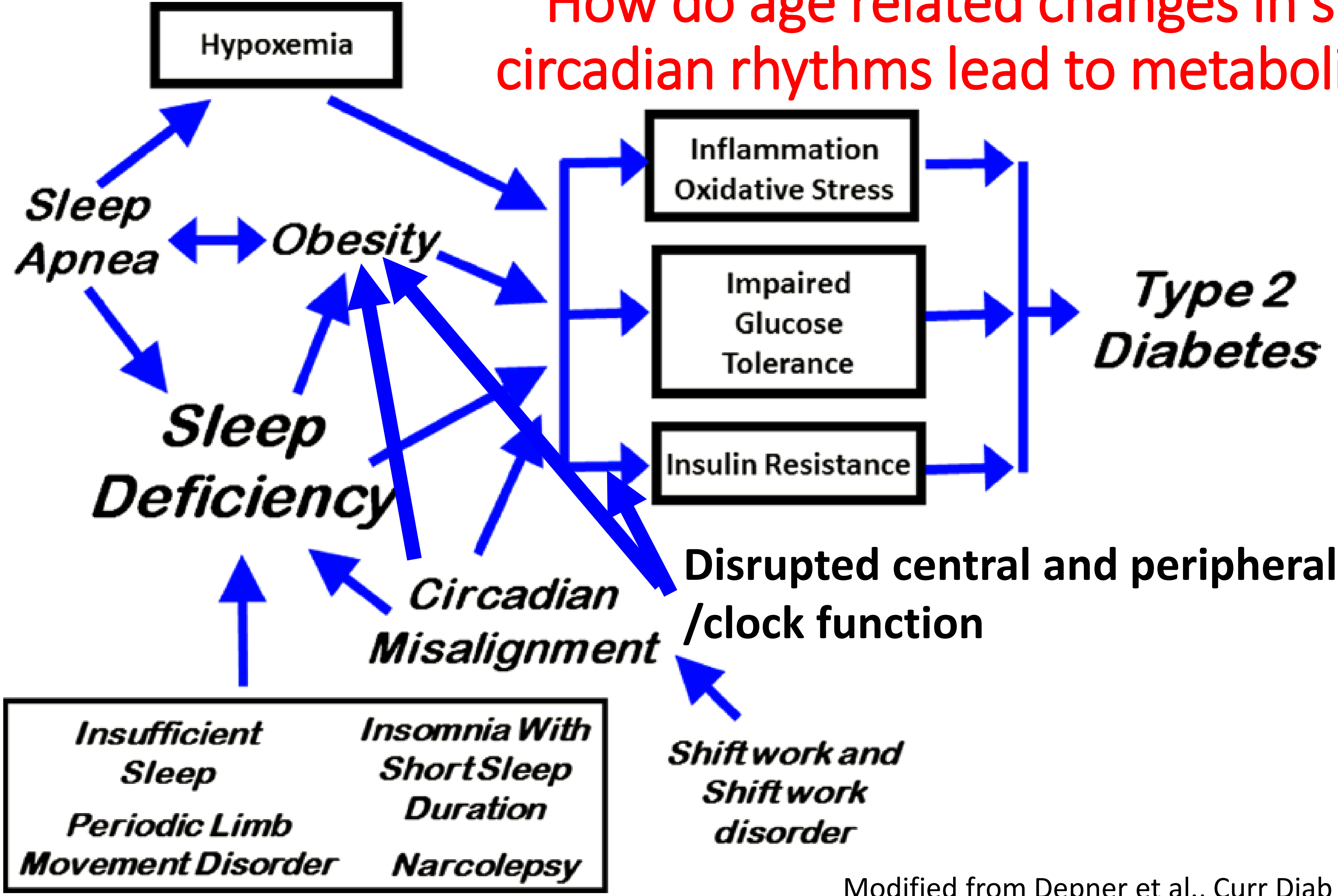
4)research opportunities

- Understanding mechanisms of how age related changes in sleep & circadian rhythms impact metabolic health & disease
  - How do central and peripheral clocks contribute to age-related changes in metabolic health?
    - Vary by organ? Reversible?
  - Biomarkers
  - Hormonal / sympathetic
    - hgh, IGF-1, appetitive hormones
    - Chronic sympathetic activation and reduced tissue responsiveness
  - Nutrition intake / Energy expenditure/ resting metabolic rate
  - Physical Activity (exercise, non-exercise, sedentary time)
  - Sarcopenia

4)research opportunities

- Work hours
  - Metabolic dysregulation and disease in shift work (aging working population)
- Sex differences
  - Role of sex hormones (estrogen, testosterone, sex related sleep disorders, mech prior slide)
- Bi-directional effects
  - The effect of chronic metabolic disorders on sleep
  - The effect of sleep and circadian disruptions on worsening of chronic metabolic disorders
- Development of treatment strategies

How do age related changes in sleep and circadian rhythms lead to metabolic disease?



Modified from Depner et al., Curr Diab Rep. 2014;14(7):507.

Sleep duration, general and abdominal obesity, and weight change among the older adult population of Spain[1–4]

Esther López-García, Raquel Faubel, Luz León-Muñoz, María C Zuluaga, José R Banegas, and Fernando Rodríguez-Artalejo

Am J Clin Nutr 2008;87:310–6.

N=3576, aged 71.6

TABLE 2

Odds ratios (95% CIs) of obesity, severe obesity, and abdominal obesity in 2001, according to habitual sleep duration in 2001

	Sleep duration (hours per 24-h period)					
	≤5 (*n* = 350)	6 (*n* = 409)	7 (*n* = 532)	8 (*n* = 938)	9 (*n* = 591)	≥10 (*n* = 756)
Model adjusted for age and sex						
Obesity[2]	1.45 (1.09, 1.92)	1.18 (0.90, 1.55)	1	1.41 (1.12, 1.76)	1.14 (0.89, 1.47)	1.08 (0.85, 1.37)
Severe obesity[3]	2.36 (1.50, 3.74)	1.31 (0.80, 2.14)	1	1.86 (1.24, 2.78)	1.68 (1.08, 2.61)	1.28 (0.81, 2.00)
Abdominal obesity[4]	1.22 (0.89, 1.65)	1.01 (0.76, 1.35)	1	1.04 (0.82, 1.32)	1.09 (0.84, 1.41)	1.11 (0.87, 1.42)
Model with full adjustment[5]						
Obesity[2]	1.33 (1.00, 1.77)	1.14 (0.86, 1.50)	1	1.39 (1.11, 1.75)	1.07 (0.82, 1.38)	0.96 (0.75, 1.23)
Severe obesity[3]	2.08 (1.31, 3.32)	1.29 (0.78, 2.12)	1	1.82 (1.21, 2.73)	1.57 (1.00, 2.47)	1.13 (0.71, 1.80)
Abdominal obesity[4]	1.14 (0.84, 1.56)	1.00 (0.75, 1.34)	1	1.04 (0.82, 1.32)	1.06 (0.82, 1.39)	1.06 (0.82, 1.36)

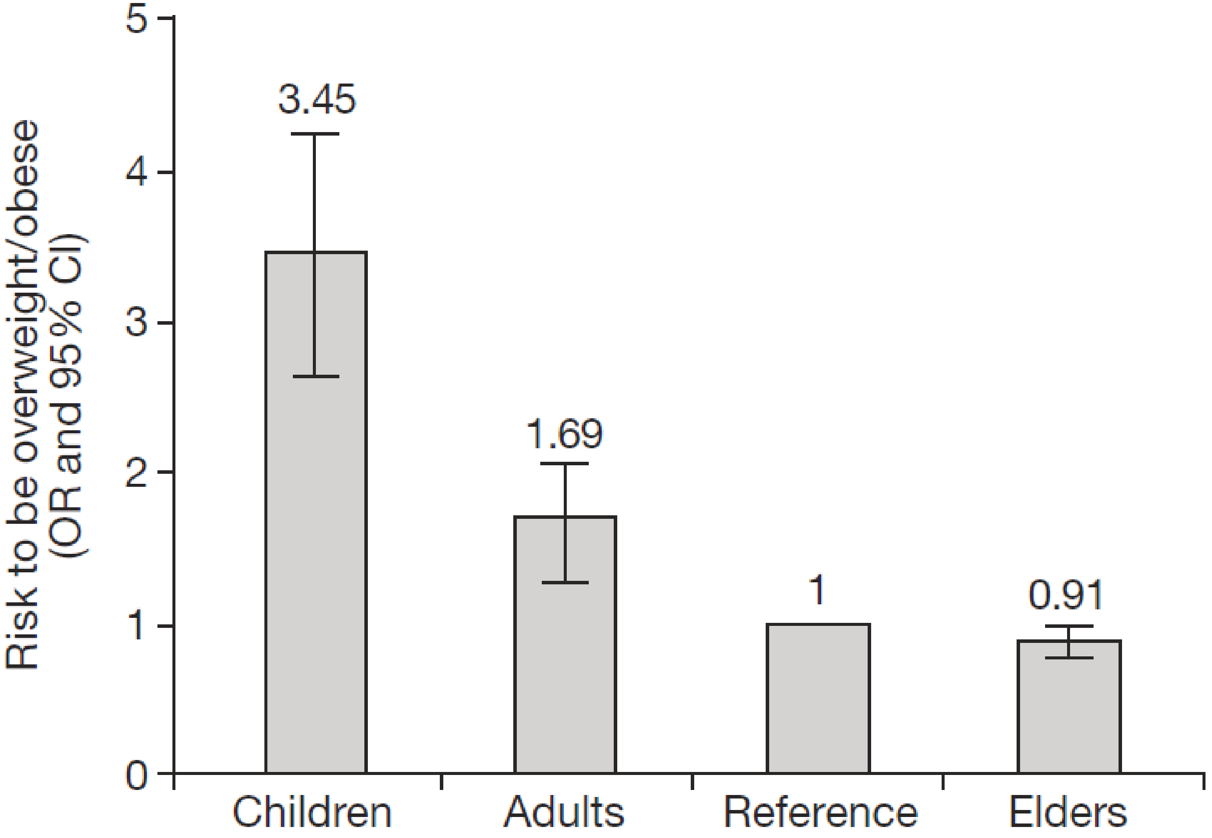
Aging Clin Exp Res 19: 290-294, 2007

Is overweight/obesity associated with short sleep duration in older women?

Jean-Philippe Chaput[1], Christine Lord[2], Mylène Aubertin-Leheudre[2,3], Isabelle J. Dionne[2,3], Abdelouahed Khalil[2,4] and Angelo Tremblay[1]

Table 2 - *Difference between means of investigated variables in relation with the number of sleeping hours in older women.*

	<7 hours/day (n=19)	**≥7 hours/day (n=71)**
Age (years)	61.0±3.0	60.8±5.2
Body weight (kg)	72.0±9.7	72.8±12.4
BMI (kg/m^2)	28.6±3.6	28.8±5.3



OR= odds ratio; 95% CI= 95%confidence interval.
Data on children are from Chaput et al. (4) and data on adults are from Chaput et al. (14).

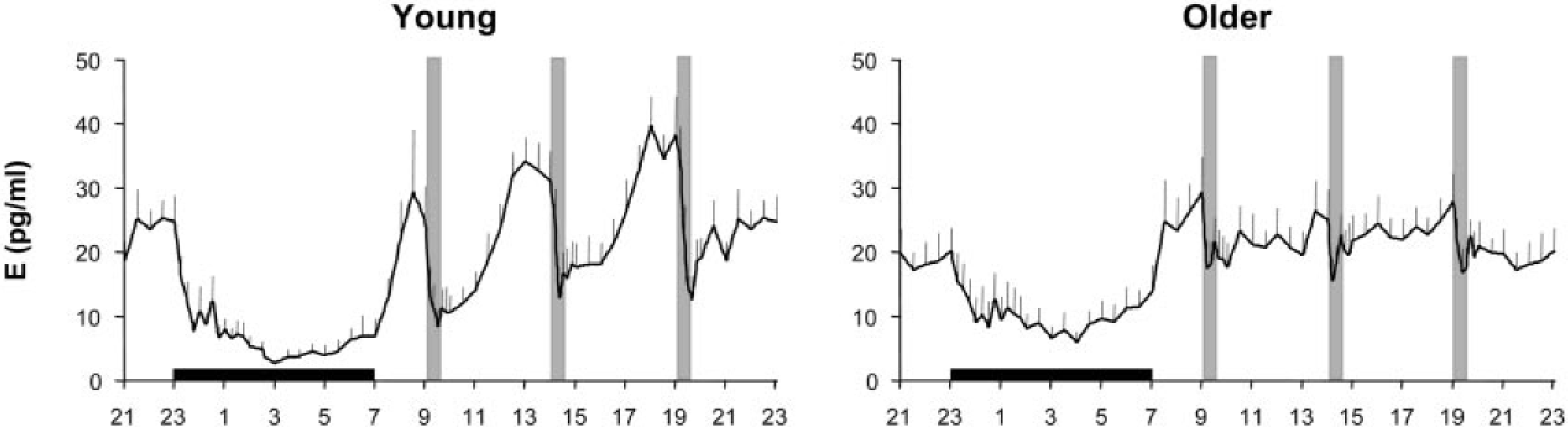
0021-972X/05/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 90(11):6198–6206

doi: 10.1210/jc.2005-0415

Impact of Carbohydrate-Rich Meals on Plasma Epinephrine Levels: Dysregulation with Aging

Plamen Penev, Karine Spiegel, Teresa Marcinkowski, and Eve Van Cauter



Journal of Gerontology: MEDICAL SCIENCES
1997, Vol. 52A, No. 3, M149–M154

Successful 6-Month Endurance Training Does Not Alter Insulin-Like Growth Factor-I in Healthy Older Men and Women

Michael V. Vitiello,[1] Charles W. Wilkinson,[1,3] George R. Merriam,[2,3] Karen E. Moe,[1]
Patricia N. Prinz,[1,3] David D. Ralph,[2] Elizabeth A. Colasurdo,[3] and Robert S. Schwartz[2]